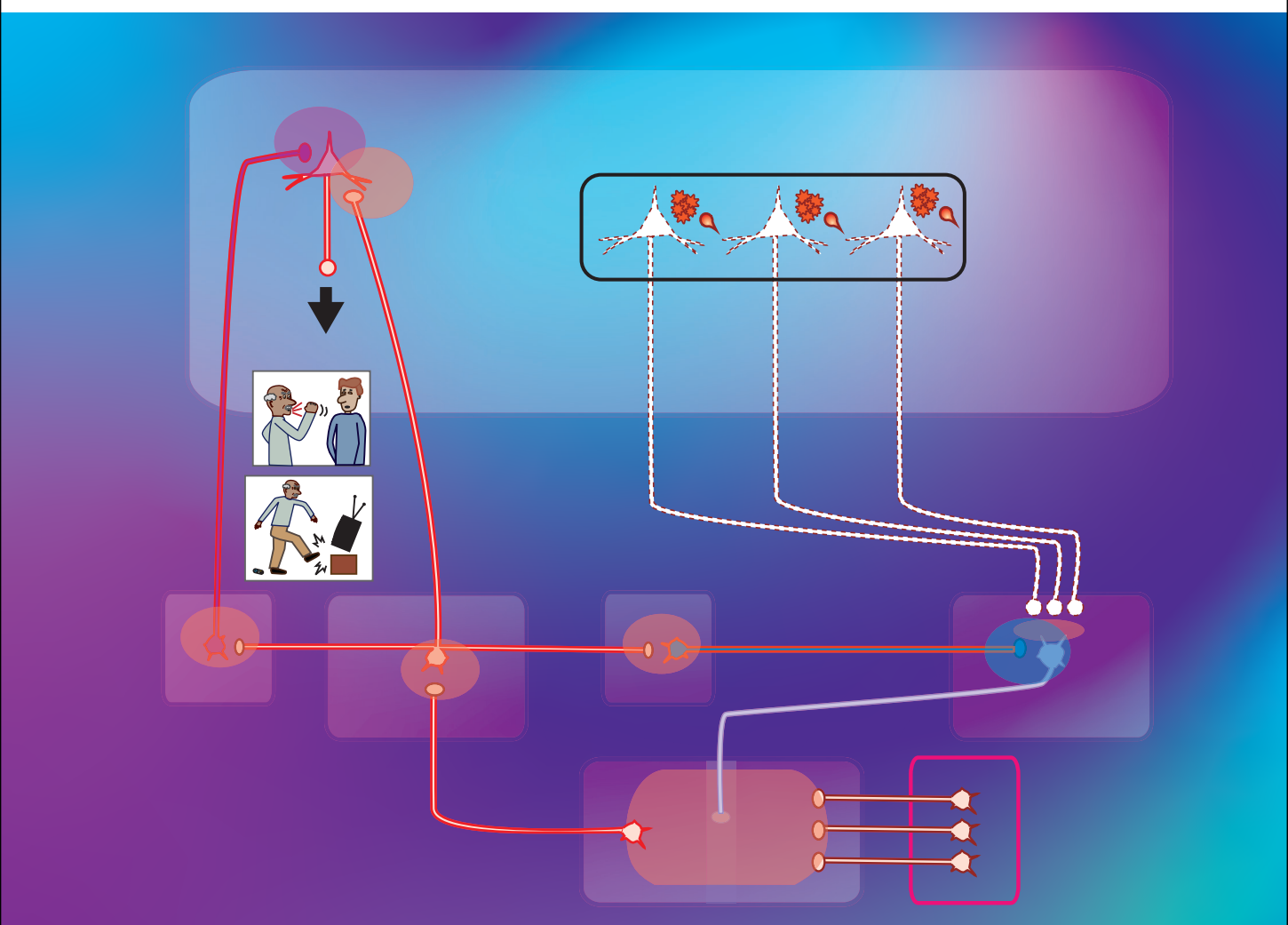
25th Anniversary

Stephen M. Stahl

Fifth Edition

Stahl's Essential Psychopharmacology

Neuroscientific Basis and Practical Applications



CAMBRIDGE

Medicine

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

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

79 Anson Road, #06–04/06, Singapore 079906

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

© Stephen M. Stahl 1996, 2000, 2008, 2013, 2021

This publication is in copyright. Subject to statutory exception and to the provisions of relevant collective licensing agreements, no reproduction of any part may take place without the written permission of Cambridge University Press.

First edition published 1996
Second edition published 2000
Third edition published 2008
Fourth edition published 2013
Fifth edition published 2021

Printed in Singapore by Markono Print Media Pte Ltd

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

Cambridge University Press has no responsibility for the persistence or accuracy of URLs for external or third-party internet websites referred to in this publication and does not guarantee that any content on such websites is, or will remain, accurate or appropriate.

Every effort has been made in preparing this book to provide accurate and up-to-date information that is in accord with accepted standards and practice at the time of publication. Although case histories are drawn from actual cases, every effort has been made to disguise the identities of the individuals involved. Nevertheless, the authors, editors, and publishers can make no warranties that the information contained herein is totally free from error, not least because clinical standards are constantly changing through research and regulation. The authors, editors, and publishers therefore disclaim all liability for direct or consequential damages resulting from the use of material contained in this book. Readers are strongly advised to pay careful attention to information provided by the manufacturer of any drugs or equipment that they plan to use.

Contents

Preface to the Fifth Edition ix
CME Information xiii

1 **Chemical Neurotransmission** 1
2 **Transporters, Receptors, and Enzymes as Targets of Psychopharmacological Drug Action** 29
3 **Ion Channels as Targets of Psychopharmacological Drug Action** 51
4 **Psychosis, Schizophrenia, and the Neurotransmitter Networks Dopamine, Serotonin, and Glutamate** 77
5 **Targeting Dopamine and Serotonin Receptors for Psychosis, Mood, and Beyond: So-Called "Antipsychotics"** 159
6 **Mood Disorders and the Neurotransmitter Networks Norepinephrine and γ-Aminobutyric Acid (GABA)** 244
7 **Treatments for Mood Disorders: So-Called "Antidepressants" and "Mood Stabilizers"** 283
8 **Anxiety, Trauma, and Treatment** 359
9 **Chronic Pain and Its Treatment** 379
10 **Disorders of Sleep and Wakefulness and Their Treatment: Neurotransmitter Networks for Histamine and Orexin** 401
11 **Attention Deficit Hyperactivity Disorder and Its Treatment** 449
12 **Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine** 486
13 **Impulsivity, Compulsivity, and Addiction** 538

Suggested Reading and Selected References 579
Index 615

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–complusive disorder (OCD) to the impulsivity chapter
  - coverage of posttraumatic stress disorder (PTSD) as a traumatic disorder rather than anxiety disorder

  - 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 H_3 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*

- *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.

NEI designates this enduring material for a maximum of 61.5 *AMA PRA Category 1 Credits* ™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurses and *Physician Assistants*: for your CE requirements, the ANCC and NCCPA will accept *AMA PRA Category 1 Credits* ™ from organizations accredited by the ACCME. The content in this activity pertains to pharmacology and is worth 61.5 continuing education hours of pharmacotherapeutics.

Optional posttests and CME credit instructions

Optional posttests and certificates of CME credit are available for each topical section of the book (total of nine sections). There is a fee for each posttest (varies per section) which is waived for NEI members.

1. Read the desired topical section
2. Pass the related posttest (70% score or higher), available only online at www.neiglobal.com/CME (under "Book")
3. Print your certificate

Questions? call 888-535-5600, or email CustomerService@neiglobal.com

Peer review

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.

Disclosures

All individuals in a position to influence or control content are required to disclose any relevant financial relationships. Although potential conflicts of interest are identified and resolved prior to the activity being presented, it remains for the participant to determine whether outside interests reflect a possible bias in either the exposition or the conclusions presented.

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

Speakers Bureau: Acadia, Lundbeck, Otsuka, Perrigo, Servier, Sunovion, Takeda, Vertex

Board Member: Genomind

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

All of Dr. Alarcón's financial relationships are through her spouse/partner.

Employee (spouse/partner): Ashfield Healthcare Communications

Peer Reviewers

William M. Sauvé, MD
Regional Medical Director, Greenbrook TMS NeuroHealth Centers, Virginia

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 relationships to disclose.

Disclosure of Off-Label Use

This educational activity may include discussion of unlabeled and/or investigational uses of agents that are not currently labeled for such use by the FDA. Please consult the product prescribing information for full disclosure of labeled uses.

Cultural and Linguistic Competency

A variety of resources addressing cultural and linguistic competency can be found at this link: www.neiglobal.com/go/cmeregs.

Support

This activity is supported solely by the provider, NEI.

1 Chemical Neurotransmission

Anatomical versus Chemical Basis of Neurotransmission 1
General Structure of a Neuron 2
Principles of Chemical Neurotransmission 5
Neurotransmitters 5
Neurotransmission: Classic, Retrograde, and Volume 6
Excitation–Secretion Coupling 8
Signal Transduction Cascades 9
Overview 9
Forming a Second Messenger 11
Beyond the Second Messenger to Phosphoprotein Messengers 13
Beyond the Second Messenger to a Phosphoprotein Cascade Triggering Gene Expression 15
How Neurotransmission Triggers Gene Expression 18
Molecular Mechanism of Gene Expression 18
Epigenetics 23
What Are the Molecular Mechanisms of Epigenetics? 23
How Epigenetics Maintains or Changes the Status Quo 24
A Brief Word about RNA 26
Alternative Splicing 26
RNA Interference 26
Summary 28

Modern psychopharmacology is largely the story of chemical neurotransmission. To understand the actions of drugs on the brain, to grasp the impact of diseases upon the central nervous system, and to interpret the behavioral consequences of psychiatric medicines, one must be fluent in the language and principles of chemical neurotransmission. The importance of this fact cannot be overstated for the student of psychopharmacology. This chapter forms the foundation for the entire book, and the roadmap for one's journey through one of the most exciting topics in science today, namely the neuroscience of how disorders and drugs act upon the central nervous system.

ANATOMICAL VERSUS CHEMICAL BASIS OF NEUROTRANSMISSION

What is neurotransmission? Neurotransmission can be described in many ways: anatomically, chemically, electrically. The *anatomical* basis of neurotransmission is neurons (Figures 1-1 to 1-3) and the connections between them, called synapses (Figure 1-4), sometimes also called the *anatomically addressed nervous system*, a complex of "hard-wired" synaptic connections between neurons, not unlike millions of telephone wires within thousands upon thousands of cables. The *anatomically addressed brain* is thus a complex wiring diagram, ferrying electrical impulses to wherever the "wire" is plugged in (i.e., at a synapse). Synapses can form on many parts of a neuron, not just from the axon of one neuron to the dendrite of another neuron as axodendritic synapses, but also from the axon of one neuron to the soma of another neuron as axosomatic synapses, and even from one neuron's axon to another neuron's axon, especially at the beginning and at the end of the receiving neuron's axons (axoaxonic synapses) (Figure 1-2). Such synapses are said to be "asymmetric" since communication is structurally designed to be in one direction, i.e., anterograde from the axon of the first neuron to the dendrite, soma, or axon of the second neuron (Figures 1-2 and 1-3). This means that there are presynaptic elements that differ from postsynaptic elements (Figure 1-4). Specifically, a neurotransmitter is packaged in the presynaptic nerve terminal like ammunition in a loaded gun, and then fired at the postsynaptic neuron to target its receptors.

Neurons are the cells of chemical communication in the brain. Human brains are comprised of tens of billions of neurons, and each is linked to thousands of other neurons. Thus, the brain has trillions of specialized connections known as synapses. Neurons have many sizes, lengths, and shapes that determine their functions. Localization within the brain also determines function. When neurons malfunction, behavioral symptoms may

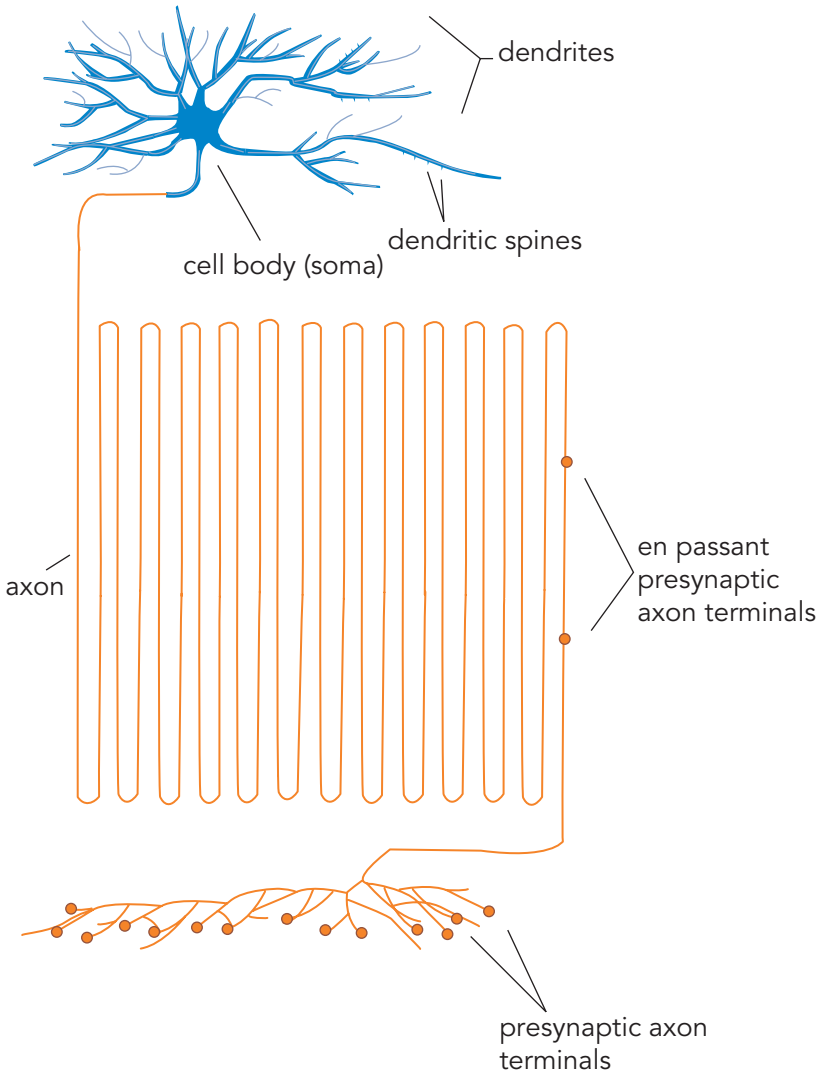


Figure 1-1 General structure of a neuron. This is an artist's conception of the generic structure of a neuron. All neurons have a cell body known as the soma, which is the command center of the nerve and contains the nucleus of the cell. All neurons are also set up structurally to both send and receive information. Neurons send information via an axon that forms presynaptic terminals as the axon passes by (en passant) or as the axon ends.

occur. When drugs alter neuronal function, behavioral symptoms may be relieved, worsened, or produced.

General Structure of a Neuron

Although this textbook will often portray neurons with a generic structure (such as that shown in Figures 1-1 to 1-3), the truth is that many neurons have unique structures depending upon where in the brain they are located and what their function is. On the one hand, all neurons have a cell body known as the soma, and are set up structurally to receive information from other neurons through dendrites, sometimes via spines on the dendrites and often through an elaborately branching "tree" of dendrites (Figure 1-2). Neurons are also set up structurally to send information to other neurons via an axon that forms presynaptic terminals as the axon passes by (en passant, Figure 1-1) or as the axon ends (presynaptic axon terminals, Figures 1-1 through 1-4).

Neurotransmission has an *anatomical* infrastructure, but it is fundamentally a very elegant *chemical* operation. Complementary to the anatomically addressed nervous system is thus the *chemically addressed nervous system*, which forms the chemical basis of neurotransmission: namely, how chemical signals are coded, decoded, transduced, and sent along the way. Understanding the principles of chemical

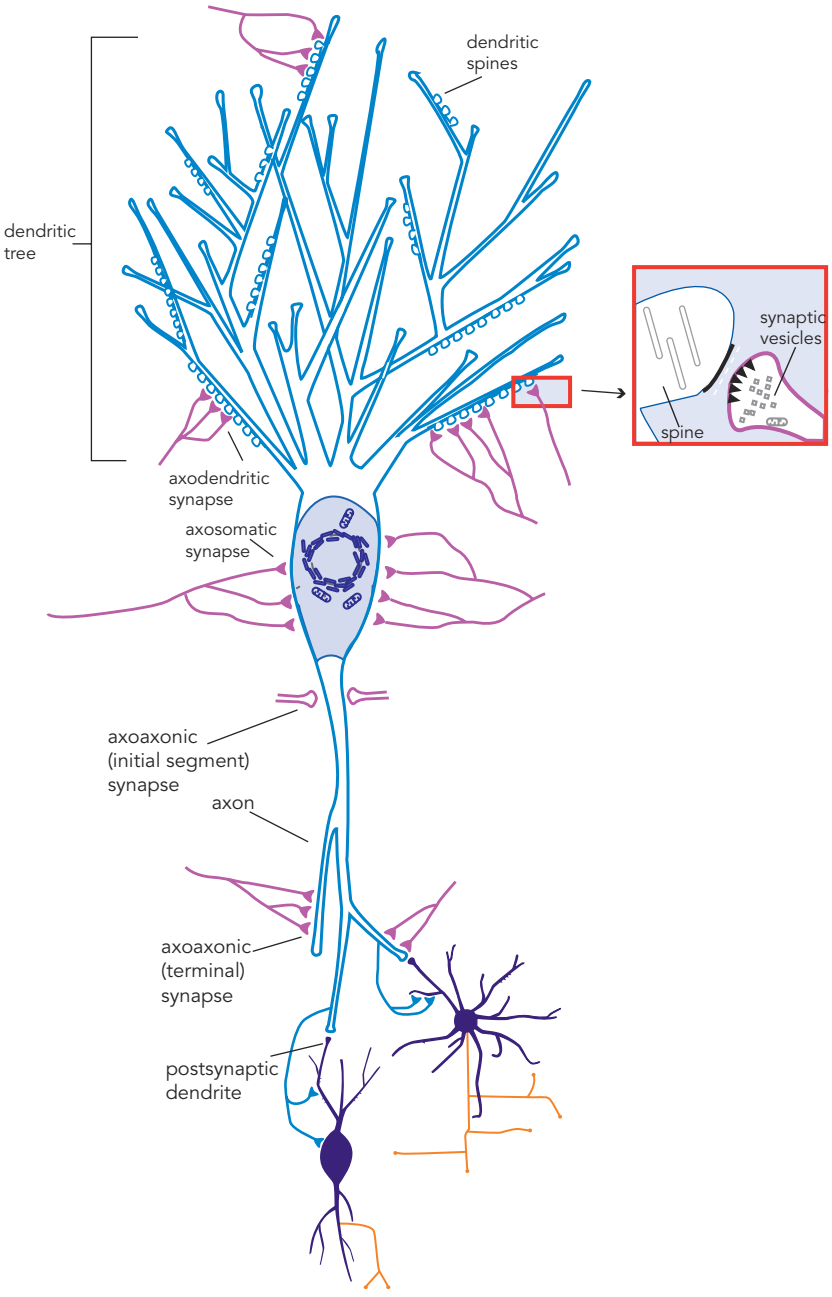


Figure 1-2 Axodendritic, axosomatic, and axoaxonic connections. After neurons migrate, they form synapses. As shown in this figure, synaptic connections can form not just between the axon and dendrites of two neurons (axodendritic) but also between the axon and the soma (axosomatic) or the axons of the two neurons (axoaxonic). Communication is anterograde from the axon of the first neuron to the dendrite, soma, or axon of the second neuron.

neurotransmission is a fundamental requirement for grasping how psychopharmacological agents work, because these agents target key molecules involved in neurotransmission. Drug targeting of specific chemical sites that influence neurotransmission is discussed in Chapters 2 and 3.

Understanding the chemically addressed nervous system is also a prerequisite for becoming a "neurobiologically informed" clinician: that is, being able to translate exciting new findings on brain circuitry, functional neuroimaging, and genetics into clinical practice, and potentially improving the manner in which

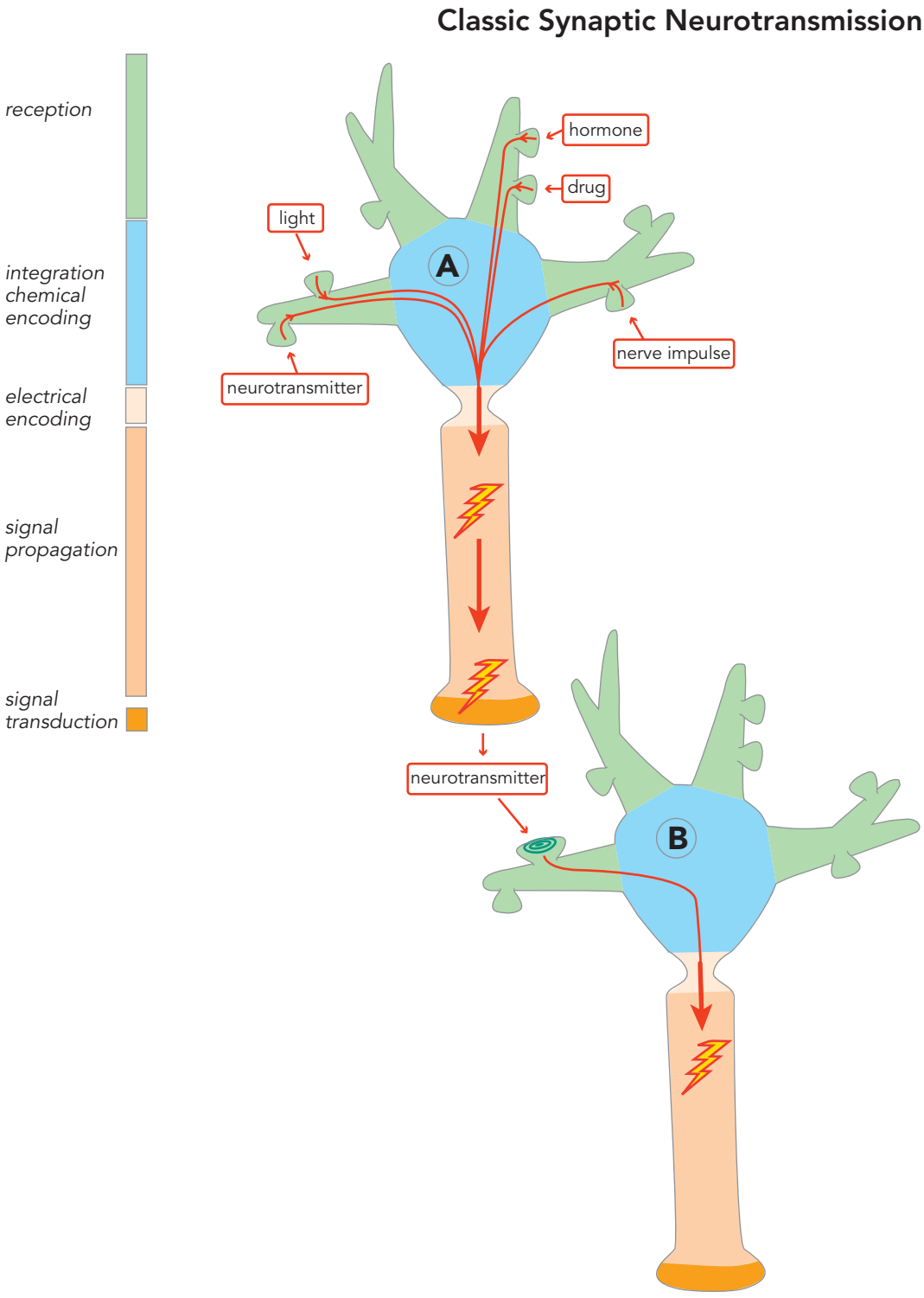


Figure 1-3 **Classic synaptic neurotransmission.** In classic synaptic neurotransmission, stimulation of a presynaptic neuron (e.g., by neurotransmitters, light, drugs, hormones, nerve impulses) causes electrical impulses to be sent to its axon terminal. These electrical impulses are then converted into chemical messengers and released to stimulate the receptors of a postsynaptic neuron. Thus, although communication *within* a neuron can be electrical, communication *between* neurons is chemical.

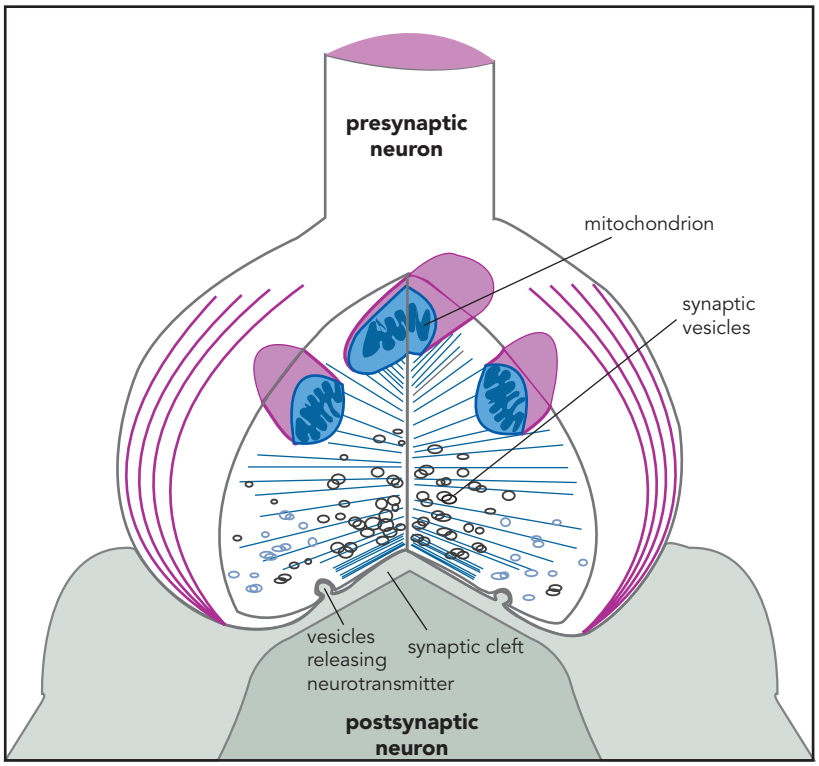


Figure 1-4 Enlarged synapse. The synapse is enlarged conceptually here showing the specialized structures that enable chemical neurotransmission to occur. Specifically, a presynaptic neuron sends its axon terminal to form a synapse with a postsynaptic neuron. Energy for neurotransmission from the presynaptic neuron is provided by mitochondria there. Chemical neurotransmitters are stored in small vesicles, ready for release upon firing of the presynaptic neuron. The synaptic cleft is the gap between the presynaptic neuron and the postsynaptic neuron; it contains proteins and scaffolding and molecular forms of "synaptic glue" to reinforce the connection between the neurons. Receptors are present on both sides of this cleft and are key elements of chemical neurotransmission.

psychiatric disorders and their symptoms are diagnosed and treated. The chemistry of neurotransmission in specific brain regions and how these principles are applied to various specific psychiatric disorders, treated with various specific psychotropic drugs, are discussed throughout the rest of the book.

PRINCIPLES OF CHEMICAL NEUROTRANSMISSION

Neurotransmitters

There are more than a dozen known or suspected neurotransmitters in the brain. For psychopharmacologists, it is particularly important to know the six key neurotransmitter systems targeted by psychotropic drugs:

serotonin
norepinephrine
dopamine
acetylcholine
glutamate
GABA (γ-aminobutyric acid)

Each is discussed in detail in the clinical chapters related to the specific drugs that target them.

Other neurotransmitters that are also important neurotransmitters and neuromodulators, such as histamine and various neuropeptides and hormones, are mentioned in brief throughout the relevant clinical chapters in this textbook.

Some neurotransmitters are very similar to drugs and have been called "God's pharmacopeia." For example, it is well known that the brain makes its own morphine (i.e., β-endorphin) and its own marijuana (i.e., endocannabinoids). The brain may even make its own Prozac, its own Xanax, and and its own hallucinogens! Drugs often mimic the brain's natural neurotransmitters and some drugs have been discovered prior to the natural neurotransmitter. Thus, morphine was used in clinical

practice before the discovery of β-endorphin; marijuana was smoked before the discovery of cannabinoid receptors and endocannabinoids; the benzodiazepines Valium (diazepam) and Xanax (alprazolam) were prescribed before the discovery of benzodiazepine receptors; and the antidepressants Elavil (amitriptyline) and Prozac (fluoxetine) entered clinical practice before molecular clarification of the serotonin transporter site. This underscores the point that the great majority of drugs that act in the central nervous system act upon the process of neurotransmission. Indeed, this apparently occurs at times in a manner that can mimic the actions of the brain itself, when the brain uses its own chemicals.

Input to any neuron can involve many different neurotransmitters coming from many different neuronal circuits. Understanding these inputs to neurons within functioning circuits can provide a rational basis for selecting and combining therapeutic agents. This theme is discussed extensively in each chapter on the various psychiatric disorders. The idea is that for the modern psychopharmacologist to influence abnormal neurotransmission in patients with psychiatric disorders, it may be necessary to target neurons in specific circuits. Since these networks of neurons send and receive information via a variety of neurotransmitters, it may therefore be not only rational but necessary to use multiple drugs with multiple neurotransmitter actions for patients with psychiatric disorders, especially if single agents with single neurotransmitter mechanisms are not effective in relieving symptoms.

Neurotransmission: Classic, Retrograde, and Volume

Classic neurotransmission begins with an electrical process by which neurons send electrical impulses from one part of the cell to another part of the same cell via their axons (see neuron A of Figure 1-3). However, these electrical impulses do not jump directly to other neurons. Classic neurotransmission between neurons involves one neuron hurling a chemical messenger, or neurotransmitter, at the receptors of a second neuron (see the synapse between neuron A and neuron B in Figure 1-3). This happens frequently but not exclusively at the sites of synaptic connections. In the human brain, a hundred billion neurons each make thousands of synapses with other neurons for an estimated trillion chemically neurotransmitting synapses.

Communication *between* all these neurons at synapses is chemical, not electrical. That is, an electrical impulse in the first neuron is converted to a chemical signal at the synapse between it and a second neuron, in a process known as excitation–secretion coupling, the first stage of chemical neurotransmission. This occurs predominantly but not exclusively in one direction, from the *presynaptic* axon terminal to a second *postsynaptic* neuron (Figures 1-2 and 1-3). Finally, neurotransmission continues in the second neuron either by converting the chemical information from the first neuron back into an electrical impulse in the second neuron, or, perhaps more elegantly, by the chemical information from the first neuron triggering a cascade of further chemical messages within the second neuron to change that neuron's molecular and genetic functioning (Figure 1-3).

An interesting twist to chemical neurotransmission is the discovery that postsynaptic neurons can also "talk back" to their presynaptic neurons. They can do this via retrograde neurotransmission from the second neuron to the first at the synapse between them (Figure 1-5, right panel). Chemicals produced specifically as retrograde neurotransmitters at some synapses include the endocannabinoids (EC, also known as "endogenous marijuana"), which are synthesized in the postsynaptic neuron. They are then released and diffuse to presynaptic cannabinoid receptors such as the CB1 or cannabinoid 1 receptor (Figure 1-5, right panel). Another retrograde neurotransmitter is the gaseous neurotransmitter nitric oxide (NO), which is synthesized postsynaptically and then diffuses out of the postsynaptic membrane and into the presynaptic membrane to interact with cyclic guanosine monophosphate (cGMP)-sensitive targets there (Figure 1-5, right panel). A third type of retrograde neurotransmitter are neurotrophic factors such as nerve growth factor (NGF), which is released from postsynaptic sites, and then diffuses to the presynaptic neuron, where it is taken up into vesicles, and transported all the way back to the cell nucleus via retrograde transport systems to interact with the genome there (Figure 1-5, right panel). What these retrograde neurotransmitters have to say to the presynaptic neuron and how this modifies or regulates the communication between pre and postsynaptic neuron are subjects of intense active investigation.

In addition to "reverse" or retrograde neurotransmission at synapses, some neurotransmission does not need a synapse at all! Neurotransmission without a synapse is called *volume neurotransmission*, or nonsynaptic diffusion neurotransmission (examples are shown in Figures 1-6 through 1-8). Chemical messengers

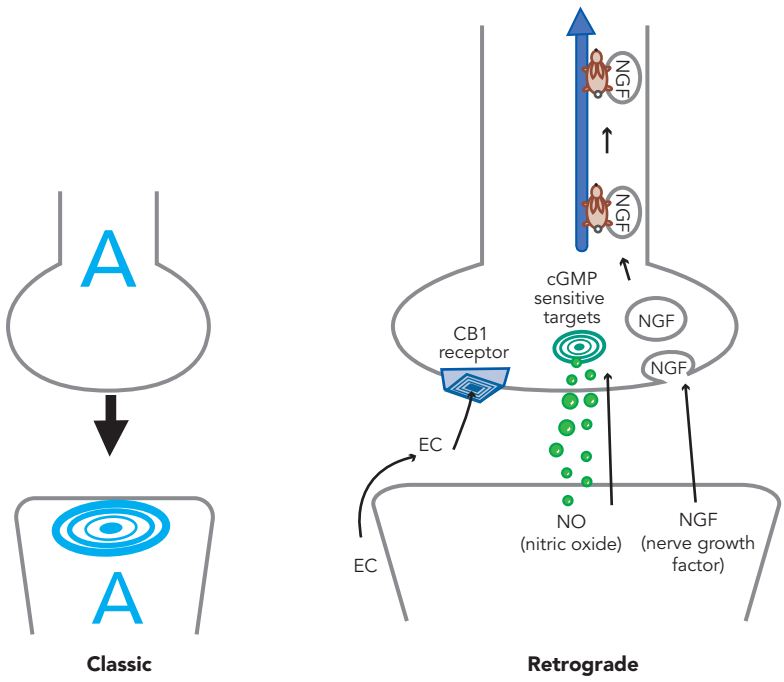


Figure 1-5 **Retrograde neurotransmission.** Not all neurotransmission is classic or anterograde or from top to bottom – namely, presynaptic to postsynaptic (left). Postsynaptic neurons may also communicate with presynaptic neurons from the bottom to the top via retrograde neurotransmission, from postsynaptic neuron to presynaptic neuron (right). Some neurotransmitters produced specifically as retrograde neurotransmitters at some synapses include the endocannabinoids (ECs, or endogenous marijuana), which are synthesized in the postsynaptic neuron, released, and diffuse to presynaptic cannabinoid receptors such as the cannabinoid 1 receptor (CB1); the gaseous neurotransmitter nitric oxide (NO), which is synthesized postsynaptically and then diffuses both out of the postsynaptic membrane and into the presynaptic membrane to interact with cyclic guanosine monophosphate (cGMP)-sensitive targets there; and neurotrophic factors such as nerve growth factor (NGF), which is released from postsynaptic sites and diffuses to the presynaptic neuron, where it is taken up into vesicles and transported all the way back to the cell nucleus via retrograde transport systems to interact with the genome there.

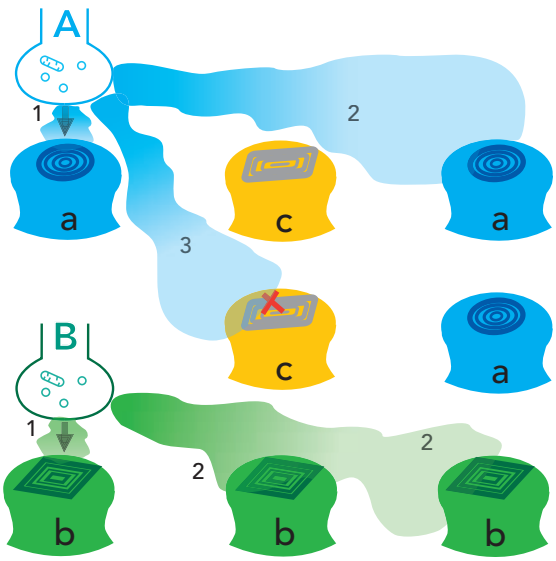


Figure 1-6 **Volume neurotransmission.** Neurotransmission can also occur without a synapse; this is called volume neurotransmission or nonsynaptic diffusion. In this figure, two anatomically addressed synapses (neurons A and B) are shown communicating with their corresponding postsynaptic receptors (a and b; 1). However, there are also receptors for neurotransmitter A, neurotransmitter B, and neurotransmitter C, which are distant from the synaptic connections of the anatomically addressed nervous system. If neurotransmitter A or B can diffuse away from its synapse before it is destroyed, it will be able to interact with other matching receptor sites distant from its own synapse (2). If neurotransmitter A or B encounters a different receptor not capable of recognizing it (receptor c), it will not interact with that receptor even if it diffuses there (3). Thus, a chemical messenger sent by one neuron to another can spill over by diffusion to sites distant from its own synapse. Neurotransmission can occur at a compatible receptor within the diffusion radius of the matched neurotransmitter. This is analogous to modern communication with cellular telephones, which function within the transmitting radius of a given cell. This concept is called the chemically addressed nervous system, in which neurotransmission occurs in chemical "puffs." The brain is thus not only a collection of wires but also a sophisticated "chemical soup."

sent by one neuron to another can spill over to sites distant to the synapse by diffusion (Figure 1-6). Thus, neurotransmission can occur at any compatible receptor within the diffusion radius of the neurotransmitter, not unlike modern communication with cellular telephones, which function within the transmitting radius of a given cell tower (Figure 1-6). This concept is part of the chemically addressed nervous system, and here neurotransmission occurs in chemical "puffs" (Figures 1–6 through 1–8). The brain is thus not only a collection of wires, but also a sophisticated "chemical soup." The chemically addressed nervous system is particularly

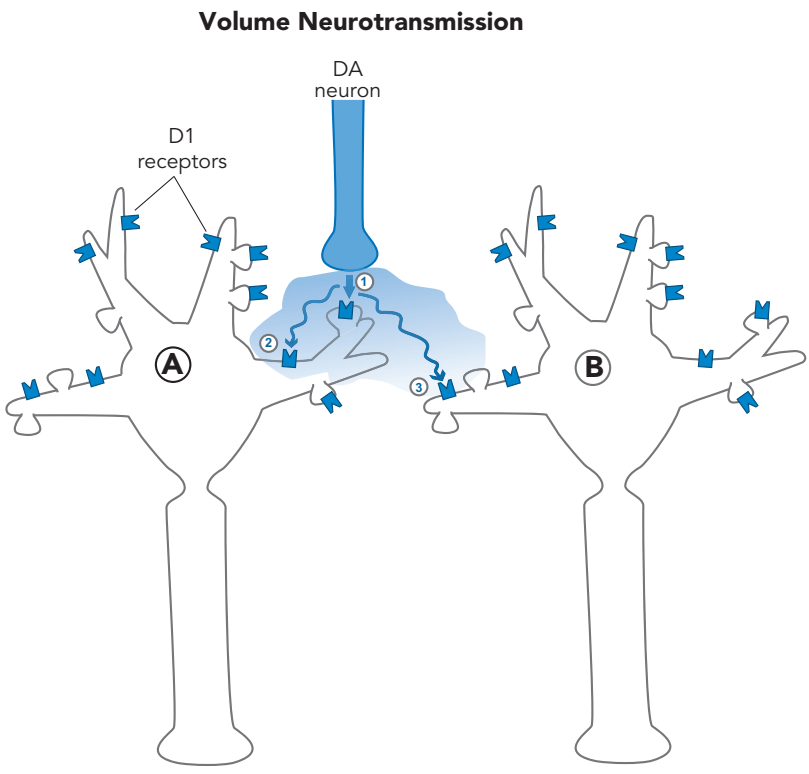


Figure 1-7 Volume neurotransmission: dopamine. An example of volume neurotransmission would be that of dopamine (DA) in the prefrontal cortex. Since there are few dopamine reuptake pumps in the prefrontal cortex, dopamine is available to diffuse to nearby receptor sites. Thus, dopamine released from a synapse (arrow 1) targeting postsynaptic neuron A is free to diffuse further in the absence of a reuptake pump and can reach dopamine receptors on that same neuron but outside of the synapse from which it was released, on neighboring dendrites (arrow 2). Shown here is dopamine also reaching extrasynaptic receptors on a neighboring neuron (arrow 3).

important in mediating the actions of drugs that act at various neurotransmitter receptors, since such drugs will act wherever there are relevant receptors, and not just where such receptors are innervated with synapses by the anatomically addressed nervous system. Modifying volume neurotransmission may indeed be a major way in which several psychotropic drugs work in the brain.

A good example of volume neurotransmission is dopamine action in the prefrontal cortex. Here there are very few dopamine reuptake transport pumps (dopamine transporters or DATs) to terminate the action of dopamine released in the prefrontal cortex during neurotransmission. This is much different from other brain areas, such as the striatum, where dopamine reuptake pumps are present in abundance. Thus, when dopamine neurotransmission occurs at a synapse in the prefrontal cortex, dopamine is free to spill over from that synapse and diffuse to neighboring dopamine receptors and stimulate them, even though there is no synapse at these "spillover" sites (Figure 1-7).

Another important example of volume neurotransmission is at the sites of autoreceptors on monoamine neurons (Figure 1-8). At the somatodendritic end of the neuron (top of the neurons in Figure 1-8) are autoreceptors that inhibit the release of neurotransmitter from the axonal end of the neuron (bottom of the neurons in Figure 1-8). Although some recurrent axon collaterals and other monoamine neurons may directly innervate somatodendritic receptors, these so-called somatodendritic autoreceptors also apparently receive neurotransmitter from dendritic release (Figure 1-8, middle and right panels). There is no synapse here, no synaptic vesicles, just neurotransmitter apparently "leaked" from the neuron's dendrites upon its own receptors in a mechanism that is still being clarified. The nature of a neuron's regulation by its somatodendritic autoreceptors is a subject of intense interest, and is theoretically linked to the mechanism of action of many antidepressants, as will be explained later in Chapter 7. The take-home point here is that not all chemical neurotransmission occurs at synapses.

Excitation–Secretion Coupling

An electrical impulse in the first – or presynaptic – neuron is converted into a chemical signal at the synapse by a process known as *excitation–secretion coupling*. Once an

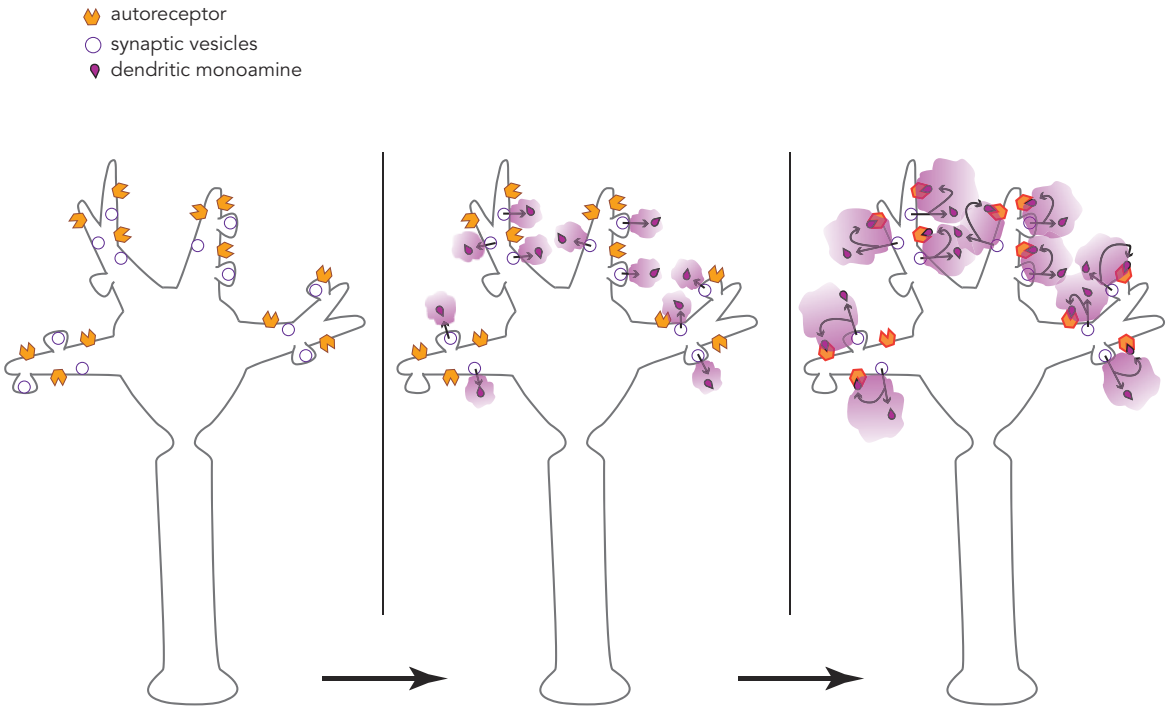


Figure 1-8 Volume neurotransmission: monoamine autoreceptors. Another example of volume neurotransmission could involve autoreceptors on monoamine neurons. Autoreceptors located on the dendrites and soma of a neuron (at the top of the neuron in the left panel) normally inhibit release of neurotransmitter from the axon of that neuron (at the bottom of the neuron in the left panel), and thus inhibit impulse flow through that neuron from top to bottom. Monoamines released from the dendrites of this neuron (at the top of the neuron in the middle panel), then bind to these autoreceptors (at the top of the neuron in the right panel) and would inhibit neuronal impulse flow in that neuron (from the bottom of the neuron in the right panel). This action occurs due to volume neurotransmission and despite the absence of synaptic neurotransmission in the somatodendritic areas of these neurons.

electrical impulse invades the presynaptic axon terminal, it causes the release of chemical neurotransmitter stored there (Figures 1-3 and 1-4). Electrical impulses open ion channels – both *voltage-sensitive sodium channels* (VSSCs) and *voltage-sensitive calcium channels* (VSCCs) – by changing the ionic charge across neuronal membranes. As sodium flows into the presynaptic nerve through sodium channels in the axon membrane, the electrical charge of the action potential moves along the axon until it reaches the presynaptic nerve terminal where it also opens calcium channels. As calcium flows into the presynaptic nerve terminal, it causes synaptic vesicles anchored to the inner membrane to spill their chemical contents into the synapse. The way is paved for chemical communication by previous synthesis of neurotransmitter and storage of neurotransmitter in the first neuron's presynaptic axon terminal.

Excitation–secretion coupling is thus the way that the neuron transduces an electrical stimulus into a chemical event. This happens very quickly once the electrical impulse enters the presynaptic neuron. It is also possible for the neuron to transduce a chemical message from a presynaptic neuron back into an electrical chemical message in the postsynaptic neuron by opening ion channels linked to neurotransmitters there. This also happens very quickly when chemical neurotransmitters open ion channels that change the flow of charge into the neuron, and ultimately, action potentials in the postsynaptic neuron. Thus, the process of neurotransmission is constantly transducing chemical signals into electrical signals, and electrical signals back into chemical signals.

SIGNAL TRANSDUCTION CASCADES

Overview

Neurotransmission can be seen as part of a much larger process than just the communication of a presynaptic axon with a postsynaptic neuron at the synapse between them. That is, neurotransmission can also be seen as

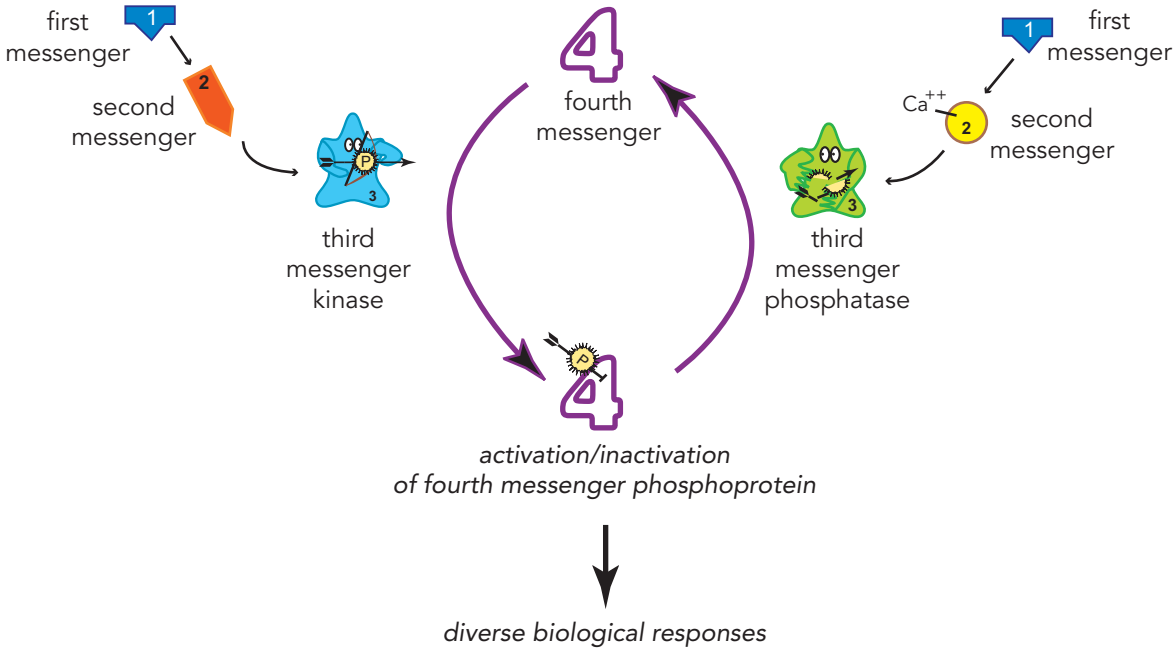


Figure 1-9 Signal transduction cascade. The cascade of events that occurs following stimulation of a postsynaptic receptor is known as signal transduction. Signal transduction cascades can activate third-messenger enzymes known as kinases, which add phosphate groups to proteins to create phosphoproteins (on the left). Other signal transduction cascades can activate third-messenger enzymes known as phosphatases, which remove phosphates from phosphoproteins (on the right). The balance between kinase and phosphatase activity, signaled by the balance between the two neurotransmitters that activate each of them, determines the degree of downstream chemical activity that gets translated into diverse biological responses, such as gene expression and synaptogenesis.

communication from the genome of the presynaptic neuron (neuron A of Figure 1-3) to the genome of the postsynaptic neuron (neuron B of Figure 1-3), and then back from the genome of the postsynaptic neuron to the genome of the presynaptic neuron via retrograde neurotransmission (right panel of Figure 1-5). Such a process involves long strings of chemical messages within both presynaptic and postsynaptic neurons, called signal transduction cascades.

Signal transduction cascades triggered by chemical neurotransmission thus involve numerous molecules, starting with neurotransmitter first messenger, and proceeding to second, third, fourth, and more messengers (Figures 1-9 through 1-30). The initial events occur in less than a second, but the long-term consequences are mediated by downstream messengers that take hours to days to activate, yet can last for many days or even for the lifetime of a synapse or neuron (Figure 1-10). Signal transduction cascades are somewhat akin to a molecular "pony express" with specialized molecules acting as a sequence of riders, handing off the message to the next specialized molecule, until the message has reached a functional destination, such as gene expression or activation of otherwise "sleeping" and inactive molecules (see for example, Figures 1-9 through 1-19).

An overview of such a molecular "pony express," from first-messenger neurotransmitter through several "molecular riders" to the production of diverse biological responses, is shown in Figure 1-9. Specifically, a first-messenger neurotransmitter on the left activates the production of a chemical second messenger that in turn activates a third messenger, namely an enzyme known as a kinase that adds phosphate groups to fourth-messenger proteins to create phosphoproteins (Figure 1-9, left). Another signal transduction cascade is shown on the right with a first-messenger neurotransmitter opening an ion channel that allows calcium to enter the neuron and act as the second messenger for this cascade system (Figure 1-9, right). Calcium then activates a different third messenger on the right, namely an enzyme known as a phosphatase that removes phosphate groups from fourth-messenger phosphoproteins and thus reverses the actions of the third messenger on the left. The balance between kinase and phosphatase activity, signaled by the balance between the two neurotransmitters that activate each of them, determines the degree of downstream

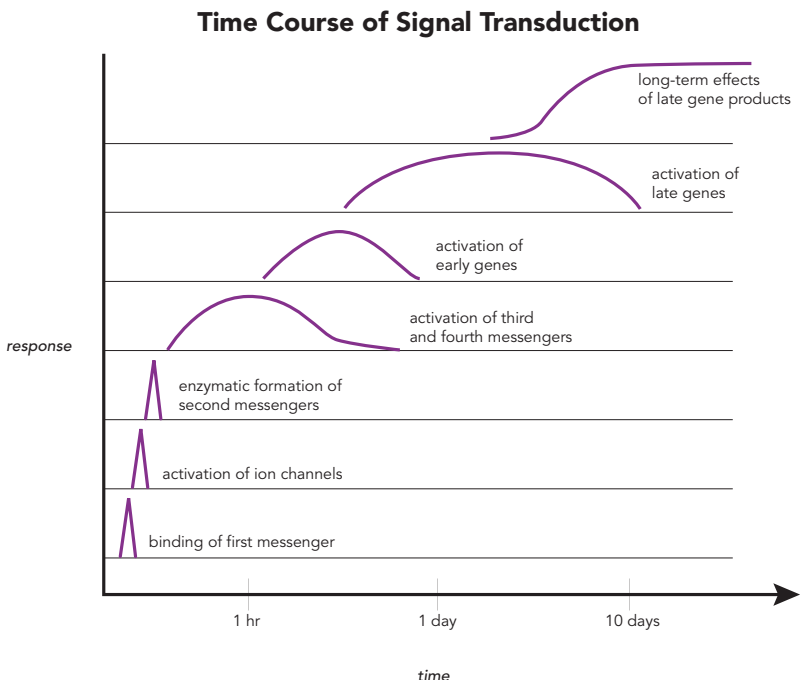


Figure 1-10 Time course of signal transduction. The time course of signal transduction is shown here. The process begins with binding of a first messenger (bottom), which leads to activation of ion channels or enzymatic formation of second messengers. This, in turn, can cause activation of third and fourth messengers, which are often phosphoproteins. If genes are subsequently activated, this leads to the synthesis of new proteins, which can alter the neuron's functions. Once initiated, the functional changes due to protein activation or new protein synthesis can last for at least many days and possibly much longer. Thus, the ultimate effects of signal transduction cascades triggered by chemical neurotransmission are not only delayed but also long-lasting.

chemical activity that gets translated into active fourth messengers able to trigger diverse biological responses, such as gene expression and synaptogenesis (Figure 1-9). Each molecular site within the cascade of transduction of chemical and electrical messages is a potential location for a malfunction associated with a mental illness; it is also a potential target for a psychotropic drug. Thus, the various elements of multiple signal transduction cascades play very important roles in psychopharmacology.

Four of the most important signal transduction cascades in the brain are shown in Figure 1-11. These include G-protein-linked systems, ion-channel-linked systems, hormone-linked systems, and neurotrophin-linked systems. There are many chemical messengers for each of these four critical signal transduction cascades; the G-protein-linked and the ion-channel-linked cascades are triggered by neurotransmitters (Figure 1-11). Many of the psychotropic drugs used in clinical practice today target one of these two signal transduction cascades. Drugs that target the G-protein-linked system are discussed in Chapter 2; drugs that target the ion channel-linked system are discussed in Chapter 3.

Forming a Second Messenger

Each of the four signal transduction cascades (Figure 1-11) passes its message from an extracellular first messenger to an intracellular second messenger.

In the case of G-protein-linked systems, the second messenger is a chemical, but in the case of an ion-channel-linked system, the second messenger can be an ion such as calcium (Figure 1-11). For some hormone-linked systems, a second messenger is formed when the hormone finds its receptor in the cytoplasm and binds to it to form a hormone–nuclear receptor complex (Figure 1-11). For neurotrophins, a complex set of various second messengers exist (Figure 1-11), including proteins that are kinase enzymes with an alphabet soup of complicated names.

The transduction of an extracellular first neurotransmitter from the presynaptic neuron into an intracellular second messenger in the postsynaptic neuron is known in detail for some second-messenger systems, such as for those that are linked to G proteins (Figures 1-12 through 1-15). There are four key elements to this second-messenger system:

- the first-messenger neurotransmitter
- a receptor for the neurotransmitter that belongs to the receptor superfamily in which all have the structure of seven transmembrane regions (designated by the number 7 on the receptor in Figures 1-12 to 1-15)
- a G protein capable of binding both to certain conformations of the neurotransmitter receptor (7) and to an enzyme system (E) that can synthesize the second messenger

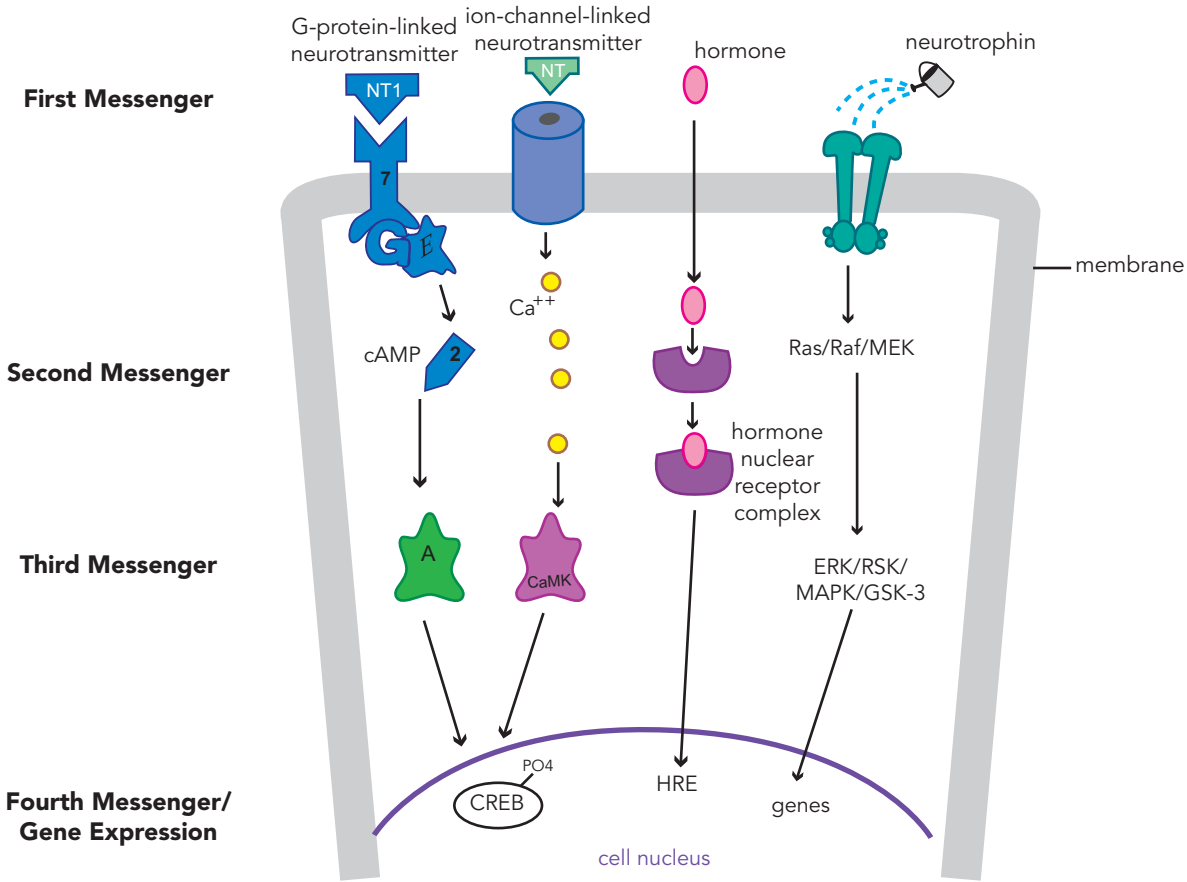


Figure 1-11 **Different signal transduction cascades.** Four of the most important signal transduction cascades in the brain are shown here. These include G-protein-linked systems, ion-channel-linked systems, hormone-linked systems, and neurotrophin-linked systems. Each begins with a different first messenger binding to a unique receptor, leading to activation of very different downstream second, third, and subsequent chemical messengers. Having many different signal transduction cascades allows neurons to respond in amazingly diverse biological ways to a whole array of chemical messaging systems. Neurotransmitters (NTs) activate both the G-protein-linked system and the ion-channel-linked system on the left, and both of these systems activate genes in the cell nucleus by phosphorylating a protein there called cAMP response element-binding protein (CREB). The G-protein-linked system works through a cascade involving cAMP (adenosine monophosphate) and protein kinase A, whereas the ion-channel-linked system works through calcium and its ability to activate a different kinase called calcium/calmodulin kinase (CaMK). Certain hormones, such as estrogen and other steroids, can enter the neuron, find their receptors in the cytoplasm, and bind them to form a hormone–nuclear receptor complex. This complex can then enter the cell nucleus to interact with hormone-response elements (HREs) there to trigger activation of specific genes. Finally, the neurotrophin system on the far right activates a series of kinase enzymes, with a confusing alphabet soup of names, to trigger gene expression, which may control such functions as synaptogenesis and neuronal survival. Ras is a G protein, Raf is a kinase, and the other elements in this cascade are proteins as well (MEK stands for mitogen-activated protein kinase/extracellular signal-regulated kinase; ERK stands for extracellular signal-regulated kinase itself; RSK is ribosomal S6 kinase; MAPK is MAP kinase itself, and GSK-3 is glycogen synthase kinase 3).

- and finally the enzyme system itself for the second messenger (Figures 1-12 through 1-15)

The first step is the neurotransmitter binding to its receptor (Figure 1-13). This changes the conformation of the receptor so it can now fit with the G protein, as indicated by the receptor (7) turning green and its shape changing at the bottom. Next comes the binding of the G protein to this new conformation of the receptor–neurotransmitter complex (Figure 1-14). The two receptors cooperate with each other: namely, the neurotransmitter receptor itself, and the G protein, which can be thought of as another type of receptor associated with the inner membrane of the cell. This cooperation is indicated in Figure 1-14 by the G protein turning green and its conformation changing on the right so it is now capable of binding to an enzyme (E) that synthesizes the second messenger. Finally, the enzyme, in this case adenylate cyclase, binds to the G protein and synthesizes

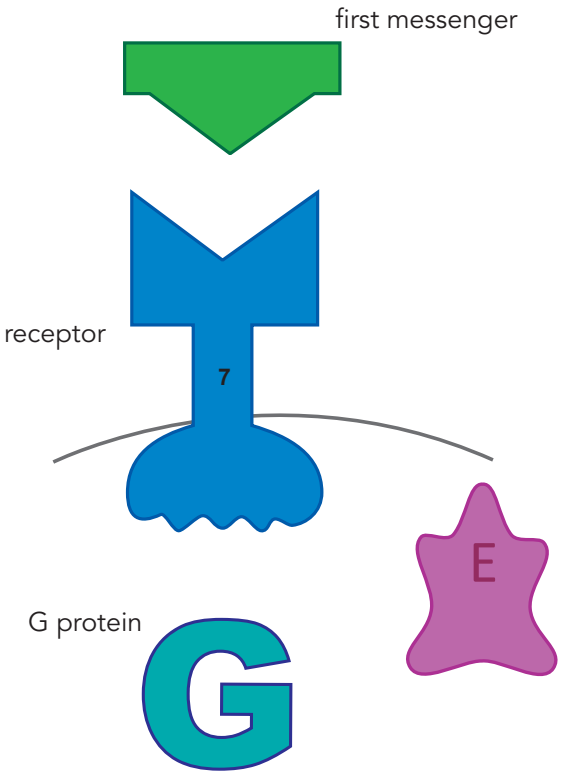


Figure 1-12 Elements of G-protein-linked system. Shown here are the four elements of a G-protein-linked second-messenger system. The first element is the neurotransmitter itself, sometimes also referred to as the first messenger. The second element is the G-protein-linked neurotransmitter receptor, which is a protein with seven transmembrane regions. The third element, a G protein, is a connecting protein. The fourth element of the second-messenger system is an enzyme, which can synthesize a second messenger when activated.

cAMP (cyclic adenosine monophosphate), which serves as second messenger (Figure 1-15). This is indicated in Figure 1-15 by the enzyme turning green and generating cAMP (the icon with number 2 on it).

Beyond the Second Messenger to Phosphoprotein Messengers

Recent research has begun to clarify the complex molecular links between the second messenger and its ultimate effects upon cellular functions. These links are specifically the third, fourth, and subsequent chemical messengers in the signal transduction cascades shown in Figures 1-9, 1-11, 1-16 through 1-30). Each of the four classes of signal transduction cascades shown in Figure 1-11 not only begins with a different first messenger binding to a unique receptor, but this also leads to activation of very different downstream second, third,

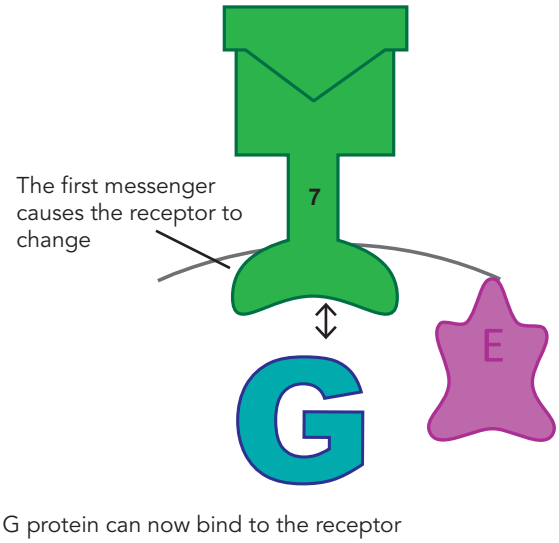
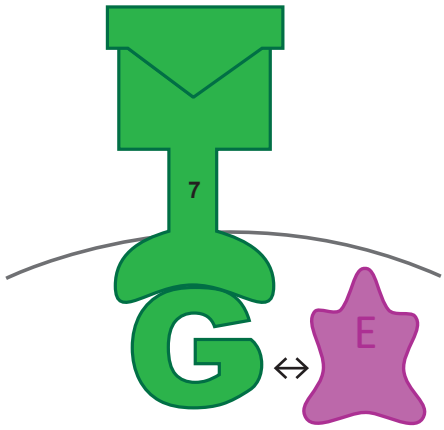


Figure 1-13 First messenger. In this figure, the neurotransmitter has docked into its receptor. The first messenger does its job by transforming the conformation of the receptor so that the receptor can bind to the G protein, indicated here by the receptor turning the same color as the neurotransmitter and changing its shape at the bottom in order to make it capable of binding to the G protein.

and subsequent chemical messengers. Having many different signal transduction cascades allows neurons to respond in amazingly diverse biological ways to a whole array of chemical messaging systems.

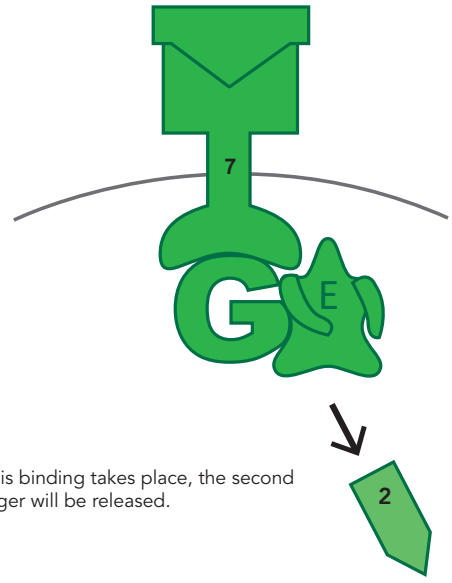
What is the ultimate target of signal transduction? There are two major targets of signal transduction: phosphoproteins and genes. Many of the intermediate targets along the way to the gene are phosphoproteins, such as the fourth-messenger phosphoproteins shown in Figures 1-18 and 1-19 that lie dormant in the neuron until signal transduction wakes them up and they can spring into action.

The actions shown in Figure 1-9 on fourth-messenger phosphoproteins as targets of signal transduction can be seen in more detail in Figures 1-16 through 1–19. Thus, one signal transduction pathway can activate a third-messenger kinase through the second-messenger cAMP (Figure 1-16), whereas another signal transduction pathway can activate a third-messenger phosphatase through the second-messenger calcium (Figure 1-17). In the case of kinase activation, two copies of the second messenger target each regulatory unit of dormant or "sleeping" protein kinase (Figure 1-16). When some protein kinases are inactive, they exist in dimers (two copies of the enzyme) while binding to a regulatory unit, thus rendering them in a conformation that is not active.



Once bound to the receptor, the G protein changes shape so it can bind to an enzyme capable of synthesizing a second messenger.

Figure 1-14 G protein. The next stage in producing a second messenger is for the transformed neurotransmitter receptor to bind to the G protein, depicted here by the G protein turning the same color as the neurotransmitter and its receptor. Binding of the binary neurotransmitter–receptor complex to the G protein causes yet another conformational change, this time in the G protein, represented here as a change in the shape of the right-hand side of the G protein. This prepares the G protein to bind to the enzyme capable of synthesizing the second messenger.



Once this binding takes place, the second messenger will be released.

Figure 1-15 Second messenger. The final step in formation of the second messenger is for the ternary complex neurotransmitter–receptor–G protein to bind to a messenger-synthesizing enzyme, depicted here by the enzyme turning the same color as the ternary complex. Once the enzyme binds to this ternary complex, it becomes activated and capable of synthesizing the second messenger. Thus, it is the cooperation of all four elements, wrapped together as a quaternary complex, that leads to the production of the second messenger. Information from the first messenger thus passes to the second messenger through use of receptor–G protein–enzyme intermediaries.

Activating a Third-Messenger Kinase through Cyclic AMP

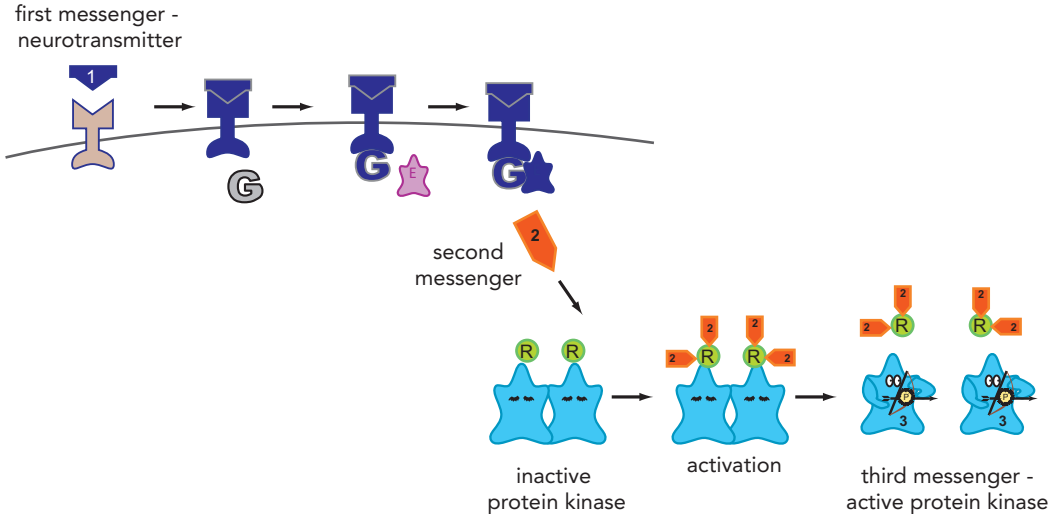


Figure 1-16 Third-messenger protein kinase. This figure illustrates activation of a third-messenger protein kinase through the second-messenger cAMP. Neurotransmitters begin the process of activating genes by producing a second messenger (cAMP), as shown previously in Figures 1-12 through 1-15. Some second messengers activate intracellular enzymes known as protein kinases. This enzyme is shown here as inactive when it is paired with another copy of the enzyme plus two regulatory units (R). In this case, two copies of the second messenger interact with the regulatory units, dissociating them from the protein kinase dimer. This dissociation activates each protein kinase, readying this enzyme to phosphorylate other proteins.

Activating a Third-Messenger Phosphatase through Calcium

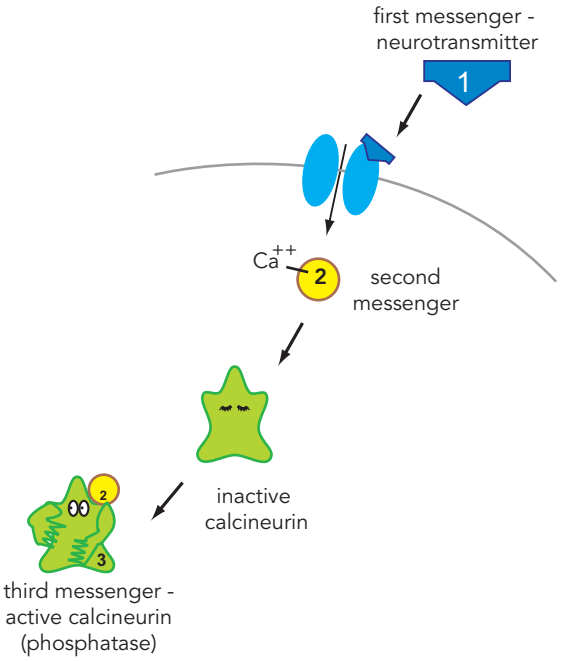


Figure 1-17 Third-messenger phosphatase. This figure illustrates activation of a third-messenger phosphatase through the second-messenger calcium. Shown here is calcium binding to an inactive phosphatase known as calcineurin, thereby activating it and thus readying it to remove phosphates from fourth-messenger phosphoproteins.

In this example, when two copies of cAMP bind to each regulatory unit, the regulatory unit dissociates from the enzyme, and the dimer dissociates into two copies of the enzyme, and the protein kinase is now activated, shown with a bow and arrow ready to shoot phosphate groups into unsuspecting fourth-messenger phosphoproteins (Figure 1-16).

Meanwhile, the nemesis of protein kinase is also forming in Figure 1-17, namely a protein phosphatase. Another first messenger is opening an ion channel here, allowing the second-messenger calcium to enter, which activates the phosphatase enzyme calcineurin. In the presence of calcium, calcineurin becomes activated, shown with scissors ready to rip phosphate groups off fourth-messenger phosphoproteins (Figure 1-17).

The clash between kinase and phosphatase can be seen by comparing what happens in Figures 1-18 and 1-19. In Figure 1-18, the third-messenger kinase is putting phosphates onto various fourth-messenger phosphoproteins such as ligand-gated ion channels, voltage-gated ion channels, and enzymes. In Figure 1-19, the third-messenger phosphatase is taking those phosphates off. Sometimes phosphorylation activates a dormant phosphoprotein; for other phosphoproteins, dephosphorylation can be activating. Activation of fourth-messenger phosphoproteins can change the synthesis of neurotransmitters, alter neurotransmitter release, change the conductance of ions, and generally maintain the chemical neurotransmission apparatus in either a state of readiness or dormancy. The balance between phosphorylation and dephosphorylation of fourth-messenger kinases and phosphatases plays a vital role in regulating many molecules critical to the chemical neurotransmission process.

Beyond the Second Messenger to a Phosphoprotein Cascade Triggering Gene Expression

The ultimate cellular function that neurotransmission often seeks to modify is gene expression, either turning a gene on or turning a gene off. All four signal transduction cascades shown in Figure 1-11 end with the last molecule influencing gene transcription. Both cascades triggered by neurotransmitters are shown acting upon the CREB system, which is responsive to phosphorylation of its regulatory units (Figure 1-11, left). CREB is cAMP response element-binding protein, a transcription factor

Third-Messenger Kinases Put Phosphates on Critical Proteins

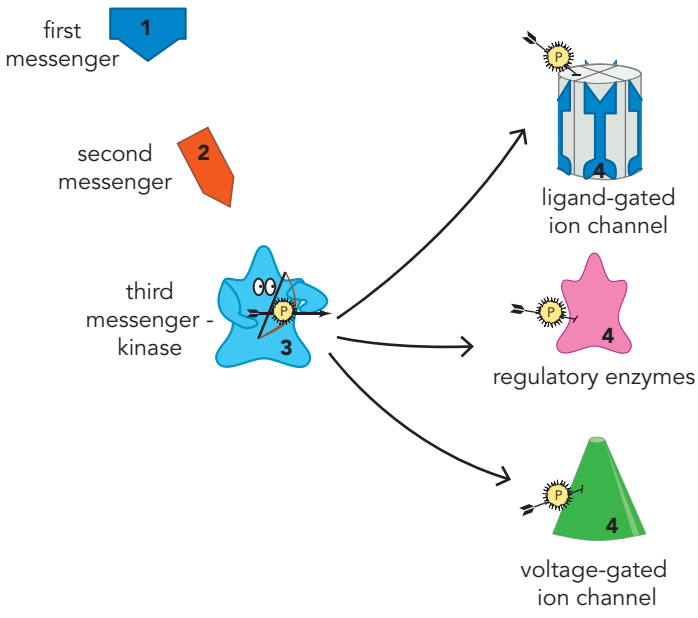


Figure 1-18 **Third-messenger kinase puts phosphates on critical proteins.** Here the activation of a third-messenger kinase adds phosphates to a variety of phosphoproteins, such as ligand-gated ion channels, voltage-gated ion channels, and various regulatory enzymes. Adding a phosphate group to some phosphoproteins activates them; for other proteins, this inactivates them.

Third-Messenger Phosphatases Undo What Kinases Create - Take Phosphates Off Critical Proteins

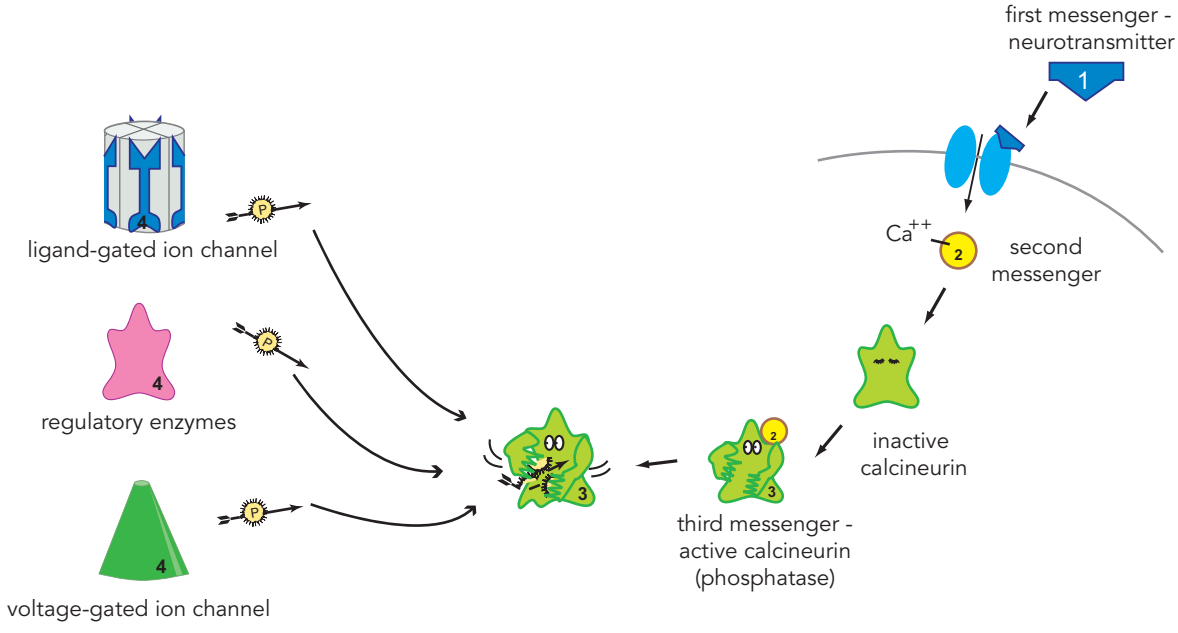


Figure 1-19 **Third-messenger phosphatase removes phosphates from critical proteins.** In contrast to the previous figure, the third messenger here is a phosphatase; this enzyme removes phosphate groups from phosphoproteins such as ligand-gated ion channels, voltage-gated ion channels, and various regulatory enzymes. Removing a phosphate group from some phosphoproteins activates them; for others, it inactivates them.

in the cell nucleus capable of activating expression of genes, especially a type of gene known as immediate genes or immediate early genes. When G-protein-linked receptors activate protein kinase A, this activated enzyme can translocate or move into the cell nucleus and stick a phosphate group on CREB, thus activating this transcription factor and causing the nearby gene to become activated. This leads to gene expression, first as RNA and then as the protein coded by the gene.

Interestingly, it is also possible for ion-channel-linked receptors that enhance intracellular second-messenger calcium levels to activate CREB by phosphorylating it. A protein known as calmodulin, which interacts with calcium, can lead to activation of certain kinases called calcium/calmodulin-dependent protein kinases (Figure 1-11). This is an entirely different enzyme than the phosphatase shown in Figures 1-9, 1-17, and 1-19. Here, a kinase and not a phosphatase is activated. When activated, this kinase can translocate into the cell nucleus and, just like the kinase activated by the G-protein system, add a phosphate group to CREB and activate this transcription factor so that gene expression is triggered.

It is important to bear in mind that calcium is thus able to activate both kinases and phosphatases. There is a very rich and sometimes confusing array of kinases and phosphatases, and the net result of calcium action is dependent upon what substrates are activated, because different phosphatases and kinases target very different substrates. Thus, it is important to keep in mind the specific signal transduction cascade under discussion and the specific phosphoproteins acting as messengers in the cascade in order to understand the net effect of various signal transduction cascades. In the case illustrated in Figure 1-11, the G-protein system and the ion-channel system are working together to produce more activated kinases and thus more activation of CREB. However, in Figures 1-9 and 1-16 through 1-19, they are working in opposition.

Genes are also the ultimate target of the hormone signal transduction cascade in Figure 1-11. Some hormones, such as estrogen, thyroid, and cortisol, act at cytoplasmic receptors, bind them, and produce a hormone–nuclear receptor complex that translocates to the cell nucleus, finds elements in the gene that it can influence (called hormone-response elements, or HREs), and then acts as a transcription factor to trigger activation of nearby genes (Figure 1-11).

Finally, a very complicated signal transduction system with terrible sounding names for their downstream signal cascade messengers is activated by neurotrophins and related molecules. Activating this system by first-messenger neurotrophins leads to activation of enzymes that are mostly kinases, one kinase activating another until finally one of them phosphorylates a transcription factor in the cell nucleus and starts transcribing genes (Figure 1-11). Ras is a G protein that activates a cascade of kinases with confusing names. For those who are good sports with an interest in the specifics, this cascade starts with Ras activating Raf, which phosphorylates and activates MEK (MAPK kinase/ERK kinase or mitogen-activated protein kinase kinase/extracellular signal regulated kinase kinase), which activates ERK kinase (extracellular signal-regulated kinase itself), RSK (ribosomal S6 kinase), MAPK (MAP kinase itself), or GSK-3 (glycogen synthase kinase), leading ultimately to changes in gene expression. Confused? It is actually not important to know the names, but to remember the take-away point that neurotrophins trigger an important signal transduction pathway that activates kinase enzyme after kinase enzyme, ultimately changing gene expression. This is worth knowing because this signal transduction pathway may be responsible for the expression of genes that regulate many critical functions of the neuron, such as synaptogenesis and cell survival, as well as the plastic changes that are necessary for learning, memory, and even disease expression in various brain circuits. Both drugs and the environment target gene expression in ways that are just beginning to be understood, including how such actions contribute to the cause of mental illnesses and to the mechanism of action of effective treatments for mental illnesses.

In the meantime, it is mostly important to realize that a very wide variety of genes are targeted by all four of these signal transduction pathways. These range from the genes that make synthetic enzymes for neurotransmitters, to growth factors, cytoskeleton proteins, cellular adhesion proteins, ion channels, receptors, and the intracellular signaling proteins themselves, among many others. When genes are expressed by any of the signal transduction pathways shown in Figure 1-11, this can lead to making more or fewer copies of any of these proteins. Synthesis of such proteins is obviously a critical aspect of the neuron performing its many and varied functions. Numerous diverse biological actions are effected within neurons that alter behaviors in individuals due to gene expression that is triggered by the four major signal transduction cascades. These range widely from neuronal responses such as synaptogenesis, strengthening of

a synapse, neurogenesis, apoptosis, increasing or decreasing the efficiency of information processing in cortical circuits to behavioral responses such as learning, memory, antidepressant responses to antidepressant administration, symptom reduction by psychotherapy, and possibly even the production of a mental illness.

How Neurotransmission Triggers Gene Expression

How does the gene express the protein it codes? The discussion above has shown how the molecular "pony express" of signal transduction has a message encoded with chemical information from the neurotransmitter–receptor complex that is passed along from molecular rider to molecular rider until the message is delivered to the appropriate phosphoprotein mailbox (Figures 1-9 and 1-16 through 1-19) or DNA mailbox in the postsynaptic neuron's genome (Figures 1-11 and 1-20 through 1-30). Since the most powerful way for a neuron to alter its function is to change which genes are being turned on or off, it is important to understand the molecular mechanisms by which neurotransmission regulates gene expression.

How many potential genes can neurotransmission target? It is estimated that the human genome contains approximately *20,000 genes* located within *3 million base pairs* of DNA on 23 chromosomes. Incredibly, however, genes only occupy a few percent of this DNA. The other 96% used to be called "junk" DNA since it does not code proteins, but it is now known that these sections of DNA are critical for structure and for regulating whether or not a gene is expressed or is silent. It is not just the number of genes we have, it is whether and when and how often and under which circumstances they are expressed that seems to be the important factor in regulating neuronal function. These same factors of gene expression are now thought to also underlie the actions of psychopharmacological drugs and the mechanisms of psychiatric disorders within the central nervous system.

Molecular Mechanism of Gene Expression

Chemical neurotransmission converts receptor occupancy by a neurotransmitter into the creation of third, fourth, and subsequent messengers that eventually activate transcription factors that turn on genes (Figures 1-20 through 1-30). Most genes have two regions, a *coding region* and a *regulatory region* with enhancers and promoters of gene transcription (i.e., DNA being transcribed into RNA) (Figure 1-20). The coding region of DNA is the direct template for making its corresponding RNA. This DNA is "transcribed" into its RNA with the help of an enzyme called *RNA polymerase*. However, RNA polymerase must be activated, or it won't work.

Luckily, the regulatory region of the gene can make this happen. It has an *enhancer element* and a *promotor element* (Figure 1-20), which can initiate gene expression with the help of transcription factors (Figure 1-21). Transcription factors themselves can be activated when they are phosphorylated, which allows them to bind to the regulatory region of the gene (Figure 1-21). This in turn activates RNA polymerase and off we go with the coding part of the gene *transcribing* itself into its messenger RNA (mRNA) (Figure 1-22). Once transcribed, of course, this messenger RNA goes on to *translate* itself into the corresponding protein (Figure 1-22). However, there is a great deal of RNA that never gets translated into proteins and instead exerts regulatory functions as explained below.

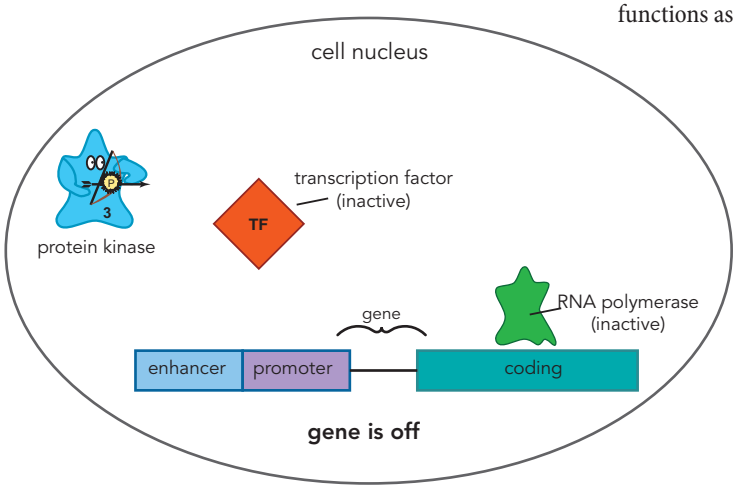


Figure 1-20 Activation of a gene, part 1: gene is off. The elements of gene activation shown here include the enzyme protein kinase; a transcription factor, a type of protein that can activate a gene; RNA polymerase, the enzyme that synthesizes RNA from DNA when the gene is transcribed; the regulatory regions of DNA, such as enhancer and promoter areas; and finally the gene itself. This particular gene is off because the transcription factor has not yet been activated. The DNA for this gene contains both a regulatory region and a coding region. The regulatory region has both an enhancer element and a promoter element, which can initiate gene expression when they interact with activated transcription factors. The coding region is directly transcribed into its corresponding RNA once the gene is activated.

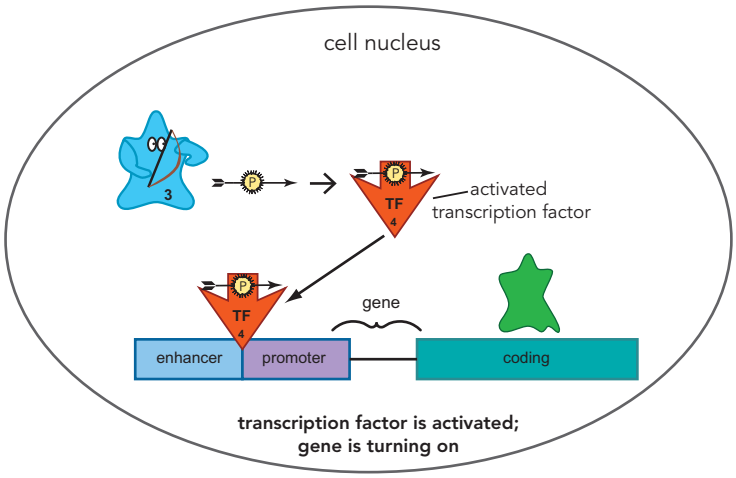


Figure 1-21 **Activation of a gene, part 2: gene turns on.** The transcription factor is now activated because it has been phosphorylated by protein kinase, allowing it to bind to the regulatory region of the gene.

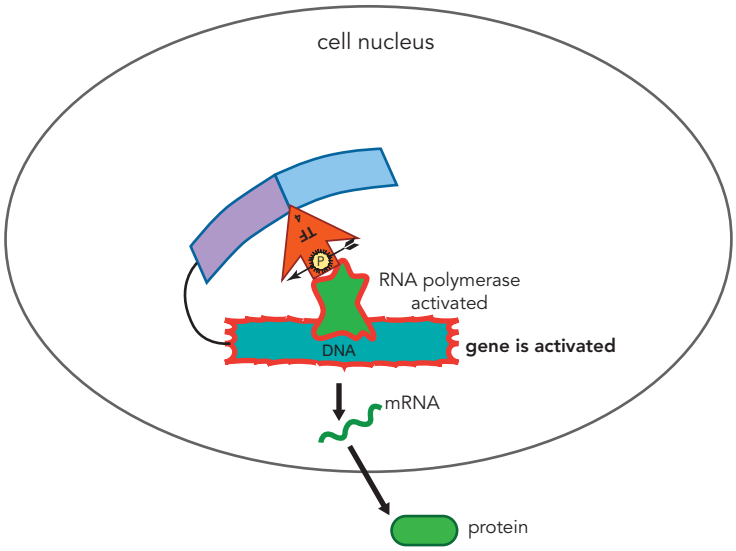


Figure 1-22 **Activation of a gene, part 3: gene product.** The gene itself is now activated because the transcription factor has bound to the regulatory region of the gene, in turn activating the enzyme RNA polymerase. Thus, the gene is transcribed into messenger RNA (mRNA), which in turn is translated into its corresponding protein. This protein is thus the product of activation of this particular gene.

Third Messenger Activating a Transcription Factor for an Early Gene

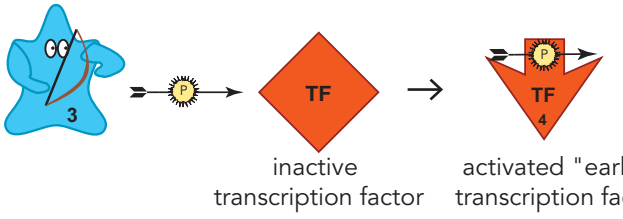


Figure 1-23 **Immediate early gene.** Some genes are known as immediate early genes. Shown here is a third-messenger protein kinase enzyme activating a transcription factor, or fourth messenger, capable of activating, in turn, an early gene.

Some genes are known as immediate early genes (Figure 1-23). They have weird names such as *cJun* and *cFos* (Figures 1-24 and 1-25) and belong to a family called "leucine zippers" (Figure 1-25). These immediate early genes function as rapid responders to the neurotransmitter's input, like the special ops troops sent into combat quickly and ahead of the full army. Such rapid deployment forces of immediate early genes

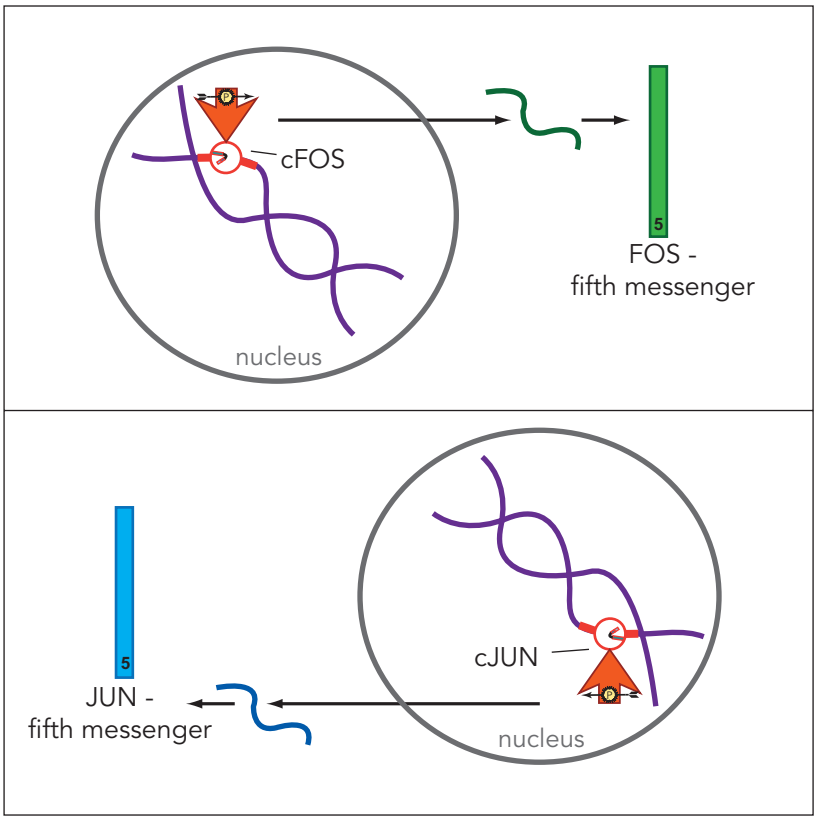


Figure 1-24 **Early genes activate late genes, part 1.** In the top panel, a transcription factor is activating the immediate early gene *cFos* and producing the protein product Fos. While the *cFos* gene is being activated, another immediate early gene, *cJun*, is being simultaneously activated and producing its protein, Jun, as shown in the bottom panel. Fos and Jun can be thought of as fifth messengers.

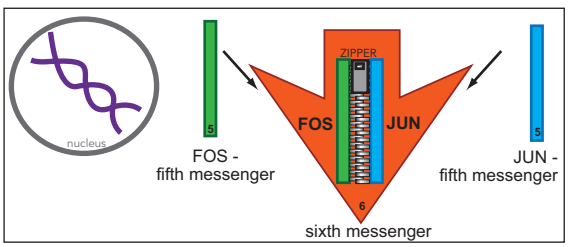




Figure 1-25 **Early genes activate late genes, part 2.** Once Fos and Jun proteins are synthesized, they can collaborate as partners and produce a Fos–Jun combination protein, which now acts as a sixth-messenger transcription factor for late genes.

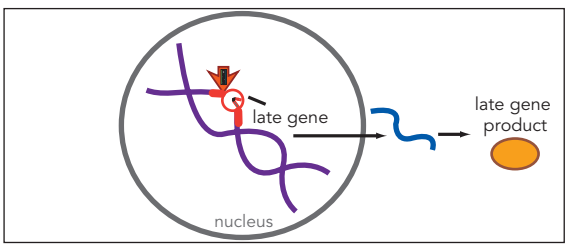


Figure 1-26 **Early genes activate late genes, part 3.** The Fos-Jun transcription factor belongs to a family of proteins called leucine zippers. The leucine zipper transcription factor formed by the products of the activated early genes *cFos* and *cJun* now returns to the genome and finds another gene. Since this gene is being activated later than the others, it is called a late gene. Thus, early genes activate late genes when the products of early genes are themselves transcription factors. The product of the late gene can be any protein the neuron needs, such as an enzyme, a transport factor, or a growth factor.

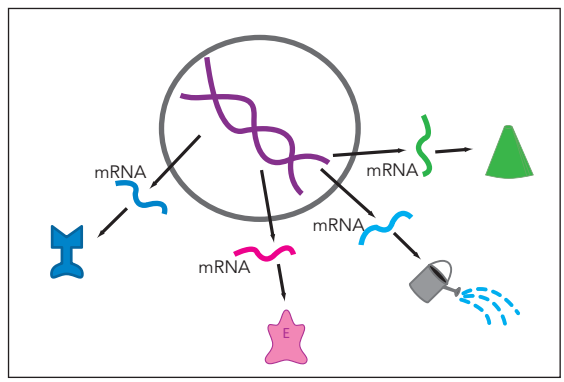


Figure 1-27 **Examples of late gene activation.** A receptor, an enzyme, a neurotrophic growth factor, and an ion channel are all being expressed owing to activation of their respective genes. Such gene products go on to modify neuronal function for many hours or days.

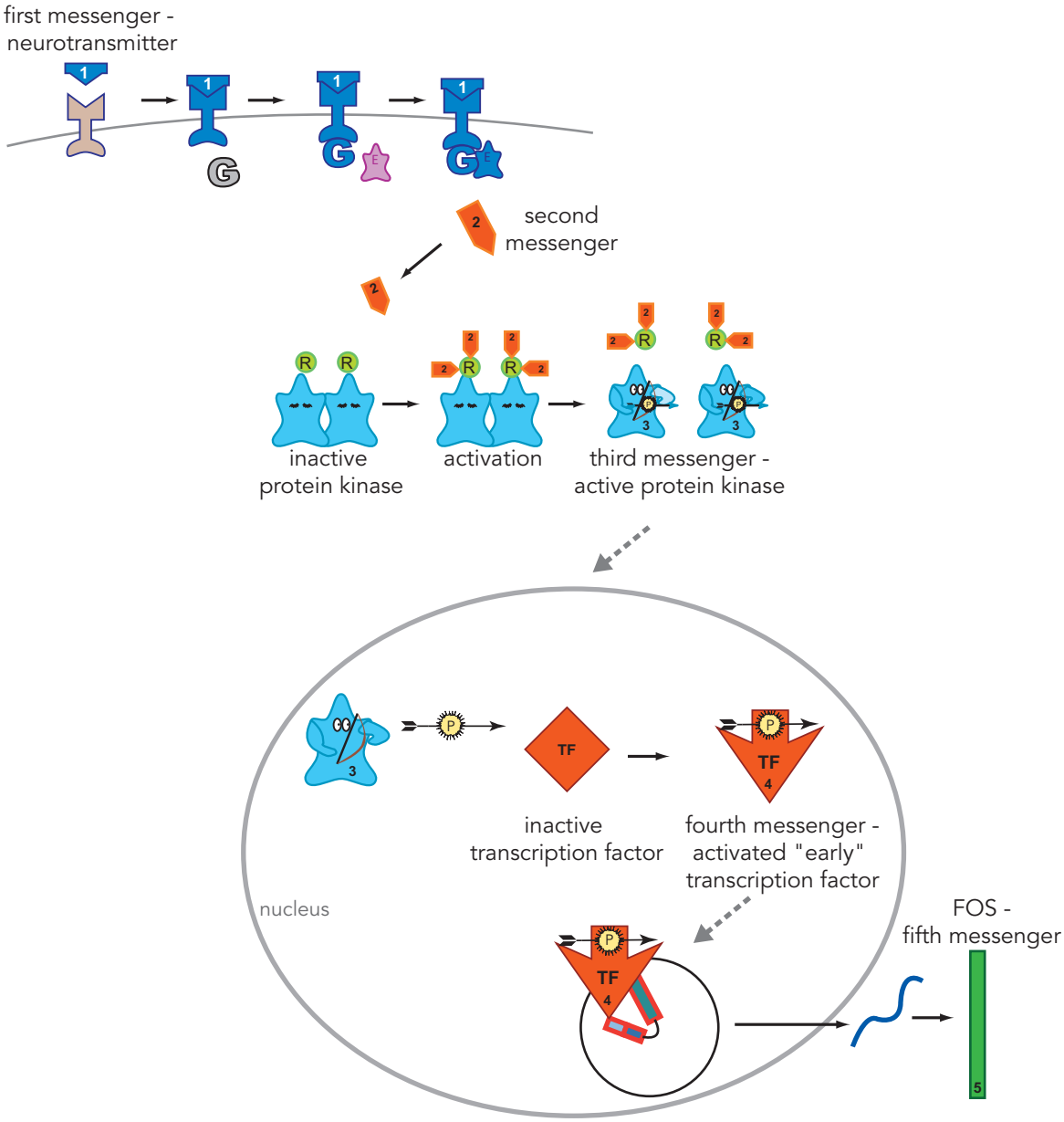


Figure 1-28 Gene regulation by neurotransmitters. This figure summarizes gene regulation by neurotransmitters, from first-messenger extracellular neurotransmitter to intracellular second messenger, to third-messenger protein kinase, to fourth-messenger transcription factor, to fifth-messenger protein, which is the gene product of an early gene.

are thus the first to respond to the neurotransmission signal by making the proteins they encode. In this example, it is Jun and Fos proteins coming from *cJun* and *cFos* genes (Figure 1-24). These are nuclear proteins; that is, they live and work in the nucleus. They get started within 15 minutes of receiving a neurotransmission, but only last for a half hour to an hour (Figure 1-10).

When Jun and Fos team up, they form a leucine zipper type of transcription factor (Figure 1-25), which in turn activates many kinds of later-onset genes (Figures 1-26, 1-27, 1-29). Thus, Fos and Jun serve to wake up the much larger army of inactive genes. Which individual "late" soldier genes are so drafted to active gene duty depends upon a number of factors, not the least of which is which neurotransmitter is sending the message, how frequently

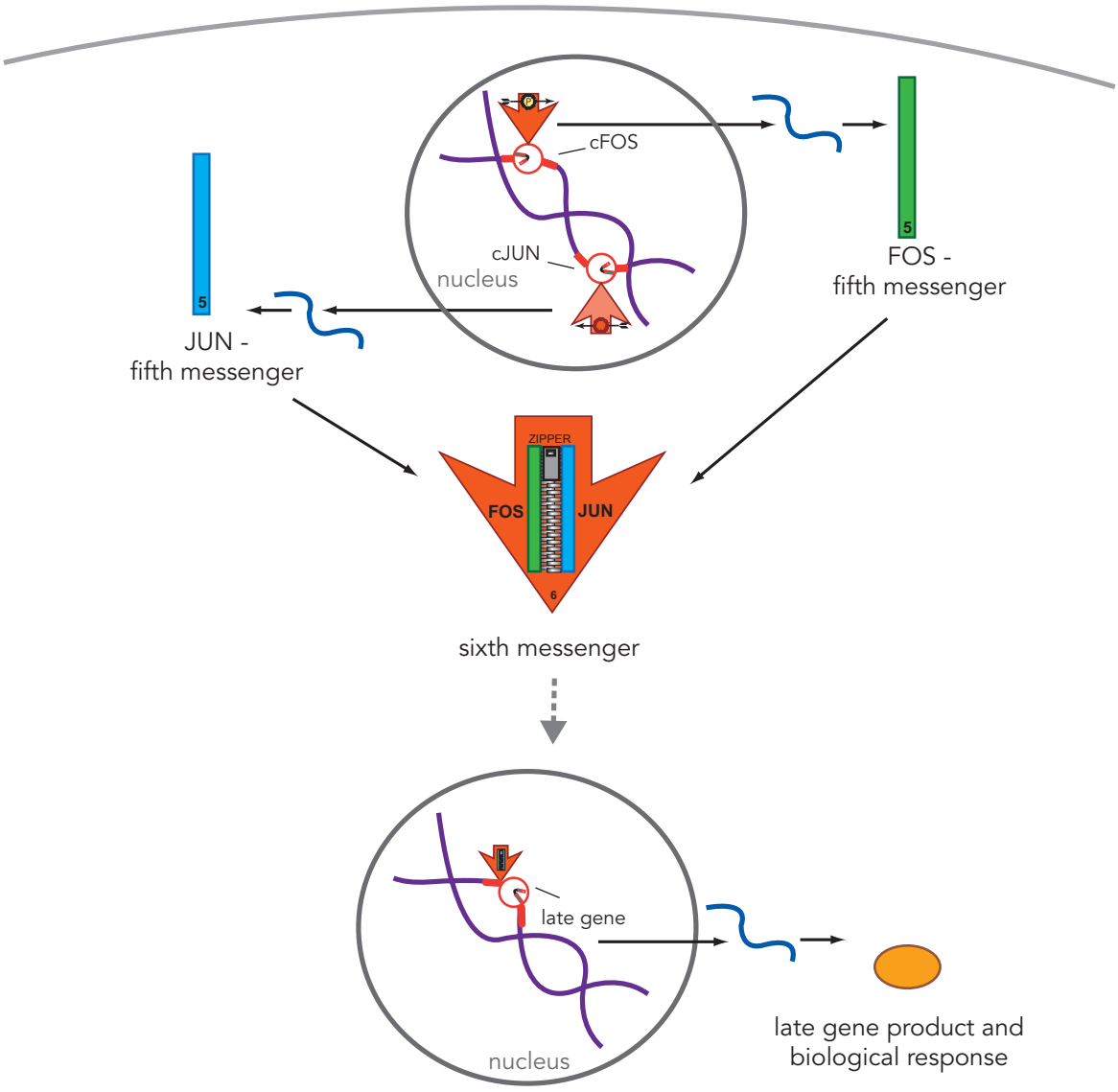


Figure 1-29 Activating a late gene. This figure summarizes the process of activating a late gene. At the top, immediate early genes *cFos* and *cJun* are expressed and their fifth-messenger protein products Fos and Jun are formed. Next, a transcription factor, namely a leucine zipper, is created by the cooperation of Fos and Jun together, combining to form the sixth messenger. Finally, this transcription factor goes on to activate a late gene, resulting in the expression of its own gene product and the biological response triggered by that late gene product.

it is sending the message, and whether it is working in concert or in opposition with other neurotransmitters talking to other parts of the same neuron at the same time. When Fos and Jun partner together to form a leucine zipper type of transcription factor, this can lead to the activation of genes to make anything you can think of, from enzymes to receptors to structural proteins (see Figure 1-27).

In summary, one can trace the events from the neurotransmitting first messenger, through gene transcription (Figures 1-9, 1-11, 1-28, and 1-29). Once the second-messenger cAMP is formed from its first-messenger neurotransmitter (Figure 1-28), it can interact with a protein kinase third messenger. cAMP binds to the inactive or sleeping version of this enzyme, wakes it up, and thereby activates protein kinase. Once awakened,

the protein kinase third messenger's job is to activate transcription factors by phosphorylating them (Figure 1-28). It does this by traveling straight to the cell nucleus and finding a sleeping transcription factor. By sticking a phosphate onto the transcription factor, protein kinase is able to "wake up" that transcription factor and form a fourth messenger (Figure 1-28). Once a transcription factor is aroused, it will bind to genes and cause protein synthesis, in this case, the product of an immediate early gene, and this functions as a fifth messenger. Two such gene products bind together to form yet another activated transcription factor, and this is the sixth messenger (Figure 1-29). Finally, the sixth messenger causes the expression of a late gene product, which could be thought of as a seventh-messenger protein product of the activated gene. This late gene product then mediates some biological response important to the functioning of the neuron.

Of course, neurotransmitter-induced molecular cascades into the cell nucleus lead to changes not only in the synthesis of its own receptors, but also in that of many other important postsynaptic proteins, including enzymes and receptors for other neurotransmitters. If such changes in genetic expression lead to changes in connections and in the functions that these connections perform, it is easy to understand how genes can *modify behavior*. The details of nerve functioning – and thus the behavior derived from this nerve functioning – are controlled by genes and the products they produce. Since mental processes and the behaviors they cause come from the connections between neurons in the brain, genes therefore exert significant control over behavior. But can behavior modify genes? Learning as well as experiences from the environment can indeed alter which genes are expressed and thus can give rise to changes in neuronal connections. In this way, human experiences, education, and even psychotherapy may change the expression of genes that alter the distribution and "strength" of specific synaptic connections. This in turn may produce long-term changes in behavior caused by the original experience and mediated by the genetic changes triggered by that original experience. Thus, genes modify behavior and behavior modifies genes. Genes do not directly regulate neuronal functioning. Rather, they directly regulate the proteins which create neuronal functioning. Changes in function have to wait until the changes in protein synthesis occur, and the events which they cause start to happen.

EPIGENETICS

Genetics is the DNA code for what a cell can transcribe into specific types of RNA or translate into specific proteins. However, just because there are about 20,000 genes in the human genome, it does not mean that every gene is expressed, even in the brain. Epigenetics is a parallel system that determines whether any given gene is actually made into its specific RNA and protein, or if it is instead ignored or silenced. If the genome is a lexicon of all protein "words," then the epigenome is a "story" resulting from arranging the "words" into a coherent tale. The genomic lexicon of all potential proteins is the same in every one of the 100+ billion neurons in the brain, and indeed is the same in all of the 200+ types of cells in the body. So, the plot of how a normal neuron becomes a malfunctioning neuron in a psychiatric disorder, as well as how a neuron becomes a neuron instead of a liver cell, is the selection of which specific genes are expressed or silenced. In addition, malfunctioning neurons are impacted by inherited genes that have abnormal nucleotide sequences, which if expressed contribute to mental disorders. Thus, the story of the brain depends not only upon which genes are inherited but also whether any abnormal genes are expressed or even whether normal genes are expressed when they should be silent or silenced when they should be expressed. Neurotransmission, genes themselves, drugs, and the environment all regulate which genes are expressed or silenced, and thus all affect whether the story of the brain is a compelling narrative such as learning and memory, a regrettable tragedy such as drug abuse, stress reactions, and psychiatric disorders, or therapeutic improvement of a psychiatric disorder by medications or psychotherapy.

What Are the Molecular Mechanisms of Epigenetics?

Epigenetic mechanisms turn genes on and off by modifying the structure of chromatin in the cell nucleus (Figure 1-30). The character of a cell is fundamentally determined by its chromatin, a substance composed of nucleosomes (Figure 1-30). Nucleosomes are an octet of proteins called histones around which DNA is wrapped (Figure 1-30). Epigenetic control over whether a gene is read (i.e., expressed) or is not read (i.e., silenced), is done by modifying the structure of chromatin. Chemical modifications that can do this include not only methylation, but also acetylation, phosphorylation, and others, and these processes are regulated by neurotransmission, drugs, and the environment (Figure 1-30). For example, when DNA or histones are

methylated, this compacts the chromatin and acts to close off access of molecular transcription factors to the promoter regions of DNA, with the consequence that the gene in this region is silenced, and not expressed, so no RNA or protein is manufactured (Figure 1-30). Silenced DNA means molecular features that are not part of a given cell's personality.

Histones are methylated by enzymes called histone methyltransferases, and this is reversed by enzymes called histone demethylases (Figure 1-30). Methylation of histones can silence genes whereas demethylation of histones can thus activate genes. DNA can also be methylated and this, too, silences genes. Demethylation of DNA reverses this. Methylation of DNA is regulated by DNA methyltransferase (DNMT) enzymes, and demethylation of DNA by DNA demethylase enzymes (Figure 1-30). There are many forms of methyltransferase enzymes, and they all tag their substrates with methyl groups donated from L-methylfolate via S-adenosyl-methionine (SAMe) (Figure 1-30). When neurotransmission, drugs, or the environment impact methylation, for example, this regulates whether genes are epigenetically silenced or expressed.

Methylation of DNA can eventually lead to deacetylation of histones as well, by activating enzymes called histone deacetylases (HDACs). Deacetylation of histones also has a silencing action on gene expression (Figure 1-30). Methylation and deacetylation compress chromatin, as though a molecular gate has been closed, and thus transcription factors that activate genes cannot get access to their promoter regions, and thus the genes are silenced and not transcribed into RNA or translated into proteins (Figure 1-30). On the other hand, demethylation and acetylation do just the opposite: they decompress chromatin as though a molecular gate has been opened, and thus transcription factors can get to the promoter regions of genes, and do activate them (Figure 1-30). Activated genes thus become part of the molecular personality of a given cell.

How Epigenetics Maintains or Changes the Status Quo

Some enzymes try to maintain the status quo of a cell, enzymes such as DNMT1 (DNA methyltransferase 1), which maintain the methylation of specific areas of DNA and keep various genes quiet for a lifetime. For example, this process keeps a neuron always a neuron, and a liver cell always a liver cell, including when a cell divides into another one. Presumably methylation is maintained at genes that one cell does not need, even though another cell type might.

It used to be thought that, once a cell differentiated, the epigenetic pattern of gene activation and gene silencing remained stable for the lifetime of that cell. Now, however, it is known that there are various circumstances in which epigenetics may change in mature, differentiated neurons. Although the initial epigenetic pattern of a neuron is indeed set during neurodevelopment to give each neuron its own lifelong "personality," it now appears that the storyline of some neurons is that they respond to their narrative experiences throughout life with a changing character arc, thus causing de novo alterations in their epigenome. Depending upon what happens to a neuron (such as experiencing child abuse, adult stress, dietary deficiencies, productive new encounters, psychotherapy, drugs of abuse, or psychotropic therapeutic medications), it now seems that previously silenced genes can become activated and/or previously active genes can become silenced (Figure 1-30). When this happens, both favorable and unfavorable developments can occur in the character of neurons. Favorable epigenetic mechanisms may be triggered in order for one to learn (e.g., spatial memory formation) or to experience the therapeutic actions of psychopharmacological agents. On the other hand, unfavorable epigenetic mechanisms may be triggered in order for one to become addicted to drugs of abuse, or to experience various forms of "abnormal learning," such as when one develops fear conditioning, an anxiety disorder, or a chronic pain condition.

How these epigenetic mechanisms arrive at the scene of the crime remains a compelling neurobiological and psychiatric mystery. Nevertheless, a legion of scientific detectives is working these cases and is beginning to show how epigenetic mechanisms are mediators of psychiatric disorders. There is also the possibility that epigenetic mechanisms can be harnessed to treat addictions, extinguish fear, prevent the development of chronic pain states, and maybe even prevent disease progression of psychiatric disorders such as schizophrenia by identifying high-risk individuals before the "plot thickens" and the disorder is irreversibly established and relentlessly marches on to an unwanted destiny.

One of the mechanisms for changing the status quo of epigenomic patterns in a mature cell is via de novo DNA methylation by a type of DNMT enzyme known as DNMT2 or DNMT3 (Figure 1-30). These enzymes target neuronal genes for silencing that were previously active in a mature neuron. Of course, deacetylation of histones near previously active genes would do the same thing, namely silence them, and this is mediated

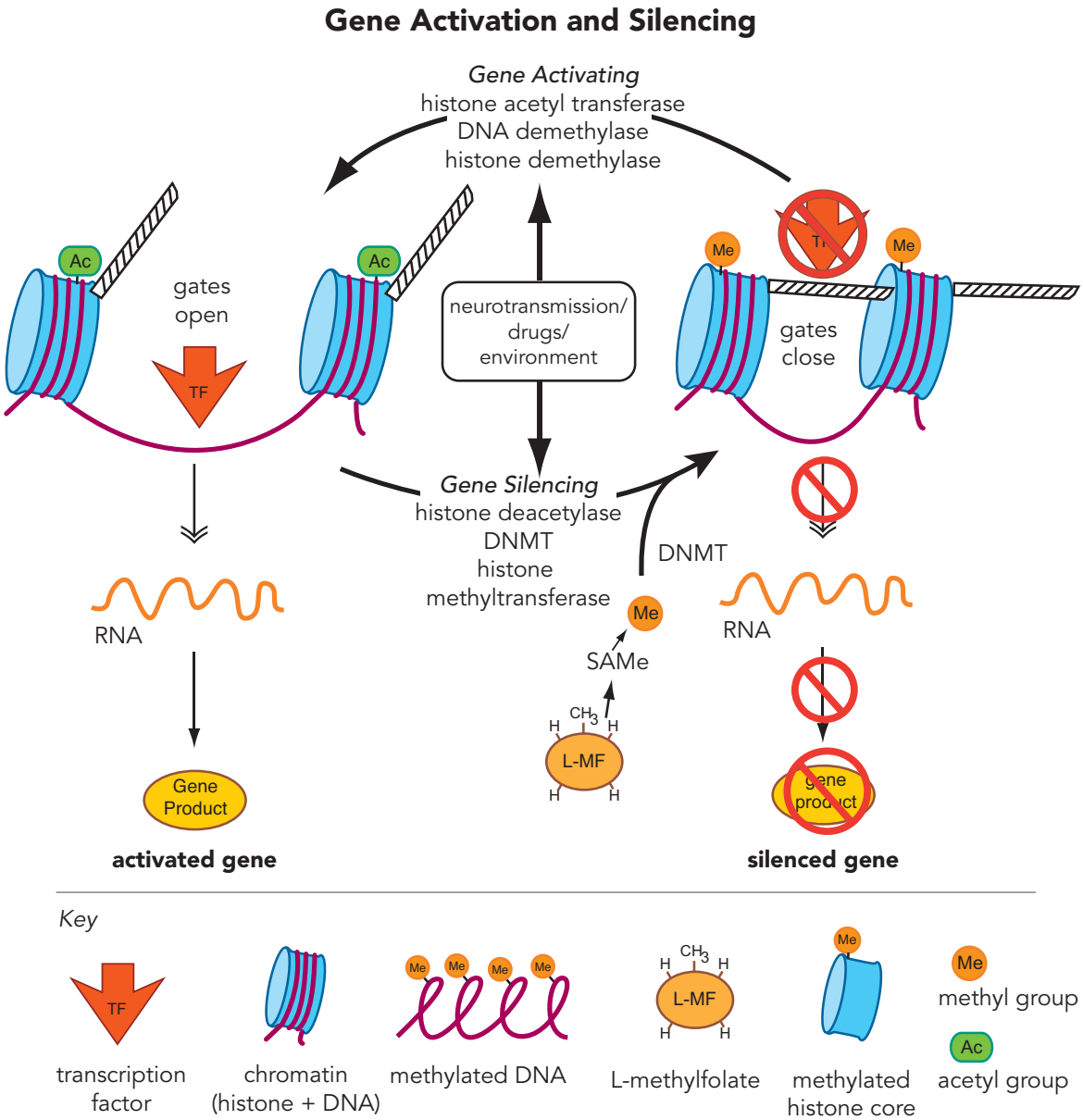


Figure 1-30 Gene activation and silencing. Molecular gates are opened by acetylation and/or demethylation of histones, allowing transcription factors access to genes, thus activating them. Molecular gates are closed by deacetylation and/or methylation provided by the methyl donor SAMe derived from L-methylfolate. This prevents access of transcription factors to genes, thus silencing them. Ac = acetyl; Me = methyl; DNMT = DNA methyltransferase; TF = transcription factor; SAMe = S-adenosyl-methionine; L-MF = L-methylfolate.

by HDACs. In reverse, demethylation or acetylation of genes both activate genes that were previously silent. The real question is how does a neuron know which genes among its thousands to silence or activate in response to the environment, including stress, drugs, and diet? How might this go wrong when a psychiatric disorder develops? This part of the story remains a twisted mystery but some very interesting detective work has already been done by various investigators who hope to understand how some neuronal stories evolve into psychiatric tragedies. These investigations may set the stage for rewriting the narrative of various psychiatric disorders by

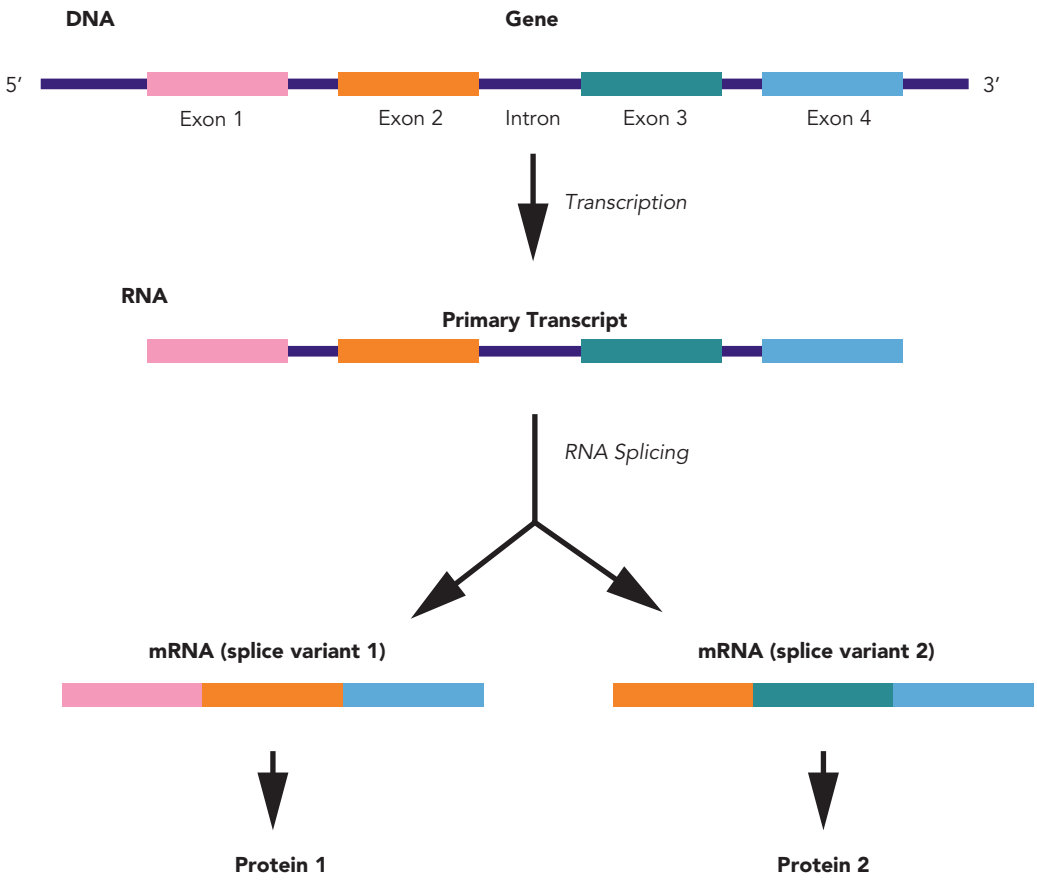


Figure 1-31 **Alternative splicing.** When DNA is transcribed into messenger RNA (mRNA), this is called the primary transcript. The primary transcript can then be translated into a protein; however, sometimes an intermediary step occurs in which the mRNA is spliced, with certain sections reorganized or removed outright. This means that one gene can give rise to more than one protein.

therapeutically altering the epigenetics of key neuronal characters so that the story has a happy ending.

A BRIEF WORD ABOUT RNA

Alternative Splicing

As mentioned above, the RNA that encodes our 20,000 genes is called messenger RNA (mRNA) and serves as an intermediate between DNA and protein. Although it might seem as if our 20,000 genes would make only 20,000 proteins, that is not so. It turns out that developing mRNA into protein is a similar process as when an old-fashioned movie producer makes cinema. That is, mRNA records the action from DNA just as the movie studio faithfully develops the film exactly as initially recorded. In the case of DNA transcription, this "first draft" is called the primary transcript (Figure 1-31). However, just as the raw footage from a movie shoot is not "translated" directly into a motion picture, in many cases, the "raw" mRNA is also not immediately translated into a protein. Now comes the interesting part: editing. It turns out that mRNA can be "spliced," much like a movie producer edits and splices movie film once the live shoot is over, organizing the splices into different sequences and leaving some on the cutting-room floor. For spliced mRNA, these sections won't be translated into protein (Figure 1-31). This "alternative splicing" means that one gene can give rise to many proteins (Figure 1-31), just like a movie can have different endings or be edited into a short trailer. Thus, thanks in part to RNA editing, the true molecular diversity of the brain is notably greater than our 20,000 genes.

RNA Interference

There are forms of RNA other than mRNA that are now known to exist and that do not code for protein

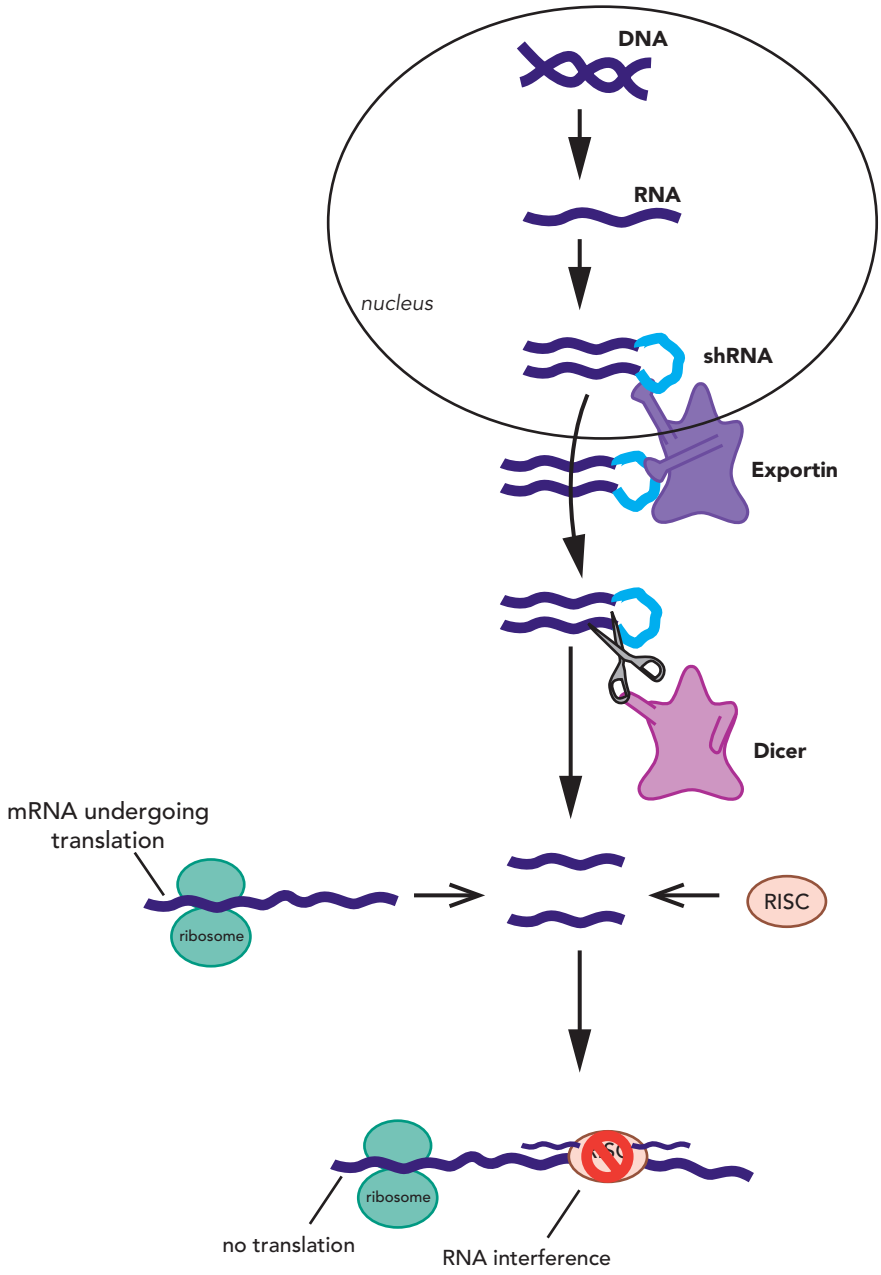


Figure 1-32 RNA interference. Some forms of RNA do not code for protein synthesis, and instead have regulatory functions. As shown here, small hairpin RNA (shRNA) is transcribed from DNA but is not translated into protein. Instead, it forms hairpin loops and is exported into the cytoplasm by the enzyme exportin, where it is then chopped into pieces by the enzyme dicer. The small pieces bind to a protein complex called RISC, which in turn binds to mRNA and inhibits protein synthesis.

synthesis; instead they have direct regulatory functions. These include ribosomal RNA (rRNA), transfer RNA (tRNA), and small nuclear RNA (snRNA), along with a large number of other noncoding RNAs (e.g., small hairpin RNAs because they are shaped like a hairpin, sometimes also called microRNA [miRNA]; interference RNA [iRNA]; and small interfering RNA [siRNA]. When miRNAs are transcribed from DNA, they do not go on to be translated into proteins. Instead, they form hairpin loops and are then exported to the cytoplasm by the enzyme exportin, where they are chopped into pieces by an enzyme called "dicer" (Figure 1-32). Small pieces of iRNA then bind to a protein complex called RISC, which binds in turn to mRNA to inhibit protein synthesis (Figure 1-32). So, forms of RNA can lead both to protein synthesis and to blocking protein synthesis.

Future therapeutics may be able to utilize iRNAs to inhibit protein synthesis in genetic disorders, such as Huntington's disease.

SUMMARY

The reader should now appreciate that chemical neurotransmission is the foundation of psychopharmacology. There are many neurotransmitters, and all neurons receive input from a multitude of neurotransmitters in classic presynaptic to postsynaptic asymmetrical neurotransmission. Presynaptic to postsynaptic neurotransmissions at the brain's trillion synapses are key to chemical neurotransmission, but some neurotransmission is retrograde from postsynaptic neuron to presynaptic neuron, and other types of neurotransmission, such as volume neurotransmission, do not require a synapse at all.

The reader should also have an appreciation for elegant if complex molecular cascades precipitated by a neurotransmitter, with molecule-by-molecule transfer of that transmitted message inside the neuron receiving that message, eventually altering the biochemical machinery of that cell in order to carry out the message that was sent to it. Thus, the function of chemical neurotransmission is not so much to have a presynaptic neurotransmitter communicate with its postsynaptic receptors, but to have a *presynaptic genome converse with a postsynaptic genome*: DNA to DNA, presynaptic "command center" to postsynaptic "command center" and back.

The message of chemical neurotransmission is transferred via three sequential "molecular pony express" routes: (1) a presynaptic neurotransmitter synthesis route from presynaptic genome to the synthesis and packaging of neurotransmitter and supporting enzymes and receptors; (2) a postsynaptic route from receptor occupancy through second messengers all the way to the genome, which turns on postsynaptic genes; and (3) another postsynaptic route starting from the newly expressed postsynaptic genes transferring information as a molecular cascade of biochemical consequences throughout the postsynaptic neuron.

It should now be clear that neurotransmission does not end when a neurotransmitter binds to a receptor or even when ion flows have been altered or second messengers have been created. Events such as these all start and end within milliseconds to seconds following release of presynaptic neurotransmitter. The ultimate goal of neurotransmission is to alter the biochemical activities of the postsynaptic target neuron in a profound and enduring manner. Since the postsynaptic DNA has to wait until molecular pony express messengers make their way from the postsynaptic receptors, often located on dendrites, to phosphoproteins within the neuron, or to transcription factors and genes in the postsynaptic neuron's cell nucleus, it can take a while for neurotransmission to begin influencing the postsynaptic target neuron's biochemical processes. The time it takes from receptor occupancy by neurotransmitter to gene expression is usually hours. Furthermore, since the last messenger triggered by neurotransmission – called a transcription factor – only initiates the very beginning of gene action, it takes even longer for the gene activation to be fully implemented via the series of biochemical events it triggers. These biochemical events can begin many hours to days after the neurotransmission occurred, and can last days or weeks once they are put in motion.

Thus, a brief puff of chemical neurotransmission from a presynaptic neuron can trigger a profound postsynaptic reaction that takes hours to days to develop and that can last days to weeks or even a lifetime. Every conceivable component of this entire process of chemical neurotransmission is a candidate for modification by drugs. Most psychotropic drugs act upon the processes that control chemical neurotransmission at the level of the neurotransmitters themselves or their enzymes and especially their receptors. Future psychotropic drugs will undoubtedly act directly upon the biochemical cascades, particularly upon those elements that control the expression of pre- and postsynaptic genes. Also, mental and neurological illnesses are known or suspected to affect these same aspects of chemical neurotransmission. The neuron is dynamically modifying its synaptic connections throughout its life, in response to learning, life experiences, genetic programming, epigenetic changes, drugs, and diseases, with chemical neurotransmission being the key aspect underlying the regulation of all these important processes.

2 Transporters, Receptors, and Enzymes as Targets of Psychopharmacological Drug Action

Neurotransmitter Transporters as Targets of Drug Action 29
Classification and Structure 29
Monoamine Transporters (SLC6 Gene Family) as Targets of Psychotropic Drugs 31
Other Neurotransmitter Transporters (SLC6 and SLC1 Gene Families) as Targets of Psychotropic Drugs 34
Where Are the Transporters for Histamine and Neuropeptides? 35
Vesicular Transporters: Subtypes and Function 35
Vesicular Transporters (SLC18 Gene Family) as Targets of Psychotropic Drugs 35
G-Protein-Linked Receptors 36
Structure and Function 36
G-Protein-Linked Receptors as Targets of Psychotropic Drugs 36
Enzymes as Sites of Psychopharmacological Drug Action 45
Cytochrome P450 Drug Metabolizing Enzymes as Targets of Psychotropic Drugs 49
Summary 50

Psychotropic drugs have many mechanisms of action, but they all target specific molecular sites that have profound effects upon neurotransmission. It is thus necessary to understand the anatomical infrastructure and chemical substrates of neurotransmission (Chapter 1) in order to grasp how psychotropic drugs work. Although there are over 100 essential psychotropic drugs utilized in clinical practice today (see *Stahl's Essential Psychopharmacology: the Prescriber's Guide*), there are only a few sites of action for all these therapeutic agents (Figure 2-1). Specifically, about a third of psychotropic drugs target one of the transporters for a neurotransmitter; another third target receptors coupled to G proteins; and perhaps only 10% target enzymes. All three of these sites of action will be discussed in this chapter. The balance of psychotropic drugs target various types of ion channels, which will be discussed in Chapter 3. Thus, mastering how just a few molecular sites regulate neurotransmission allows the psychopharmacologist to understand the theories about the mechanisms of action of virtually all psychopharmacological agents.

In fact, these molecular targets form the basis of how psychotropic drugs are now named. That is, there is a modern movement afoot to name psychotropic drugs for their pharmacological mechanism of action (e.g., serotonin transport inhibitor, dopamine D_2, and serotonin $5HT_{2A}$ antagonist) rather than for their therapeutic indication (e.g., antidepressant, antipsychotic, etc.). Naming drugs for therapeutic indication has led to endless confusion, because many drugs are used for indications far beyond their original use (e.g., so-called antipsychotics that are used for depression). Thus, throughout this textbook we will use the new nomenclature for drugs (neuroscience-based nomenclature), which is based upon mechanism of action and not therapeutic indication, wherever possible. This chapter and the next will explain all known mechanisms targeted by psychotropic drugs that form the basis for how they are named.

Finally, since there are genetic variants known for many targets of psychotropic drugs, there is an ongoing effort to determine to what extent such genetic variants may increase or decrease the odds that a patient will have a good clinical response or side effects to drugs that engage that target, in a process called pharmacogenomics. The scientific foundation for clinical application of genetic variants of psychotropic drug targets is still evolving, but current insights will be mentioned briefly when the specific target is described throughout this textbook.

NEUROTRANSMITTER TRANSPORTERS AS TARGETS OF DRUG ACTION

Classification and Structure

Neuronal membranes normally serve to keep the internal milieu of the neuron constant by acting as barriers to the intrusion of outside molecules and to the leakage of internal molecules. However, selective permeability

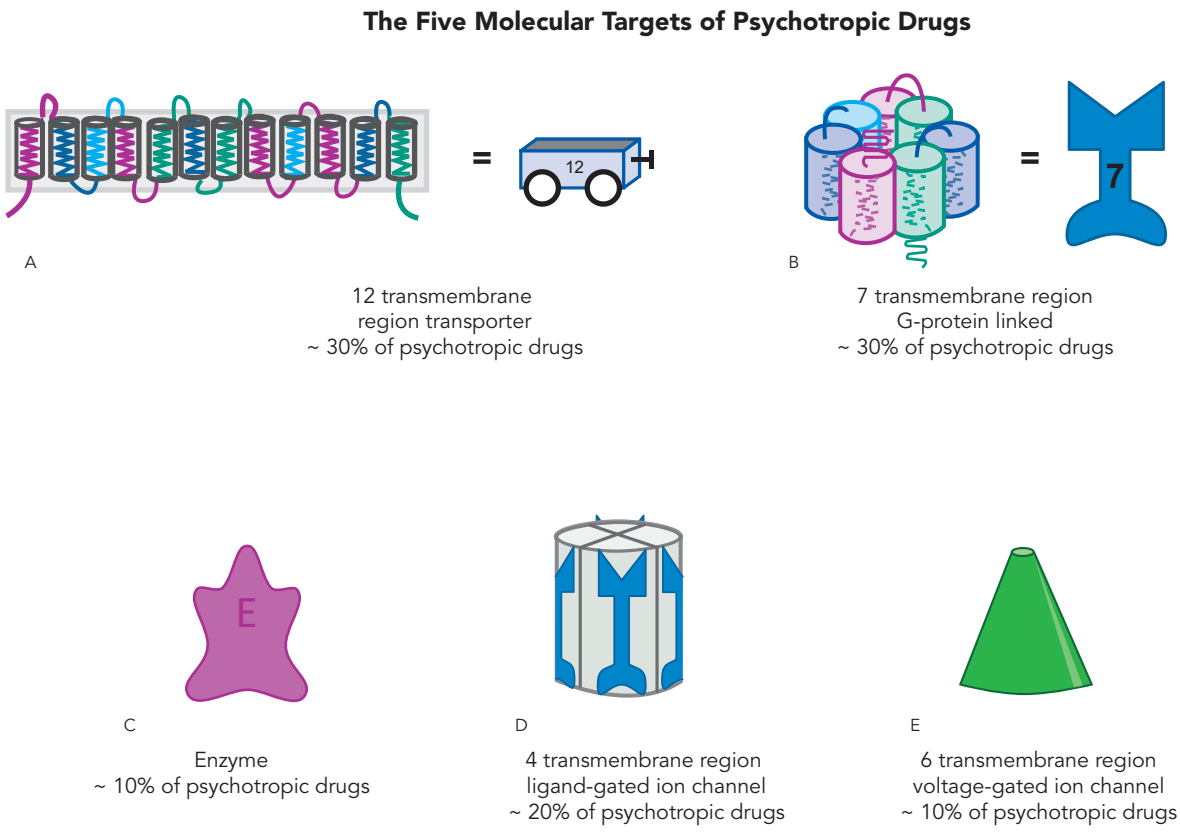


Figure 2-1 The molecular targets of psychotropic drugs. There are only a few major sites of action for the wide expanse of psychotropic drugs utilized in clinical practice. Approximately one-third of psychotropic drugs target one of the twelve-transmembrane-region transporters for a neurotransmitter (A), while another third target seven-transmembrane-region receptors coupled to G proteins (B). The sites of action for the remaining third of psychotropic drugs include enzymes (C), four-transmembrane-region ligand-gated ion channels (D), and six-transmembrane-region voltage-sensitive ion channels (E).

of the membrane is required to allow discharge as well as uptake of specific molecules to respond to the needs of cellular functioning. Good examples of this are neurotransmitters, which are released from neurons during neurotransmission, and in many cases are also transported back into presynaptic neurons as a recapture mechanism following their release. This recapture – or reuptake – is done in order for neurotransmitter to be reused in a subsequent neurotransmission. Also, once inside the neuron, most neurotransmitters are transported again into synaptic vesicles for storage, protection from metabolism, and immediate use during a volley of future neurotransmission.

Both types of neurotransmitter transport – presynaptic reuptake as well as vesicular storage – utilize a molecular transporter belonging to a "superfamily" of 12-transmembrane-region proteins (Figures 2-1A and 2-2). That is, neurotransmitter transporters have in common the structure of going in and out of the membrane 12 times (Figure 2-1A). These transporters are a type of receptor that binds to the neurotransmitter prior to transporting that neurotransmitter across the membrane.

Recently, details of the structures of neurotransmitter transporters have been determined and this has led to a proposed subclassification of neurotransmitter transporters. That is, there are two major subclasses of *plasma membrane transporters* for neurotransmitters (Tables 2-1 and 2-2). Some of these transporters are presynaptic and others are on glial membranes. The first subclass is comprised of sodium/chloride-coupled transporters, called the solute carrier SLC6 gene family, and includes transporters for the monoamines serotonin, norepinephrine, and dopamine (Table 2-1 and Figure 2-2A) as well as for the neurotransmitter GABA (γ-aminobutyric acid) and the amino acid glycine (Table

Table 2-1 Presynaptic monamine transporters

Transporter	Common abbreviation	Gene family	Endogenous substrate	False substrate
Serotonin transporter	SERT	SLC6	Serotonin	Ecstasy (MDMA)
Norepinephrine transporter	NET	SLC6	Norepinephrine	Dopamine Epinephrine Amphetamine
Dopamine transporter	DAT	SLC6	Dopamine	Norepinephrine Epinephrine Amphetamine

MDMA = 3.4-methylenedioxymethamphetamine

Table 2-2 Neuronal and glial GABA and amino acid transporters

Transporter	Common abbreviation	Gene family	Endogenous substrate
GABA transporter 1 (neuronal and glial)	GAT1	SLC6	GABA
GABA transporter 2 (neuronal and glial)	GAT2	SLC6	GABA beta-alanine
GABA transporter 3 (mostly glial)	GAT3	SLC6	GABA beta-alanine
GABA transporter 4 also called betaine transporter (neuronal and glial)	GAT4 BGT1	SLC6	GABA betaine
Glycine transporter 1 (mostly glial)	GlyT1	SLC6	Glycine
Glycine tranporter 2 (neuronal)	GlyT2	SLC6	Glycine
Excitatory amino acid transporters 1–5	EAAT1–5	SLC1	L-glutamate L-aspartate

2-2 and Figure 2-2A). The second subclass is comprised of high-affinity glutamate transporters, also called the solute carrier SLC1 gene family (Table 2-2 and Figure 2-2A).

In addition, there are three subclasses of *intracellular synaptic vesicle transporters* for neurotransmitters: the SLC18 gene family comprised both of vesicular monoamine transporters (VMATs) for serotonin, norepinephrine, dopamine, and histamine and the vesicular acetylcholine transporter (VAChT); the SLC32 gene family and their vesicular inhibitory amino acid transporters (VIAATs); and finally the SLC17 gene family and their vesicular glutamate transporters, such as vGluT1–3 (Table 2-3 and Figure 2-2B).

Monoamine Transporters (SLC6 Gene Family) as Targets of Psychotropic Drugs

Reuptake mechanisms for monoamines utilize unique presynaptic transporters (Figure 2-2A) in each different monoamine neuron but the same vesicular transporter (Figure 2-2B) in the synaptic vesicle membranes of all three monoamine neurons plus histamine neurons. That is, the unique presynaptic transporter for the monoamine serotonin is known as SERT, for norepinephrine is known as NET, and for dopamine, DAT (Table 2-1 and Figure 2-2A). All three of these monoamines are then transported into synaptic vesicles of their respective neurons by the same vesicular transporter, known as VMAT2 (vesicular monoamine transporter 2) (Figure 2-2B and Table 2-3).

Although the presynaptic transporters for these three neurotransmitters – SERT, NET, and DAT – are unique in their amino acid sequences and binding affinities for monoamines, each presynaptic monoamine transporter nevertheless has appreciable affinity for amines other than the one matched to its own neuron (Table 2-1). Thus, if other transportable neurotransmitters or drugs are in the vicinity of a given monoamine transporter, they may also be transported into the presynaptic neuron by hitchhiking a ride on certain transporters that can carry them into the neuron.

For example, the norepinephrine transporter NET has high affinity for the transport of dopamine as well as for norepinephrine; the dopamine transporter DAT has

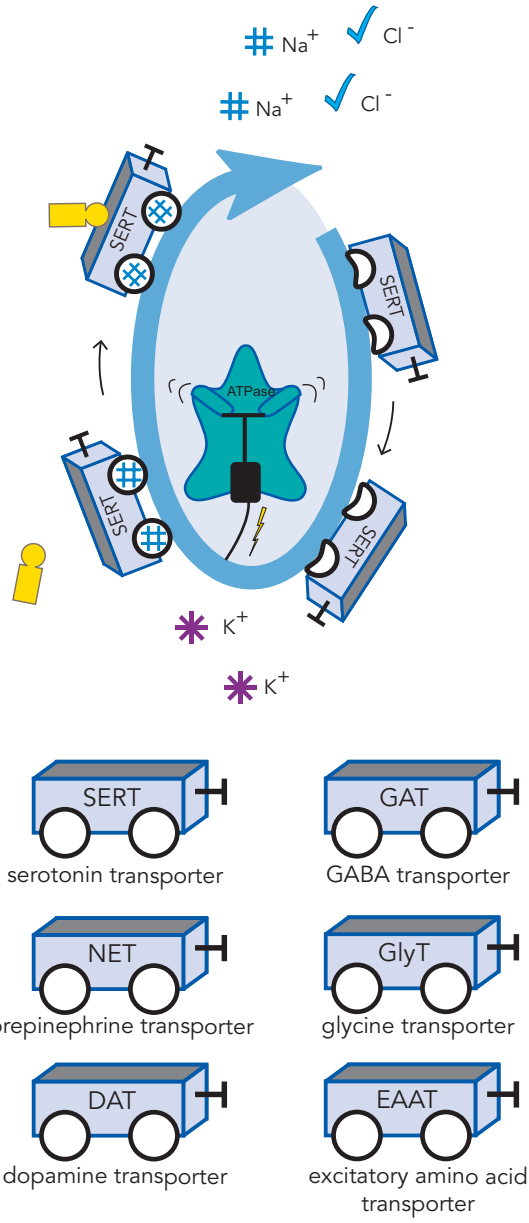


Figure 2-2A Sodium–potassium ATPase. Transport of many neurotransmitters into the presynaptic neuron is not passive, but rather requires energy. This energy is supplied by sodium–potassium ATPase, an enzyme that is also sometimes referred to as the sodium pump. Sodium-potassium ATPase continuously pumps sodium out of the neuron, creating a downhill gradient. The "downhill" transport of sodium is coupled to the "uphill" transport of the neurotransmitter. In many cases this also involves cotransport of chloride and in some cases countertransport of potassium. Examples of neurotransmitter transporters include the serotonin transporter (SERT), the norepinephrine transporter (NET), the dopamine transporter (DAT), the GABA transporter (GAT), the glycine transporter (GlyT), and the excitatory amino acid transporter (EAAT).

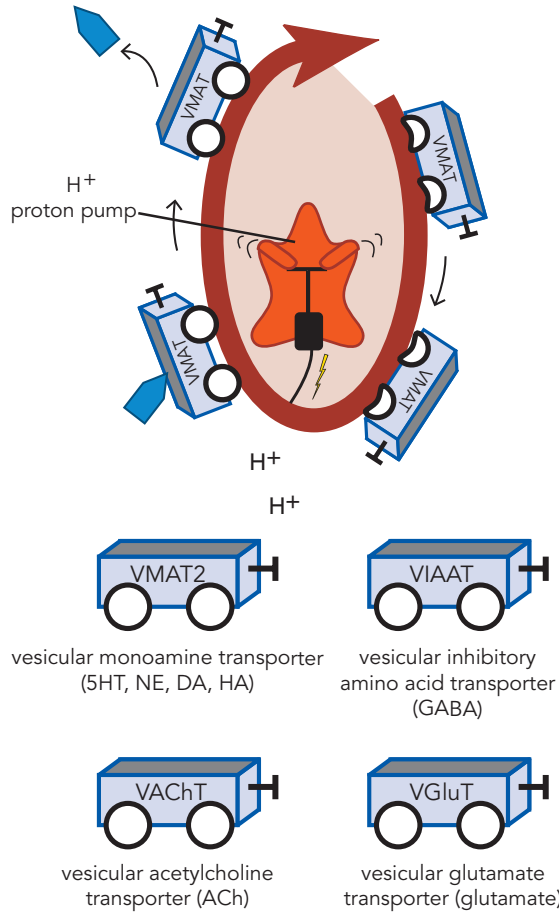


Figure 2-2B Vesicular transporters. Vesicular transporters package neurotransmitters into synaptic vesicles through the use of a proton ATPase, or proton pump. The proton pump utilizes energy to pump positively charged protons continuously out of the synaptic vesicle. Neurotransmitter can then be transported into the synaptic vesicle, keeping the charge inside the vesicle constant. Examples of vesicular transporters include the vesicular monoamine transporter (VMAT2), which transports serotonin (5HT), norepinephrine (NE), dopamine (DA), and histamine (HA); the vesicular acetylcholine transporter (VAChT), which transports acetylcholine; the vesicular inhibitory amino acid transporter (VIAAT), which transports GABA; and the vesicular glutamate transporter (VGluT), which transports glutamate.

high affinity for the transport of amphetamines as well as for dopamine; the serotonin transporter SERT has high affinity for the transport of "Ecstasy" (the drug of abuse MDMA or 3,4-methylenedioxymethamphetamine) as well as for serotonin (Table 2-1).

How are neurotransmitters transported? Monoamines are not passively shuttled into the presynaptic neuron,

Table 2-3 Vesicular neurotransmitter transporters

Transporter	Common abbreviation	Gene family	Endogenous substrate
Vesicular monoamine transporters 1 and 2	VMAT1 VMAT2	SLC18	Serotonin Dopamine Histamine Norepinephrine
Vesicular acetylcholine transporter	VAChT	SLC18	Acetylcholine
Vesicular inhibitory amino acid transporter	VIAAT	SLC32	GABA
Vesicular glutamate transporters 1–3	vGluT1–3	SLC17	Glutamate

because it requires energy to concentrate monoamines into a presynaptic neuron. That energy is provided by transporters in the SLC6 gene family coupling the "downhill" transport of sodium (down a concentration gradient) with the "uphill" transport of the monoamine (up a concentration gradient) (Figure 2-2A). Thus, the monoamine transporters are really sodium-dependent cotransporters; in most cases, this involves the additional cotransport of chloride, and in some cases the countertransport of potassium. All of this is made possible by coupling monoamine transport to the activity of a sodium–potassium ATPase (adenosine triphosphatase), an enzyme sometimes called the "sodium pump" that creates the downhill gradient for sodium by continuously pumping sodium out of the neuron (Figure 2-2A).

The structure of a monoamine neurotransmitter transporter from the SLC6 family has recently been proposed to have binding sites not only for the monoamine, but also for two sodium ions (Figure 2-2A). In addition, these transporters may exist as dimers, or two copies working together with each other, but the manner in which they cooperate is not yet well understood and is not shown in the figures. There are other binding sites on this transporter – not well defined – for several drugs such as the many selective serotonin reuptake inhibitors (known as SSRIs) and other related agents used to treat unipolar depression. When these drugs bind to the transporter, they inhibit reuptake of monoamines. These drugs do not bind to the substrate site (where the monoamine itself binds to the transporter) and are not transported into the neuron, and thus are said to be allosteric (i.e., "other site").

In the absence of sodium, there is low affinity of the monoamine transporter for its monoamine substrate, and in this case, there is binding of neither sodium nor monoamine. An example of this is shown for the serotonin transporter SERT in Figure 2-2A where the transport "wagon" has flat tires indicating no binding of sodium, as well as absence of binding of serotonin to its substrate binding site since the transporter has low affinity for serotonin in the absence of sodium. The allosteric site for a drug that inhibits this transporter is also empty (the front seat in Figure 2-2A). However, in Figure 2-2A in the presence of sodium ions, the tires are now "inflated" by sodium binding and serotonin can now also bind to its substrate site on SERT. The situation is now primed for serotonin transport back into the serotonergic neuron, along with cotransport of sodium and chloride down the gradient and into the neuron and countertransport of potassium out of the neuron (Figure 2-2A). If a drug binds to an inhibitory allosteric site, namely the front seat on the SERT transporter wagon in Figure 2-2A (i.e., drugs such as the selective serotonin reuptake inhibitor fluoxetine [Prozac]), this reduces the affinity of the serotonin transporter SERT for its substrate serotonin, and serotonin binding is prevented.

Why does this matter? Blocking the presynaptic monoamine transporter has a huge impact on neurotransmission at any synapse that utilizes that neurotransmitter. The normal recapture of neurotransmitter by the presynaptic neurotransmitter transporter in Figure 2-2A keeps the levels of this neurotransmitter from accumulating in the synapse. Normally, following release from the presynaptic neuron, neurotransmitters only have time for a brief dance on their synaptic receptors, and the party is soon over because the monoamines climb back into the presynaptic neuron on their transporters (Figure 2-2A). If one wants to enhance normal synaptic activity of

these neurotransmitters, or restore their diminished synaptic activity, this can be accomplished by blocking these transporters in Figure 2-2A. Although this might not seem to be a very dramatic thing, the fact is that this alteration in chemical neurotransmission – namely the enhancement of synaptic monoamine action – is thought to underlie the clinical effects of all the agents that block monoamine transporters, including most drugs that treat ADHD (attention deficit hyperactivity disorder). "Stimulants" for ADHD, such as methylphenidate and amphetamine, as well as the drug of abuse cocaine, all act on DAT and NET. Also, most drugs that treat unipolar depression act at SERT, NET, DAT, or some combination of these transporters. However, it is a misnomer to call these agents simply "antidepressants," since they are not first-line treatments for all forms of depression, and they are used for many, many other indications in addition to unipolar depression. Specifically, many drugs that block monoamine transporters are not only effective in the treatment of unipolar depression. They are also used to treat many forms of anxiety, from generalized anxiety disorder to social anxiety disorder to panic disorder; for reducing neuropathic pain in fibromyalgia, postherpetic neuralgia, diabetic peripheral neuropathic pain, and other pain conditions; for improving eating disorders, impulsive–compulsive disorders, obsessive–compulsive disorder, and trauma- and stress-related disorders such as posttraumatic stress disorder. They have additional therapeutic actions as well. Furthermore, some forms of depression, notably bipolar depression and depression with mixed features, are **not** treated first-line with drugs that block monoamine transporters. No wonder we don't call agents that block monoamine transporters simply "antidepressants" anymore!

Given the high prevalence of disorders that inhibitors of monoamine transporters treat, it may come as no surprise that these drugs are among the most frequently prescribed psychotropic drugs. In fact, some estimates are that a monoamine transport inhibitor is prescribed every second of every minute of every hour of every day in the US alone (many millions of prescriptions a year)! Also, about a third of the currently prescribed essential 100 psychotropic drugs act by targeting one or more of the three monoamine transporters. Thus, the reader can see why understanding monoamine transporters and how various drugs act at these transporters is so important to grasping how one of the critical classes of agents in psychopharmacology works.

Other Neurotransmitter Transporters (SLC6 and SLC1 Gene Families) as Targets of Psychotropic Drugs

In addition to the three transporters for monoamines discussed in detail above, there are several other transporters for various different neurotransmitters or their precursors. Although this includes a dozen additional transporters, there is only one psychotropic drug used clinically that is known to bind to any of these transporters. Thus, there is a presynaptic transporter for choline, the precursor to the neurotransmitter acetylcholine, but no known drugs target this transporter. There are also several transporters for the ubiquitous inhibitory neurotransmitter GABA, known as GAT1–4 (Table 2-2). Although debate continues about the exact localization of these subtypes to presynaptic neurons, neighboring glia, or even postsynaptic neurons, it is clear that a key presynaptic transporter of GABA is the GAT1 transporter, which is selectively blocked by the anticonvulsant tiagabine, thereby increasing synaptic GABA concentrations. In addition to anticonvulsant actions, this increase in synaptic GABA may have therapeutic actions in anxiety, sleep disorders, and pain. No other inhibitors of this transporter are available for clinical use.

Finally, there are multiple transporters for two amino acid neurotransmitters, glycine and glutamate (Table 2-2). There are no drugs utilized in clinical practice that are known to block glycine transporters although new agents are in clinical trials for treating schizophrenia and other disorders. The glycine transporters, along with the choline and GABA transporters, are all members of the SLC6 gene family, the same family to which the monoamine transporters belong and have a similar structure (Figure 2-2A and Tables 2-1 and 2-2). However, the glutamate transporters belong to a unique family, SLC1, and have a somewhat unique structure and somewhat different functions compared to those transporters of the SLC6 family (Table 2-2).

Specifically, there are several transporters for glutamate, known as excitatory amino acid transporters 1–5 (EAAT1–5; Table 2-2). The exact localization of these various transporters to presynaptic neurons, postsynaptic neurons, or glia is still under investigation, but the uptake of glutamate into glia is well known to be a key system for recapturing glutamate for re-use once it has been released. Transport into glia results in conversion of glutamate into glutamine, and then glutamine enters the presynaptic neuron for reconversion back into glutamate. No drugs utilized in clinical practice are known to block glutamate transporters.

One difference between transport of neurotransmitters by the SLC6 gene family and transport of glutamate by the SLC1 gene family is that glutamate does not seem to cotransport chloride with sodium when it also cotransports glutamate. Also, glutamate transport is almost always characterized by the countertransport of potassium, whereas this is not always the case with SLC6 gene family transporters. Glutamate transporters may work together as trimers rather than dimers, as the SLC6 transporters seem to do. The functional significance of these differences remains obscure, but may become more apparent if clinically useful psychopharmacological agents that target glutamate transporters are discovered. Since it may often be desirable to diminish rather than enhance glutamate neurotransmission, the future utility of glutamate transporters as therapeutic targets is also unclear.

Where Are the Transporters for Histamine and Neuropeptides?

It is an interesting observation that apparently not all neurotransmitters are regulated by reuptake transporters. The central neurotransmitter histamine apparently does not have a transporter for it presynaptically (although it is transported into synaptic vesicles by VMAT2, the same transporter used by the monoamines – see Figure 2-2B). Histamine's inactivation is thus thought to be entirely enzymatic. The same can be said for neuropeptides, since reuptake pumps and presynaptic transporters have not been found for them, and are thus thought to be lacking for this class of neurotransmitter. Inactivation of neuropeptides is apparently by diffusion, sequestration, and enzymatic destruction, but not by presynaptic transport. It is always possible that a transporter will be discovered in the future for some of these neurotransmitters, but at the present time there are no known presynaptic transporters for either histamine or neuropeptides.

Vesicular Transporters: Subtypes and Function

Vesicular transporters for the monoamines (VMATs) are members of the SLC18 gene family and have already been discussed above. They are shown in Figure 2-2B and listed in Table 2-3. The vesicular transporter for acetylcholine – also a member of the SLC18 gene family but known as VAChT – is shown in Figure 2-2B and listed in Table 2-3. The GABA vesicular transporter is a member of the SLC32 gene family and is called VIAAT (vesicular inhibitory amino acid transporter; shown in Figure 2-2B and Table 2-3). Finally, vesicular transporters for glutamate, called vGluT1–3 (vesicular glutamate transporters 1, 2, and 3), are members of the SLC17 gene family and are also shown in Figure 2-2B and listed in Table 2-3. A novel 12-transmembrane-region synaptic vesicle transporter of uncertain mechanism and with unclear substrates, called the SV2A transporter and localized within the synaptic vesicle membrane, binds the anticonvulsant levetiracetam, perhaps interfering with neurotransmitter release and thereby reducing seizures.

How do neurotransmitters get inside synaptic vesicles? In the case of vesicular transporters, storage of neurotransmitters is facilitated by a proton ATPase, known as the "proton pump" that utilizes energy to pump positively charged protons continuously out of the synaptic vesicle (Figure 2-2B). The neurotransmitters can then be concentrated against a gradient by substituting their own positive charge inside the vesicle for the positive charge of the proton being pumped out. Thus, neurotransmitters are not so much transported as they are "antiported" – i.e., they go in while the protons are actively transported out, keeping charge inside the vesicle constant. This concept is shown in Figure 2-2B for the VMAT transporting dopamine, in exchange for protons. Contrast this with Figure 2-2A where a monoamine transporter on the presynaptic membrane is cotransporting a monoamine along with sodium and chloride, but with the help of a sodium–potassium ATPase (sodium pump) rather than a proton pump.

Vesicular Transporters (SLC18 Gene Family) as Targets of Psychotropic Drugs

Vesicular transporters for acetylcholine (SLC18 gene family), GABA (SLC32 gene family), and glutamate (SLC17 gene family) are not known to be targeted by any drug utilized by humans. However, vesicular transporters for monoamines in the SLC18 gene family (VMATs), particularly those in dopamine neurons, are targeted by several drugs, including amphetamine (as a transported substrate) and tetrabenazine and its derivatives deutetrabenazine and valbenazine (as inhibitors, see Chapter 5) . Amphetamine thus has two targets: monoamine transporters discussed above as well as VMATs discussed here. In contrast, other drugs for ADHD, such as methylphenidate, and the so-called "stimulant" drug of abuse cocaine, target only the monoamine transporters, and in much the same manner as described for SSRIs at the serotonin transporter.

G-PROTEIN-LINKED RECEPTORS

Structure and Function

Another major target of psychotropic drugs is the class of receptors linked to G proteins. These receptors all have the structure of seven-transmembrane regions, meaning that they span the membrane seven times (Figure 2-1). Each of the transmembrane regions clusters around a central core that contains a binding site for a neurotransmitter. Drugs can interact at this neurotransmitter binding site or at other sites (allosteric sites) on the receptor. This can lead to a wide range of modifications of receptor actions due to mimicking or blocking, partially or fully, the neurotransmitter function that normally occurs at this receptor. Drug actions at G-protein-linked receptors can thus change downstream molecular events – e.g., determining which phosphoproteins are activated or inactivated and therefore which enzymes, receptors, or ion channels are modified by neurotransmission. Drug actions at G-protein-linked receptors can also determine whether a downstream gene is expressed or silenced, and thus which proteins are synthesized and which neuronal functions are amplified, from synaptogenesis, to receptor and enzyme synthesis, to communication with downstream neurons innervated by the neuron with the G-protein-linked receptor.

These actions on neurotransmission at G-protein-linked receptors are described in detail in Chapter 1 on signal transduction and chemical neurotransmission. The reader should have a good command of the function of G-protein-linked receptors and their role in signal transduction from specific neurotransmitters as described in Chapter 1 in order to understand how drugs acting at G-protein-linked receptors modify the signal transduction that arises from these receptors. This is important to understand because such drug-induced modifications in signal transduction from G-protein-linked receptors can have profound actions on psychiatric symptoms. In fact, the single most common action of psychotropic drugs utilized in clinical practice is to modify the actions of one or more G-protein-linked receptors, resulting in either therapeutic actions or side effects. More than a dozen G-protein-linked receptors as targets of various drugs are discussed in the various clinical chapters that follow. Here we will describe how various drugs stimulate or block these receptors in general, and throughout the textbook we will show how particular drugs acting at specific G-protein-linked receptors have unique actions on improving distinct psychiatric symptoms as well as causing characteristic side effects.

G-Protein-Linked Receptors as Targets of Psychotropic Drugs

G-protein-linked receptors are a large superfamily of receptors that interact with many neurotransmitters and with many psychotropic drugs (Figure 2-1B). There are many ways to subtype these receptors, but pharmacological subtypes are perhaps the most important to understand for clinicians who wish to target specific receptors with psychotropic drugs utilized in

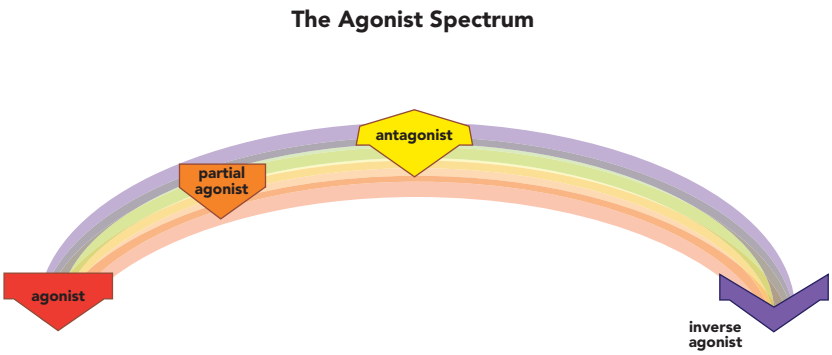


Figure 2-3 Agonist spectrum. Shown here is the agonist spectrum. Naturally occurring neurotransmitters stimulate receptors and are thus agonists. Some drugs also stimulate receptors and are therefore agonists as well. It is possible for drugs to stimulate receptors to a lesser degree than the natural neurotransmitter; these are called partial agonists or stabilizers. It is a common misconception that antagonists are the opposite of agonists because they block the actions of agonists. However, although antagonists prevent the actions of agonists, they have no activity of their own in the absence of the agonist. For this reason, antagonists are sometimes called "silent." Inverse agonists, on the other hand, do have opposite actions compared to agonists. That is, they not only block agonists but can also reduce activity below the baseline level when no agonist is present. Thus, the agonist spectrum reaches from full agonists to partial agonists through to "silent" antagonists and finally inverse agonists.

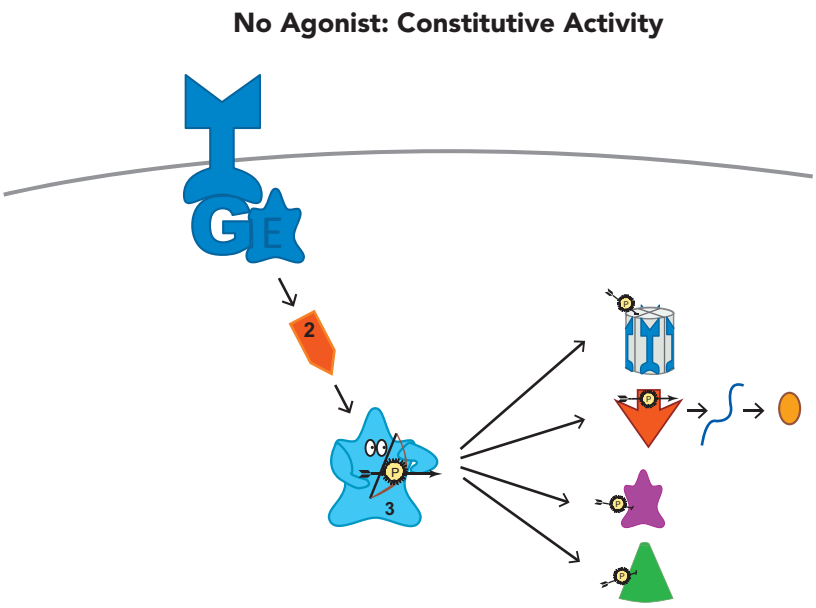


Figure 2-4 **Constitutive activity.** The absence of agonist does not mean that there is no activity related to G-protein-linked receptors. Rather, in the absence of agonist, the receptor's conformation is such that it leads to a low level of activity, or constitutive activity. Thus, signal transduction still occurs, but at a low frequency. Whether this constitutive activity leads to detectable signal transduction is affected by the receptor density in that brain region.

clinical practice. That is, the natural neurotransmitter interacts at all of its receptor subtypes, but many drugs are more selective than the neurotransmitter itself for just certain receptor subtypes and thus define a pharmacological subtype of receptor at which they specifically interact. This is not unlike the concept of the neurotransmitter being a master key that opens all the doors, and selective drugs that interact at pharmacologically specific receptor subtypes functioning as a specific key opening only one door. Here we will develop the concept that drugs have many ways of interacting at pharmacological subtypes of G-protein-linked receptors, across what is called an "agonist spectrum" (Figure 2-3).

No Agonist

An important concept for the "agonist spectrum" is that the absence of agonist does not necessarily mean that nothing at all is happening with signal transduction at G-protein-linked receptors. Agonists are thought to produce a conformational change in G-protein-linked receptors that leads to full receptor activation, and thus full signal transduction. In the absence of agonist, this same conformational change may still be occurring at some receptor systems, but only at very low frequency. This is referred to as *constitutive activity*, which may be present especially in receptor systems and brain areas where there is a high density of receptors. Thus, when something occurs at very low frequency but among a high number of receptors, it can still produce detectable signal transduction output. This is represented as a small – but not absent – amount of signal transduction in Figure 2-4.

Agonists

An agonist produces a conformational change in the G-protein-linked receptor that turns on the synthesis of second messenger to the greatest extent possible (i.e., the action of a *full agonist*) (Figure 2-5). The full agonist is generally represented by the naturally occurring neurotransmitter itself, although some drugs can also act in as full a manner as the natural neurotransmitter itself. What this means from the perspective of chemical neurotransmission is that the full array of downstream signal transduction is triggered by a full agonist (Figure 2-5). Thus, downstream proteins are maximally phosphorylated, and genes are maximally impacted. Loss of the agonist actions of a neurotransmitter at G-protein-linked receptors, due to deficient neurotransmission of any cause, would lead to the loss of this rich downstream chemical tour de force. Thus, agonists that restore this natural action would be potentially useful in states where reduced signal transduction leads to undesirable symptoms.

There are two major ways to stimulate G-protein-linked receptors with full agonist action. Firstly, several drugs *directly* bind to the neurotransmitter site on the G-protein-linked receptor itself and can produce the same full array of signal transduction effects as a full agonist (see Table 2-4). These are called direct-acting

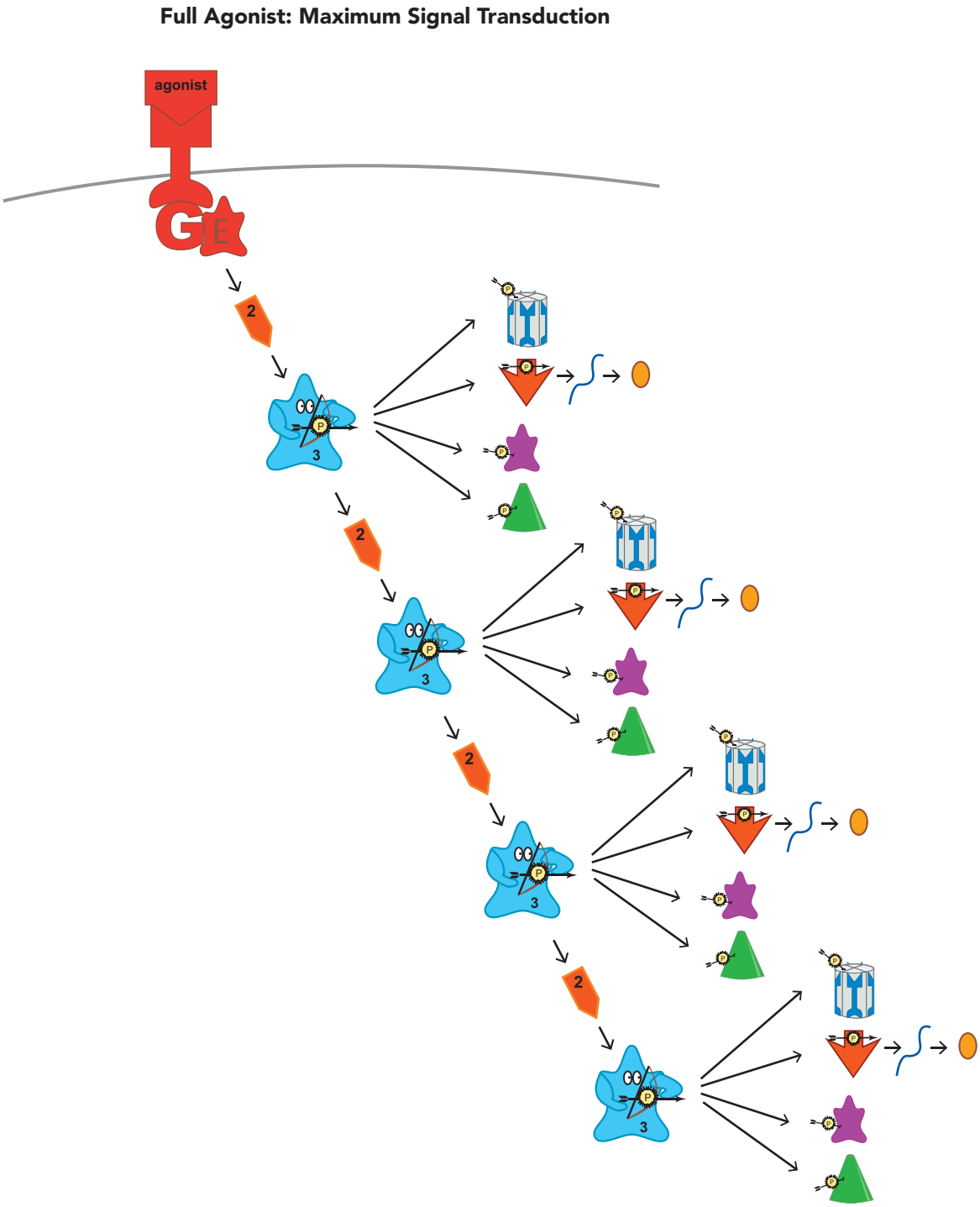


Figure 2-5 Full agonist: maximum signal transduction. When a full agonist binds to G-protein-linked receptors, it causes conformational changes that lead to maximum signal transduction. Thus, all the downstream effects of signal transduction, such as phosphorylation of proteins and gene activation, are maximized.

Table 2-4 Key G-protein-linked receptors directly targeted by psychotropic drugs

Neurotransmitter	G-protein receptor and pharmacological subtype directly targeted	Pharmacological action	Therapeutic action
Dopamine	D_2	Antagonist or partial agonist	Antipsychotic; antimanic
Serotonin	$5HT_{2A}$	Antagonist or inverse agonist	Antipsychotic actions in Parkinson's disease psychosis Antipsychotic actions in dementia-related psychosis Reduced drug-induced parkinsonism
			Possible reduction of negative symptoms in schizophrenia Possible mood stabilizing and antidepressant actions in bipolar disorder Improve insomnia and anxiety
		Agonist	Psychotomimetic actions Experimental treatment of refractory depression and other disorders, especially accompanying psychotherapy
	$5HT_{1B/1D}$	Antagonist or partial agonist	Possible pro-cognitive and antidepressant actions
	$5HT_{2C}$	Antagonist	Antidepressant
	$5HT_6$	?	?
	$5HT_7$	Antagonist	Possible pro-cognitive and antidepressant actions
	$5HT_{1A}$	Partial agonist	Reduced drug-induced parkinsonism Anxiolytic
			Booster of antidepressant actions of SSRIs/SNRIs
Norepinephrine	Alpha 2	Antagonist	Antidepressant actions
		Agonist	Improved cognition and behavioral disturbance in ADHD
	Alpha 1	Antagonist	Improved sleep (nightmares)
			Improved agitation in Alzheimer disease
			Side effects of orthostatic hypotension and possibly sedation
GABA	GABA-B	Agonist	Cataplexy
			Sleepiness in narcolepsy Possible enhanced slow-wave sleep Pain reduction in chronic pain and fibromyalgia
			Possible utility for alcohol use disorder and alcohol withdrawal
Melatonin	MT_1	Agonist	Improvement of insomnia and circadian rhythms
	MT_2	Agonist	Improvement of insomnia and circadian rhythms

Table 2-4 (cont.)

Neurotransmitter	G-protein receptor and pharmacological subtype directly targeted	Pharmacological action	Therapeutic action
Histamine	H_1	Antagonist	Therapeutic effect for anxiety and insomnia Side effect of sedation and weight gain
	H_3	Antagonist/ inverse agonist	Improvement of daytime sleepiness
Acetylcholine	M_1	Agonist	Procognitive and antipsychotic
		Antagonist	Side effect of sedation and memory disturbance
	M_4	Agonist	Antipsychotic
	$M_{2/3}$	Antagonist	Dry mouth, blurred vision, constipation, urinary retention
			May contribute to metabolic dysregulation (dyslipidemia and diabetes)
	M_5	?	?
Orexin A, B	Ox1,2	Antagonist	Hypnotic for insomnia

Table 2-5 Key G-protein-linked receptors indirectly targeted by psychotropic drugs

Neurotransmitter	G-protein receptor and pharmacological subtype indirectly targeted	Pharmacological action	Therapeutic action
Dopamine	$D_{1,2,3,4,5}$ agonist actions	Dopamine reuptake inhibition/release by methylphenidate/ amphetamine	Improvement of ADHD, depression, wakefulness
Serotonin	$5HT_{1A}$ agonist (presynaptic somatodendritic autoreceptors)	Serotonin reuptake inhibition by SSRIs/SNRIs	Antidepressant, anxiolytic
	$5HT_{2A}$ agonist (postsynaptic receptors; possibly $5HT1_A$, $5HT_{2C}$, $5HT_6$, $5HT_7$ postsynaptic receptors)		
	$5HT_{2A/2C}$ agonist	Serotonin release by MDMA	"Empathogen" experimental treatment of PTSD especially with psychotherapy
Norepinephrine	All norepinephrine receptors agonist	Norepinephrine reuptake inhibition	Antidepressant; neuropathic pain; ADHD
Acetylcholine	M_1 (possibly M_2–M_5)	Agonist via increasing acetylcholine itself at all acetylcholine receptors via acetylcholinesterase inhibition	Cognition in Alzheimer disease

ADHD, attention deficit hyperactivity disorder; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin norepinephrine reuptake inhibitors; PTSD, posttraumatic stress disorder; MDMA, 3.4-methylenedioxymethamphetamine.

agonists. Secondly, many drugs can *indirectly* act to boost the levels of the natural full agonist neurotransmitter itself (Table 2-5) and then this increased amount of natural agonist binds to the neurotransmitter site on the G-protein-linked receptor. Enhanced amounts of full agonist happen when neurotransmitter inactivation mechanisms are blocked. The most prominent examples of indirect full agonist actions have already been discussed above, namely inhibition of the monoamine transporters SERT, NET, and DAT and the GABA transporter GAT1. Another way to accomplish indirect full agonist action is to block the enzymatic destruction of neurotransmitters (Table 2-5). Two examples of this are inhibition of the enzymes monoamine oxidase (MAO) and acetylcholinesterase which will be explained in more detail in later chapters.

Antagonists

On the other hand, it also is possible that full agonist action can be too much of a good thing and that maximal activation of the signal transduction cascade may not always be desirable, as in states of overstimulation by neurotransmitters. In such cases, blocking the action of the natural neurotransmitter agonist may be desirable. This is the property of an antagonist. Antagonists produce a conformational change in the G-protein-linked receptor that causes no change in signal transduction – including no change in whatever amount of any "constitutive" activity that may have been present in the absence of agonist (compare Figure 2-4 with Figure 2-6). Thus, true antagonists are "neutral" and, since they have no actions of their own, are also called "silent."

There are many more examples of important antagonists of G-protein-linked receptors than there are of direct-acting full agonists in clinical practice (see Table 2-4). Antagonists are well known both as the mediators of therapeutic actions in psychiatric disorders and as the cause of undesirable side effects (Table 2-4). Some of these may prove to be inverse agonists (see below), but most antagonists utilized in clinical practice are characterized simply as "antagonists."

Antagonists block the actions of everything in the agonist spectrum (Figure 2-3). In the presence of an agonist, an antagonist will block the actions of that agonist but do nothing itself (Figure 2-6). The antagonist simply returns the receptor conformation back to the same state as exists when no agonist is present (Figure 2-4). Interestingly, an antagonist will also block the actions of a partial agonist (explained below in more detail). Partial agonists are thought to produce a conformational change in the G-protein-

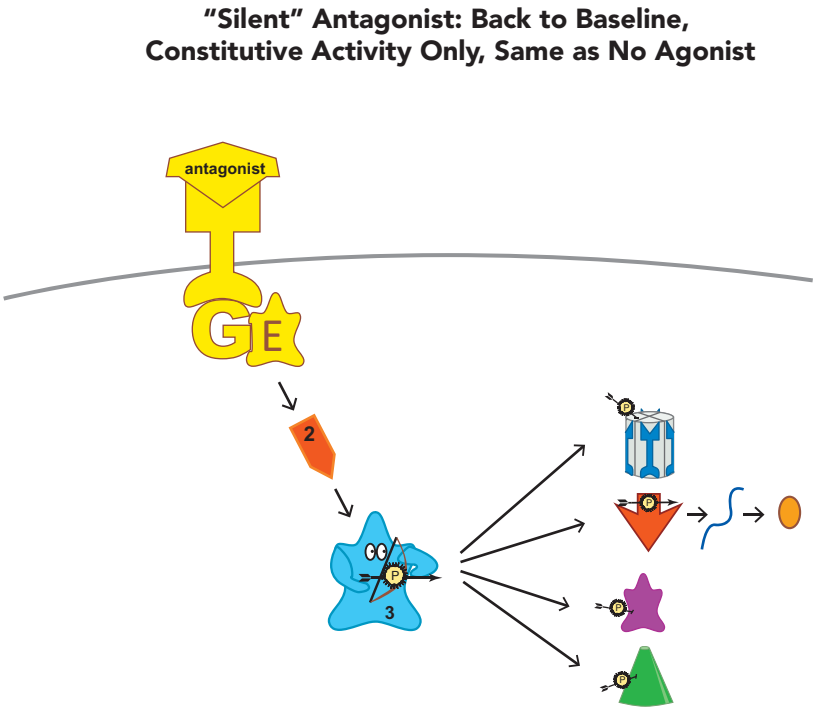


Figure 2-6 **"Silent" antagonist.** An antagonist blocks agonists (both full and partial) from binding to G-protein-linked receptors, thus preventing agonists from causing maximum signal transduction and instead changing the receptor's conformation back to the same state as exists when no agonist is present. Antagonists also reverse the effects of inverse agonists, again by blocking the inverse agonists from binding and then returning the receptor conformation to the baseline state. Antagonists do not have any impact on signal transduction in the absence of an agonist.

linked receptor that is intermediate between a full agonist and the baseline conformation of the receptor in the absence of agonist (Figures 2-7 and 2-8). An antagonist reverses the action of a partial agonist by returning the G-protein-linked receptor to that same conformation as exists when no agonist is present (Figure 2-4). Finally, an antagonist reverses an inverse agonist (also explained below in more detail). Inverse agonists are thought to produce a conformational state of the receptor that totally inactivates it and even removes the baseline constitutive activity (Figure 2-9). An antagonist reverses this back to the baseline state that allows constitutive activity (Figure 2-6), the same as exists for the receptor in the absence of the neurotransmitter agonist (Figure 2-4).

By themselves, therefore, it is easy to see that true antagonists have no activity and why they are sometimes referred to as "silent." Silent antagonists return the entire spectrum of drug-induced conformational changes in the G-protein-linked receptor (Figures 2-3 and 2-10) to

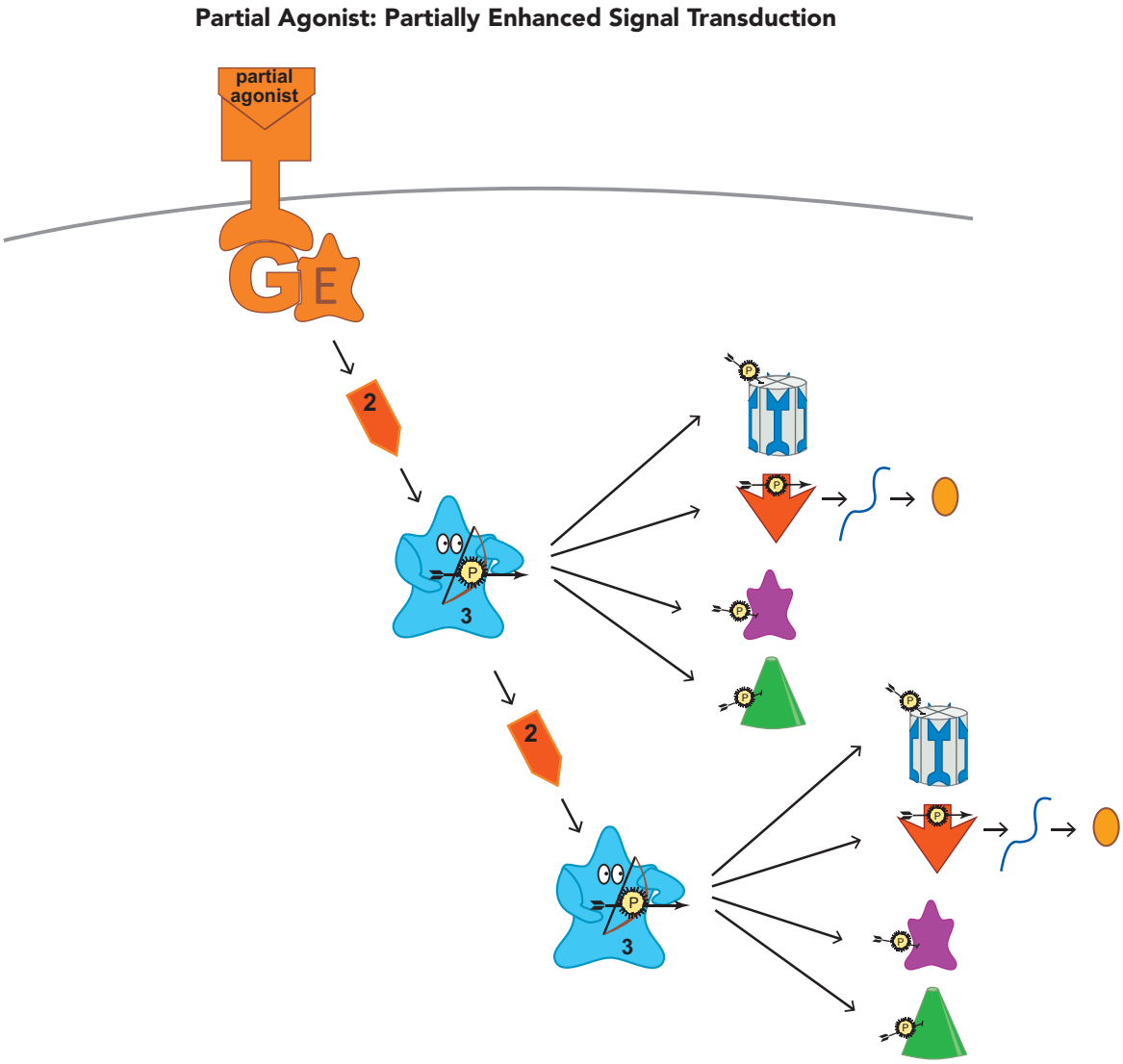


Figure 2-7 Partial agonist. Partial agonists stimulate G-protein-linked receptors to enhance signal transduction but do not lead to maximum signal transduction the way full agonists do. Thus, in the absence of a full agonist, partial agonists increase signal transduction. However, in the presence of a full agonist, the partial agonist will actually turn down the strength of various downstream signals. For this reason, partial agonists are sometimes referred to as stabilizers.

the same place (Figure 2-6) – i.e., the conformation that exists in the absence of agonist (Figure 2-4).

Partial Agonists

It is possible to produce signal transduction that is something more than an antagonist yet something less than a full agonist. Turning down the gain a bit from full agonist actions, but not all the way to zero, is the property of a partial agonist (Figure 2-7). This action can also be seen as turning up the gain a bit from silent antagonist actions, but not all the way to a full agonist. Depending upon how close this partial agonist is to a full agonist or to a silent antagonist on the agonist spectrum will determine the impact of a partial agonist on downstream signal transduction events.

The amount of "partiality" that is desired between agonist and antagonist – that is, where a partial agonist should sit on the agonist spectrum – is both a matter of debate as well as trial and error. The ideal therapeutic agent may have signal transduction through G-protein-linked receptors that is not too "hot," yet not too "cold," but "just right," sometimes called the "Goldilocks" solution (Figure 2-7). Such an ideal state may vary from one clinical situation to another, depending upon the balance between full agonism and silent antagonism that is desired.

In cases where there is unstable neurotransmission throughout the brain, such as when "out-of-tune" neurons are theoretically mediating psychiatric symptoms, it may be desirable to find a state of signal transduction that stabilizes G-protein-linked receptor output somewhere between too much and too little downstream action. For this reason, partial agonists are also called "stabilizers" since they have the theoretical capacity to find a stable solution between the extremes of too much full agonist action and no agonist action at all (Figure 2-7).

Since partial agonists exert an effect less than that of a full agonist, they are also sometimes called "weak," with the implication that partial agonism means partial clinical efficacy. That is certainly possible in some cases, but it is more sophisticated to understand the potential stabilizing and "tuning" actions of this class of therapeutic agents, and not to use terms that imply clinical actions for the entire class of drugs that may only apply to some individual agents. Several partial agonists are utilized in clinical practice (Table 2-4) and more are in clinical development.

Light and Dark as an Analogy for Partial Agonists

It was originally conceived that a neurotransmitter could only act at receptors like a light switch, turning things on when the neurotransmitter is present and turning things off when the neurotransmitter is absent. We now know that many receptors, including the G-protein-linked receptor family, can function rather more like a rheostat. That is, a full agonist will turn the lights all the way on (Figure 2-8A), but a partial agonist will only turn the light on partially (Figure 2-8B). If neither full agonist nor partial agonist is present, the room is dark (Figure 2-8C).

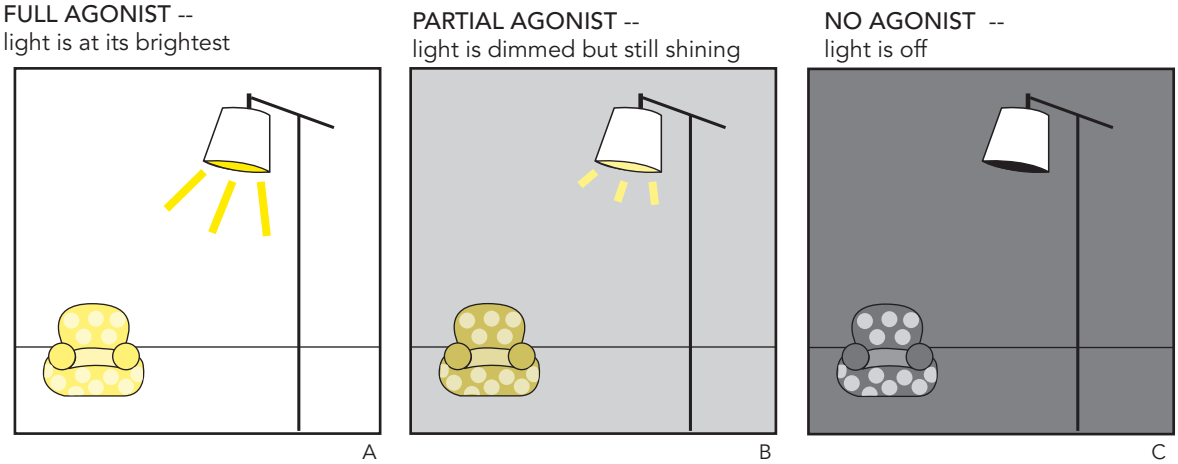


Figure 2-8 Agonist spectrum: rheostat. A useful analogy for the agonist spectrum is a light controlled by a rheostat. The light will be brightest after a full agonist turns the light switch fully on (left panel). A partial agonist will also act as a net agonist and turn the light on, but only partially, according to the level preset in the partial agonist's rheostat (middle panel). If the light is already on, a partial agonist will "dim" the lights, thus acting as a net antagonist. When no full or partial agonist is present, the situation is analogous to the light being switched off (right panel).

Each partial agonist has its own set point engineered into the molecule, such that it cannot turn the lights on brighter even with a higher dose. No matter how much partial agonist is given, only a certain degree of brightness will result. A series of partial agonists will differ one from the other in the degree of partiality, so that theoretically all degrees of brightness can be covered within the range from "off" to "on," but each partial agonist has its own unique degree of brightness associated with it.

What is so interesting about partial agonists is that they can appear as a net agonist, or as a net antagonist, depending upon the amount of naturally occurring full agonist neurotransmitter that is present. Thus, when a full agonist neurotransmitter is absent, a partial agonist will be a net agonist. That is, from the resting state, a partial agonist initiates somewhat of an increase in the signal transduction cascade from the G-protein-linked second-messenger system. However, when full agonist neurotransmitter is present, the same partial agonist will become a net antagonist. That is, it will decrease the level of full signal output to a lesser level, but not to zero. Thus, a partial agonist can simultaneously *boost* deficient neurotransmitter activity yet *block* excessive neurotransmitter activity, another reason that partial agonists are called stabilizers.

Returning to the light-switch analogy, a room will be dark when agonist is missing and the light switch is off (Figure 2-8C). A room will be brightly lit when it is full of natural full agonist and the light switch is fully on (Figure 2-8A). Adding partial agonist to the dark room where there is no natural full agonist neurotransmitter will turn the lights up, but only as far as the partial agonist works on the rheostat (Figure 2-8B). Relative to the dark room as a starting point, a partial agonist acts therefore as a net agonist. On the other hand, adding a partial agonist to the fully lit room will have the effect of turning the lights down to the intermediate level of lower brightness on the rheostat (Figure 2-8B). This is a net antagonistic effect relative to the fully lit room. Thus, after adding partial agonist to the dark room and to the brightly lit room, both rooms will be equally lit. The degree of brightness is that of being partially turned on as dictated by the properties of the partial agonist. However, in the dark room, the partial agonist has acted as a net agonist, whereas in the brightly lit room, the partial agonist has acted as a net antagonist.

Having an agonist and an antagonist in the same molecule is quite an interesting dimension to therapeutics. This concept has led to proposals that partial agonists could treat not only states which are theoretically deficient in full agonist, but also states that are theoretically with an excess of full agonist. An agent such as a partial agonist may even be able to treat simultaneously states which are mixtures of both excess and deficiency in neurotransmitter activity.

Inverse Agonists

Inverse agonists are more than simple antagonists, and are neither neutral nor silent. These agents have an action that is thought to produce a conformational change in the G-protein-linked receptor that stabilizes it in a totally inactive form (Figure 2-9). Thus, this conformation produces a functional reduction in signal transduction (Figure 2-9) that is even less than that produced when there is either no agonist present (Figure 2-4), or a silent antagonist present (Figure 2-6). The result of an inverse agonist is to shut down even the constitutive activity of the G-protein-linked receptor system. Of course, if a given receptor system has no constitutive activity, perhaps in cases when receptors are present in low density, there will be no reduction in activity and the inverse agonist will look like an antagonist.

In many ways, therefore, inverse agonists do the *opposite* of agonists. If an agonist increases signal transduction from baseline, an inverse agonist decreases it, even below baseline levels. In contrast to agonists and antagonists, therefore, an *inverse agonist* neither increases signal transduction like an agonist (Figure 2-5) nor merely blocks the agonist from increasing signal transduction like an antagonist (Figure 2-6); rather, an inverse agonist binds the receptor in a fashion so as to provoke an action opposite to that of the agonist, namely causing the receptor to *decrease* its baseline signal transduction level (Figure 2-9). It is unclear from

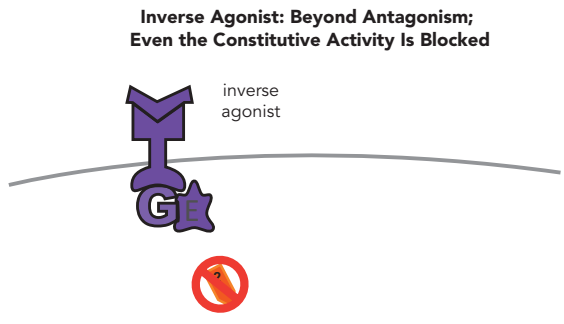


Figure 2-9 Inverse agonist. Inverse agonists produce conformational change in the G-protein-linked receptor that renders it inactive. This leads to reduced signal transduction as compared not only to that associated with agonists but also that associated with antagonists or the absence of an agonist. The impact of an inverse agonist is dependent on the receptor density in that brain region. That is, if the receptor density is so low that constitutive activity does not lead to detectable signal transduction, then reducing the constitutive activity would not have any appreciable effect.

a clinical point of view what the relevant differences are between an inverse agonist and a silent antagonist. In fact, some drugs that have long been considered to be silent antagonists, such as serotonin 2A antagonists and histamine 1 antagonists/antihistamines, may turn out in some areas of the brain actually to be inverse agonists. Thus, the concept of an inverse agonist as clinically distinguishable from a silent antagonist is still evolving and the clinical differentiation between antagonist and inverse agonist remains to be clarified.

In summary, G-protein-linked receptors act along an agonist spectrum, and drugs have been described that can produce conformational changes in these receptors to create any state from full agonist, to partial agonist, to silent antagonist, to inverse agonist (Figure 2-10). When one considers the spectrum of signal transduction along this spectrum (Figure 2-10), it is easy to understand why agents at each point along the agonist spectrum differ so much from each other, and why their clinical actions are so different.

ENZYMES AS SITES OF PSYCHOPHARMACOLOGICAL DRUG ACTION

Enzymes are involved in multiple aspects of chemical neurotransmission, as discussed extensively in Chapter 1 on signal transduction. Every enzyme is the theoretical target for a drug acting as an enzyme inhibitor. However, in practice, only a minority of currently known drugs utilized in the clinical practice of psychopharmacology are enzyme inhibitors.

Enzyme activity is the conversion of one molecule into another, namely a substrate into a product (Figure 2-11). The substrates for each enzyme are very unique and selective, as are the products. A substrate (Figure 2-11A) comes to the enzyme to bind at the enzyme's active site (Figure 2-11B), and departs as a changed molecular entity called the product (Figure 2-11C). The inhibitors of an enzyme are also very unique and selective for one enzyme compared to another. In the

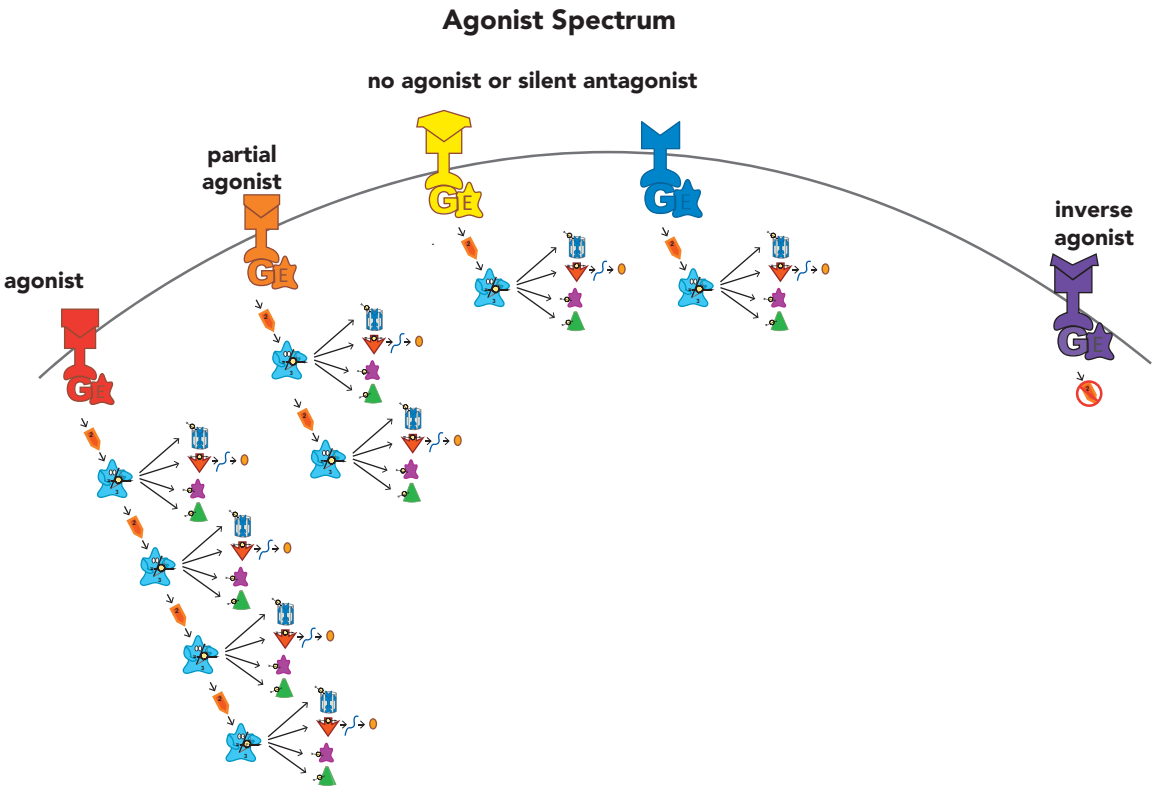


Figure 2-10 Agonist spectrum. This figure summarizes the implications of the agonist spectrum. Full agonists cause maximum signal transduction, while partial agonists increase signal transduction compared to no agonist but decrease it compared to full agonist. Antagonists lead to constitutive activity and thus, in the absence of an agonist, have no effects; in the presence of an agonist, they lead to reduced signal transduction. Inverse agonists are the functional opposites of agonists and actually reduce signal transduction beyond that produced in the absence of an agonist.

presence of an enzyme inhibitor, the enzyme cannot bind to its substrates. The binding of inhibitors can be either irreversible (Figure 2-12) or reversible (Figure 2-13).

When an irreversible inhibitor binds to the enzyme, it cannot be displaced by the substrate; thus, that inhibitor binds irreversibly (Figure 2-12). This is depicted as binding with chains (Figure 2-12A) that cannot be cut with scissors by the substrate (Figure 2-12B). The irreversible type of enzyme inhibitor is sometimes called a "suicide inhibitor" because it covalently and irreversibly binds to the enzyme protein, permanently inhibiting it and therefore essentially "killing" it by thus making the enzyme nonfunctional forever (Figure 2-12). Enzyme activity in this case is only restored when new enzyme molecules are synthesized.

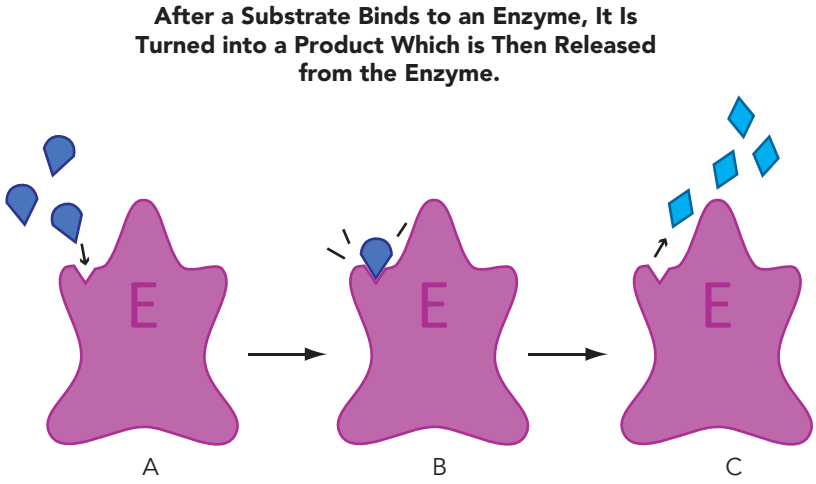


Figure 2-11 **Enzyme activity.** Enzyme activity is conversion of one molecule into another. Thus, a substrate is said to be turned into a product by enzymatic modification of the substrate molecule. The enzyme has an active site at which the substrate can bind specifically (A). The substrate then finds the active site of the enzyme and binds to it (B) so that a molecular transformation can occur, changing the substrate into the product (C).

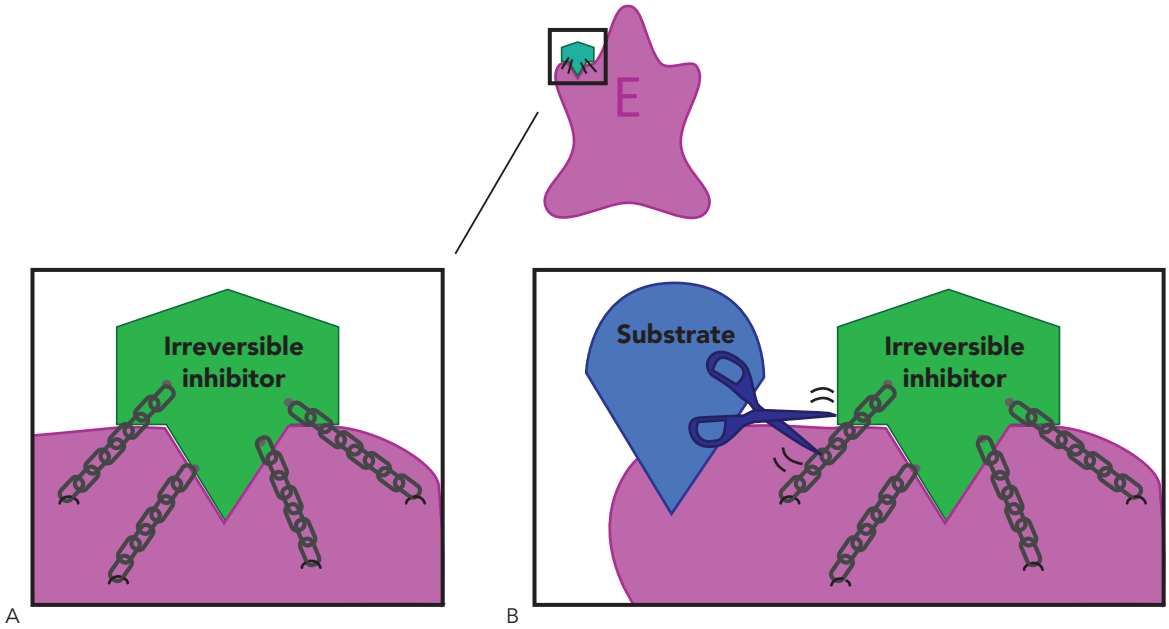


Figure 2-12 **Irreversible enzyme inhibitors.** Some drugs are inhibitors of enzymes. Shown here is an irreversible inhibitor of an enzyme, depicted as binding to the enzyme with chains (A). A competing substrate cannot remove an irreversible inhibitor from the enzyme, depicted as scissors unsuccessfully attempting to cut the chains off the inhibitor (B). The binding is locked so permanently that such irreversible enzyme inhibition is sometimes called the work of a "suicide inhibitor," since the enzyme essentially commits suicide by binding to the irreversible inhibitor. Enzyme activity cannot be restored unless another molecule of enzyme is synthesized by the cell's DNA.

However, in the case of reversible enzyme inhibitors, an enzyme's substrate is able to compete with that reversible inhibitor for binding to the enzyme, and literally shove it off the enzyme (Figure 2-13). Whether the substrate or the inhibitor "wins" or predominates depends upon which one has the greater affinity for the enzyme and/or is present in the greater concentration. Such binding is called "reversible." Reversible enzyme

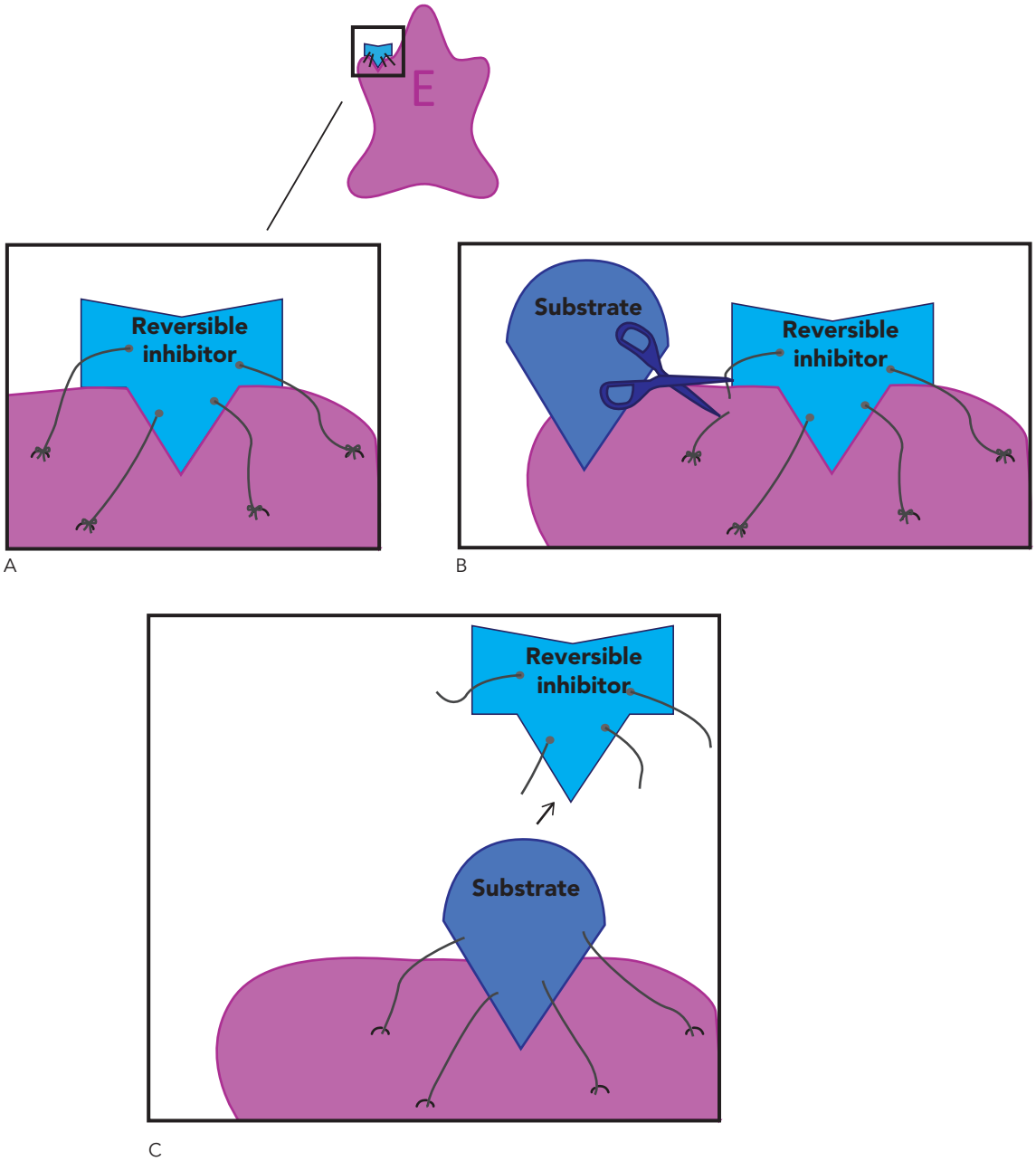


Figure 2-13 Reversible enzyme inhibitors. Other drugs are reversible enzyme inhibitors, depicted as binding to the enzyme with a string (A). A reversible inhibitor can be challenged by a competing substrate for the same enzyme. In the case of a reversible inhibitor, the molecular properties of the substrate are such that it can get rid of the reversible inhibitor, depicted as scissors cutting the string that binds the reversible inhibitor to the enzyme (B). The consequence of a substrate competing successfully for reversal of enzyme inhibition is that the substrate displaces the inhibitor and shoves it off (C). Because the substrate has this capability, the inhibition is said to be reversible.

inhibition is depicted as binding with strings (Figure 2-13A), such that the substrate can cut them with scissors (Figure 2-13B) and displace the enzyme inhibitor, and bind the enzyme itself with its own strings (Figure 2-13C).

These concepts can be applied potentially to any enzyme system. Several enzymes are involved in neurotransmission, including in the synthesis and destruction of neurotransmitters, as well as in signal transduction. Only a few enzymes are known to be targeted by psychotropic drugs currently used in clinical practice, namely monoamine oxidase (MAO), acetylcholinesterase, and glycogen synthase kinase (GSK). MAO inhibitors are discussed in more detail in Chapter 7 on treatments for mood disorders and acetylcholinesterase inhibitors are discussed in more detail in Chapter 12 on dementia. Briefly, regarding GSK, the antimanic agent lithium may target this important enzyme in the signal transduction pathway of neurotrophic factors (Figure 2-14). That is, some neurotrophins, growth factors, and other signaling pathways act through a specific downstream phosphoprotein, an enzyme called GSK-3 (glycogen synthase kinase), to promote cell death (so-called proapoptotic actions). Lithium has the capacity to inhibit this enzyme (Figure 2-14B). It is possible that inhibition of GSK-3 is physiologically relevant, because this action could lead to neuroprotective actions, long-term plasticity, and may contribute to the antimanic and mood-stabilizing actions known to be associated with lithium. It is also possible that the antimanic agent valproate and the neurostimulatory treatment for depression ECT (electroconvulsive therapy) may have actions on GSK-3 as well (Figure 2-14B). The development of novel GSK-3 inhibitors is in progress.

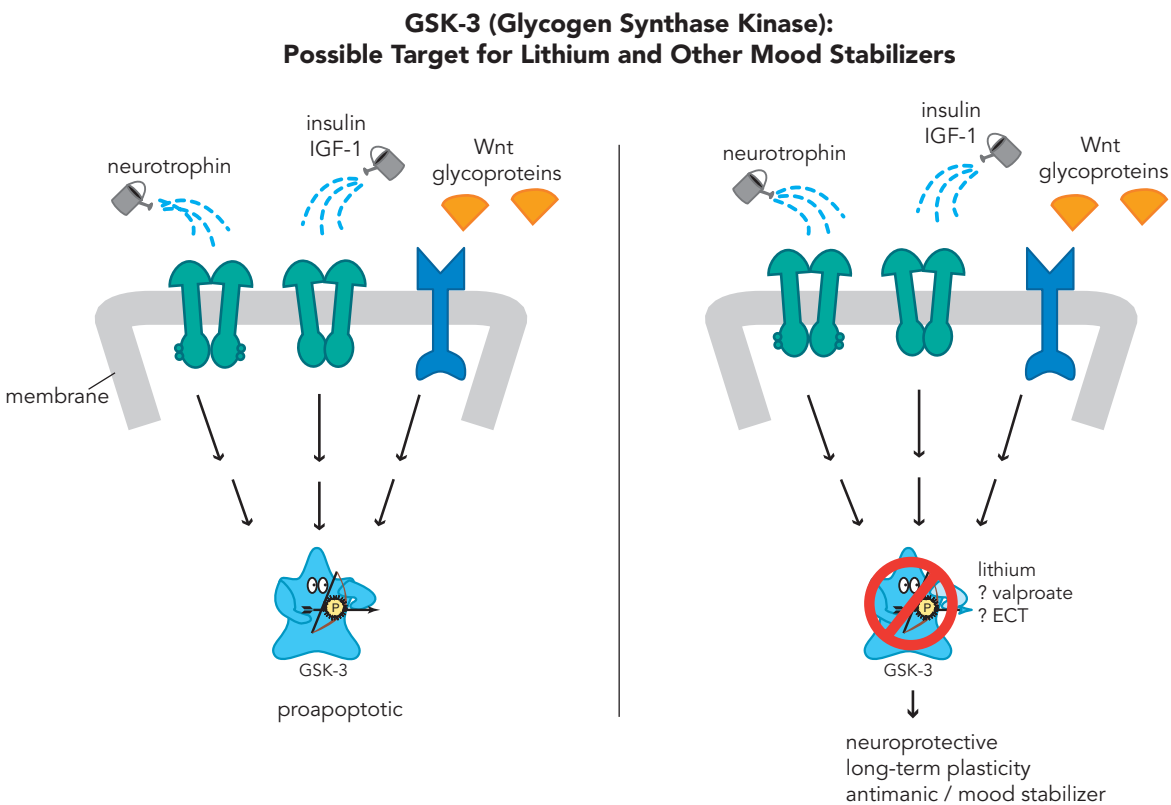


Figure 2-14 Receptor tyrosine kinases. Receptor tyrosine kinases are potential targets for novel psychotropic drugs. Left: Some neurotrophins, growth factors, and other signaling pathways act through a downstream phosphoprotein, an enzyme called GSK-3 (glycogen synthase kinase), to promote cell death (proapoptotic actions). Right: Lithium and possibly some other mood stabilizers may inhibit this enzyme, which could lead to neuroprotective actions and long-term plasticity as well as possibly contribute to mood-stabilizing actions.

CYTOCHROME P450 DRUG METABOLIZING ENZYMES AS TARGETS OF PSYCHOTROPIC DRUGS

Pharmacokinetic actions are mediated through the hepatic and gut drug metabolizing system known as the cytochrome P450 (CYP450) enzyme system. *Pharmacokinetics* is the study of how the body acts upon drugs, especially to absorb, distribute, metabolize, and excrete them. The CYP450 enzymes and the *pharmacokinetic* actions they represent must be contrasted with the *pharmacodynamic* actions of drugs, the latter being the major emphasis of this book. Pharmacodynamic actions at the specific drug targets discussed earlier in this chapter and also in Chapter 3 are known as the mechanism of action of psychotropic drugs, and account for the therapeutic effects and side effects of drugs. However, most psychotropic drugs also target the CYP450 drug metabolizing enzymes either as a substrate, inhibitor, and/or inducer, and a brief overview of these enzymes and their interactions with psychotropic drugs is in order.

CYP450 enzymes follow the same principles of enzymes transforming substrates into products as illustrated in Figures 2-11 through 2-13. Figure 2-15 depicts the concept of a psychotropic drug being absorbed through the gut wall on the left and then sent to the big blue enzyme in the liver to be biotransformed so that the drug can be sent back into the bloodstream to be excreted from the body via the kidney. Specifically, CYP450 enzymes in the gut wall or liver convert the drug substrate into a biotransformed product in the bloodstream. After passing through the gut wall and liver, the drug will exist partially as unchanged drug and partially as biotransformed product in the bloodstream (Figure 2-15).

There are several known CYP450 systems. Six of the most important enzymes for psychotropic drug metabolism are shown in Figure 2-16. There are over 30 known CYP450 enzymes, and probably many more awaiting discovery and classification. Not all individuals have all the same genetic form of the CYP450 enzymes and types of enzyme for any individual can now be readily determined with pharmacogenetic testing. These enzymes are collectively responsible for the degradation of a large number of psychotropic drugs, and variations in the genes encoding for the different CYP450 enzymes can alter the activity of these enzymes, resulting in alterations of drug levels at standard doses. Most individuals have "normal" rates of drug metabolism from the major CYP450 enzymes and are said to be "extensive metabolizers"; most drug doses are set for these individuals. However, some individuals have genetic variants of these enzymes and may be either intermediate metabolizers or poor metabolizers, with reduced enzyme activity that can result in increased risk for elevated drug levels, drug–drug interactions, and

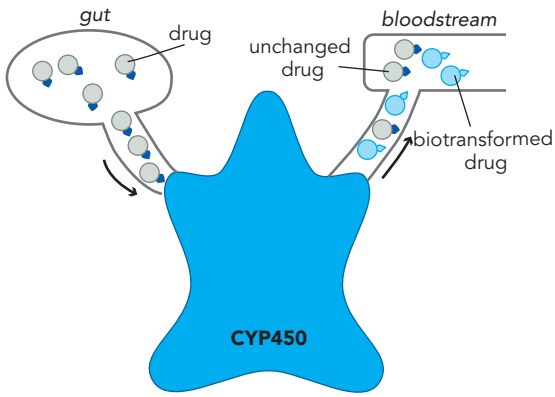


Figure 2-15 CYP450. The cytochrome P450 (CYP450) enzyme system mediates how the body metabolizes many drugs, including antipsychotics. The CYP450 enzyme in the gut wall or liver converts the drug into a biotransformed product in the bloodstream. After passing through the gut wall and liver (left), the drug will exist partly as unchanged drug and partly as biotransformed drug (right).

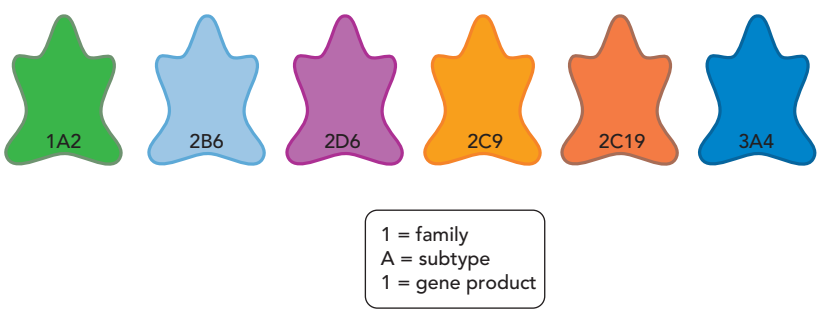


Figure 2-16 Six CYP450 enzymes. There are many cytochrome P450 (CYP450) systems; these are classified according to family, subtype, and gene product. Five of the most important are shown here, and include CYP450 1A2, 2B6, 2D6, 2C9, 2C19, and 3A4.

reduced amounts of active metabolites. Such patients may require less than standard doses of drugs metabolized by their variant CYP450 enzymes. On the other hand, some patients can also be ultra-rapid metabolizers, with elevated enzyme activity, subtherapeutic drug levels, and poor efficacy with standard doses. When genetic variations are unknown, it can lead to altered efficacy and side effects of psychotropic drugs. Since the genes for these CYP450 enzymes can now be readily measured and used to predict which patients might need to have dosage adjustments of certain drugs up or down, the practice of psychopharmacology is increasingly moving to the measurement of genes for drug metabolism, especially in patients who do not respond or do not tolerate standard doses of psychotropic drugs. This is called genotyping the patient for pharmacogenomic use. Sometimes it is useful to couple genotyping with therapeutic drug monitoring that can detect the actual levels of drug in the blood and thus confirm the predictions from genetic testing of which CYP450 enzyme type has been shown to be present. The use of pharmacogenomic testing in combination with therapeutic drug monitoring (sometimes also called phenotyping) can help in the management particularly of treatment-resistant patients.

Drug interactions mediated by CYP450 enzymes and their genetic variants are constantly being discovered, and the active clinician who combines drugs must be alert to these, and thus be continually updated on what drug interactions are important. Here we present only the general concepts of drug interactions at CYP450 enzyme systems, but the specifics should be found in a comprehensive and up-to-date comprehensive reference source (such as *Stahl's Essential Psychopharmacology: the Prescriber's Guide*, a companion to this textbook) before prescribing.

SUMMARY

Nearly a third of psychotropic drugs in clinical practice bind to a neurotransmitter transporter, and another third of psychotropic drugs bind to G-protein-linked receptors. These two molecular sites of action, their impact upon neurotransmission, and various specific drugs that act at these sites have all been reviewed in this chapter.

Specifically, there are two subclasses of plasma membrane transporters for neurotransmitters and three subclasses of intracellular synaptic vesicle transporters for neurotransmitters. The monoamine transporters (SERT for serotonin, NET for norepinephrine, and DAT for dopamine) are key targets for most of the known drugs that treat unipolar depression, ADHD, and numerous other disorders ranging from anxiety to pain. The vesicular transporter for all three of these monoamines is known as VMAT2 (vesicular monoamine transporter 2), which not only stores monoamines and histamine in synaptic vesicles, but is also inhibited by drugs recently introduced to treat movement disorders such as tardive dyskinesia.

G-protein receptors are the most common targets of psychotropic drugs, and their actions can lead to both therapeutic effects and side effects. Drug actions at these receptors occur in a spectrum, from full agonist actions, to partial agonist actions, to antagonism, and even to inverse agonism. Natural neurotransmitters are full agonists, and so are some drugs used in clinical practice. However, most drugs that act directly on G-protein-linked receptors act as antagonists. A few act as partial agonists, and some as inverse agonists. Each drug interacting at a G-protein-linked receptor causes a conformational change in that receptor that defines where on the agonist spectrum it will act. Thus, a full agonist produces a conformational change that turns on signal transduction and second-messenger formation to the maximum extent. One novel concept is that of a partial agonist, which acts somewhat like an agonist, but to a lesser extent. An antagonist causes a conformational change that stabilizes the receptor in the baseline state and thus is "silent." In the presence of agonists or partial agonists, an antagonist causes the receptor to return to this baseline state as well, and thus reverses their actions. A novel receptor action is that of an inverse agonist, which leads to a conformation of the receptor that stops all activity, even baseline actions. Understanding the agonist spectrum can lead to prediction of downstream consequences on signal transduction, including clinical actions.

Finally, a minority of psychotropic drugs target enyzmes for their therapeutic effects. Several enzymes are involved in neurotransmission, including in the synthesis and destruction of neurotransmitters as well as in signal transduction, but in practice only three are known to be targeted by psychotropic drugs. A larger portion of psychotropic drugs target the cytochrome P450 drug metabolizing enzymes, which is relevant to their pharmacokinetic profiles but not their pharmacodynamic profiles.

3 Ion Channels as Targets of Psychopharmacological Drug Action

Ligand-Gated Ion Channels as Targets of Psychopharmacological Drug Action 51
Ligand-Gated Ion Channels, Ionotropic Receptors, and Ion-Channel-Linked Receptors 51
Ligand-Gated Ion Channels: Structure and Function 53
Pentameric Subtypes 53
Tetrameric Subtypes 54
The Agonist Spectrum 56
Different States of Ligand-Gated Ion Channels 63
Allosteric Modulation: PAMs and NAMs 64
Voltage-Sensitive Ion Channels as Targets of Psychopharmacological Drug Action 66
Structure and Function 66
VSSCs (Voltage-Sensitive Sodium Channels) 67
VSCCs (Voltage-Sensitive Calcium Channels) 70
Ion Channels and Neurotransmission 73
Summary 76

Many important psychopharmacological drugs target ion channels. The role of ion channels as important regulators of synaptic neurotransmission has been covered in Chapter 1. Here we discuss how targeting these molecular sites causes alterations in synaptic neurotransmission that are linked in turn to the therapeutic actions of various psychotropic drugs. Specifically, we will cover ligand-gated ion channels and voltage-sensitive ion channels as targets of psychopharmacological drug action.

LIGAND-GATED ION CHANNELS AS TARGETS OF PSYCHOPHARMACOLOGICAL DRUG ACTION

Ligand-Gated Ion Channels, Ionotropic Receptors, and Ion-Channel-Linked Receptors

The terms ligand-gated ion channels, ionotropic receptors, and ion-channel-linked receptors are in fact different terms for the same receptor/ion-channel complex. Ions normally cannot penetrate membranes because of their charge. In order to selectively control access of ions into and out of neurons, their membranes are decorated with all sorts of ion channels. The most important ion channels in psychopharmacology regulate calcium, sodium, chloride, and potassium. Many can be modified by various drugs, and this will be discussed throughout this chapter.

There are two major classes of ion channels, and each class has several names. One class of ion channels is opened by neurotransmitters and goes by the names *ligand-gated ion channels*, *ionotropic receptors*, and *ion-channel-linked receptors*. These channels and their associated receptors will be discussed next. The other major class of ion channel is opened by the charge or voltage across the membrane and is called either a *voltage-gated* or a *voltage-sensitive* ion channel, and these will be discussed later in this chapter.

Ion channels that are opened and closed by actions of neurotransmitter ligands at receptors acting as gatekeepers are shown conceptually in Figure 3-1. When a neurotransmitter binds to a gatekeeper receptor on an ion channel, that neurotransmitter causes a conformational change in the receptor that opens the ion channel (Figure 3-1A). A neurotransmitter, drug, or hormone that binds to a receptor is sometimes called a *ligand* (literally, "tying"). Thus, ion channels linked to receptors that regulate their opening and closing are often called *ligand-gated ion channels*. Since these ion channels are also receptors, they are also sometimes also called *ionotropic receptors* or *ion-channel linked* receptors. These terms will be used interchangeably with ligand-gated ion channels here.

Numerous drugs act at many sites around such receptor/ion-channel complexes, leading to a wide variety of modifications of receptor/ion-channel actions. These modifications not only immediately alter the flow of ions through the channels, but with a delay can also change the downstream events that result from transduction of the signal that begins at these receptors. The downstream actions have been extensively discussed in Chapter 1 and include both activation and inactivation

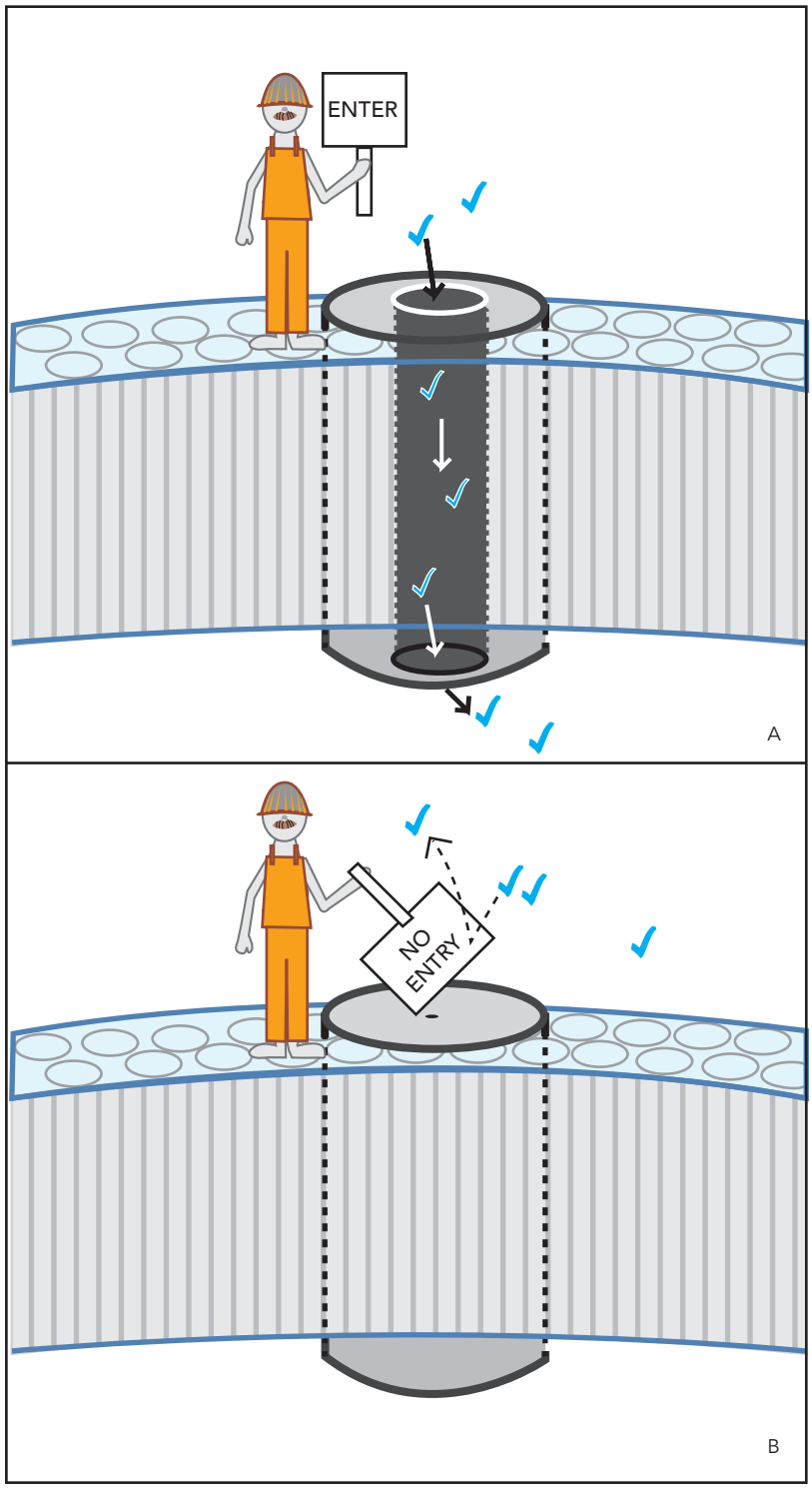


Figure 3-1 Ligand-gated ion-channel gatekeeper. This schematic shows a ligand-gated ion channel. In panel A, a receptor is serving as a molecular gatekeeper that acts on instruction from neurotransmission to open the channel and allow ions to travel into the cell. In panel B, the gatekeeper is keeping the channel closed so that ions cannot get into the cell. Ligand-gated ion channels are a type of receptor that forms an ion channel and are thus also called ion-channel-linked receptors or ionotropic receptors.

of phosphoproteins, shifting the activity of enzymes, the sensitivity of receptors, and the conductivity of ion channels. Other downstream actions include changes in gene expression and thus changes in which proteins are synthesized and which functions are amplified. Such functions can range from synaptogenesis, to receptor and enzyme synthesis, to communication with downstream neurons innervated by the neuron with the ionotropic receptor, and many more. The reader should have a good command of the function of signal transduction pathways described in Chapter 1 in order to understand how drugs acting at ligand-gated ion channels modify the signal transduction that arises from these receptors.

Drug-induced modifications in signal transduction from ionotropic (sometimes called ionotrophic) receptors can have profound actions on psychiatric symptoms. About a fifth of psychotropic drugs currently utilized in clinical practice, including many drugs for the treatment of anxiety and insomnia such as the benzodiazepines, are known to act at these receptors. Because ionotropic receptors immediately change the flow of ions, drugs that act on these receptors can have an almost immediate effect, which is why many drugs for anxiety and for sleep that act at these receptors may have immediate clinical onset. This is in contrast to the actions of many drugs at G-protein-linked receptors described in Chapter 2, some of which have clinical effects – such as actions on mood – that may occur with a delay necessitated by awaiting initiation of changes in cellular functions activated through the signal transduction cascade. Here we will describe how various drugs stimulate or block various molecular sites around the receptor/ion-channel complex. Throughout the textbook we will show how specific drugs acting at specific ionotropic receptors have specific actions on specific psychiatric disorders.

Ligand-Gated Ion Channels: Structure and Function

Are ligand-gated ion channels receptors or ion channels? The answer is "yes" – ligand-gated ion channels are both a type of receptor and they also form an ion channel. That is why they are called not only a channel (ligand-gated ion channel) but also a receptor (ionotropic receptor and ion-channel-linked receptor). These terms try to capture the dual function of these ion channels/receptors and may explain why there is more than one term for this receptor/ion-channel complex.

Ligand-gated ion channels are comprised of several long strings of amino acids assembled as subunits around an ion channel. Decorated on these subunits are also multiple binding sites for everything from neurotransmitters to ions to drugs. That is, these complex proteins have several sites where some ions travel through a channel and others also bind to the channel; where one neurotransmitter or even two cotransmitters act at separate and distinct binding sites; where numerous allosteric modulators – i.e., natural substances or drugs that bind to a site different than where the neurotransmitter binds – increase or decrease the sensitivity of channel opening.

Pentameric Subtypes

Many ligand-gated ion channels are assembled from five protein subunits, and that is why they are called pentameric. The subunits for pentameric subtypes of ligand-gated ion channels each have four transmembrane regions (Figure 3-2A). These membrane proteins go in and out of the membrane four times (Figure 3-2A). When five copies of these subunits are selected (Figure 3-2B), they come together in space to form a fully functional pentameric receptor with the ion channel in the middle (Figure 3-2C). The receptor sites are in various locations on each of the subunits; some binding sites are in the channel, but many are present at different locations outside the channel. This pentameric structure is typical for $GABA_A$ receptors, nicotinic cholinergic receptors, serotonin $5HT_3$ receptors, and certain glycine receptors (Table 3-1). Drugs that act directly on pentameric ligand-gated ion channels are listed in Table 3-2.

If this structure were not complicated enough, pentameric ionotropic receptors actually have many different subtypes. Subtypes of pentameric ionotropic receptors are defined based upon which forms of each of the five subunits are chosen for assembly into a fully

Table 3-1 Pentameric ligand-gated ion channels

Four transmembrane regions Five subunits	
Neurotransmitter	*Receptor subtype*
Acetylcholine	Nicotinic receptors (e.g. α_7 nicotinic receptors; $\alpha_4\beta_2$ nicotinic receptors)
GABA	$GABA_A$ receptors (e.g. α_1 subunits; γ subunits; δ subunits)
Glycine	Strychnine-sensitive glycine receptors
Serotonin	$5HT_3$ receptors

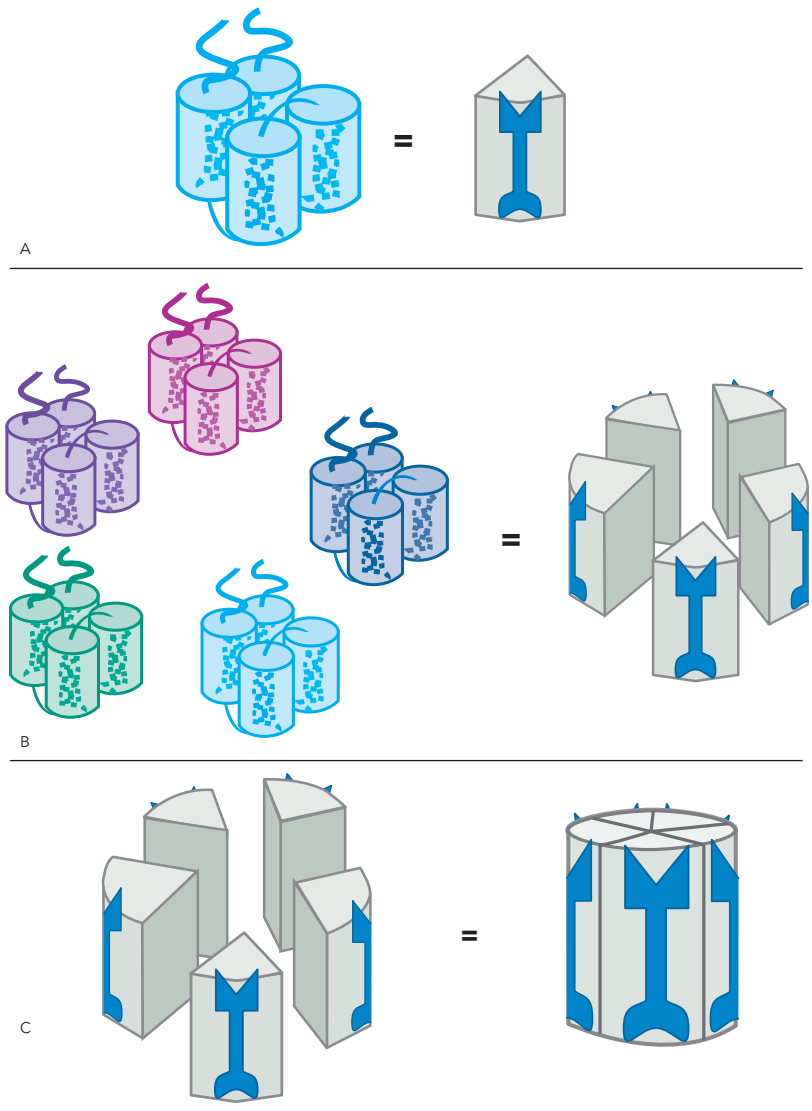


Figure 3-2 Ligand-gated ion channel structure. The four transmembrane regions of a single subunit of a pentameric ligand-gated ion channel form a cluster, as shown in panel A. An icon for this subunit is shown on the right in panel A. Five copies of the subunits come together in space (panel B) to form a functional ion channel in the middle (panel C). Ligand-gated ion channels have receptor binding sites located on all five subunits, both inside and outside the channel.

constituted receptor. That is, there are several subtypes for each of the four transmembrane subunits, making it possible to piece together several different constellations of fully constituted receptors. Although the natural neurotransmitter binds to every subtype of ionotropic receptor, some drugs used in clinical practice, and many more in clinical trials, are able to bind selectively to one or more of these subtypes, but not to others. This may have functional and clinical consequences. Specific receptor subtypes and the specific drugs that bind to them selectively are discussed in chapters that cover their specific clinical use.

Tetrameric Subtypes

Ionotropic glutamate receptors have a different structure from the pentameric ionotropic receptors just discussed. The ligand-gated ion channels for glutamate are comprised of subunits that have three full transmembrane regions and a fourth re-entrant loop (Figure 3-3A), rather than four full transmembrane regions as shown in Figure 3-2A. When four copies of these subunits are selected (Figure 3-3B), they come together in space to form a fully functional ion channel in the middle with the four re-entrant loops lining the ion channel (Figure 3-3C). Thus, tetrameric subtypes of

Table 3-2 Key ligand-gated ion channels directly targeted by psychotropic drugs

Neurotransmitter	Ligand-gated ion channel receptor subtype directly targeted	Pharmacological action	Drug class	Therapeutic action
Acetylcholine	$Alpha_4$ $Beta_2$ nicotinic	Partial agonist	Nicotinic receptor partial agonist (NRPA) (varenicline)	Smoking cessation
GABA	$GABA_A$ benzodiazepine receptors	Full agonist, phasic inhibition	Benzodiazepines	Anxiolytic
	$GABA_A$ non-benzodiazepine PAM sites	Full agonist, phasic inhibition	"Z DRUGS"/hypnotics (zolpidem, zaleplon, zopiclone, eszopiclone)	Improves insomnia
	$GABA_A$ neurosteroid sites (benzodiazepine insensitive)	Full agonist, tonic inhibition	Neuroactive steroids (allopregnanolone)	Postpartum depression Rapid-acting antidepressant Anesthetic
Glutamate	NMDA NAM channel sites/ Mg^{++} sites	Antagonist	NMDA glutamate antagonist (memantine)	Pro-cognitive in Alzheimer disease
	NMDA open-channel sites	Antagonist	PCP/phencyclidine Ketamine Dextromethorphan Dextromethadone	Dissociative hallucinogen Anesthetic Pseudobulbar affect Agitation in Alzheimer disease Rapid-acting antidepressant Treatment-resistant depression
Serotonin	$5HT_3$	Antagonist	Mirtazapine Vortioxetine	Pro-cognitive Antidepressant
	$5HT_3$	Antagonist	Anti-emetic	Reduce chemotherapy-induced emesis

PAM, positive allosteric modulator; NAM, negative allosteric modulator; NMDA, *N*-methyl-D-aspartate; Mg, magnesium.

ion channels (Figure 3-3) are analogous to pentameric subtypes of ion channels (Figure 3-2A), but just have four subunits rather than five. Receptor sites are in various locations on each of the subunits; some binding sites are in the channel, but many are present at different locations outside the channel.

This tetrameric structure is typical of the ionotropic glutamate receptors known as AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid), kainate, and NMDA (*N*-methyl-D-aspartate) subtypes (Table 3-3). Drugs that act directly at tetrameric ionotropic glutamate receptors are listed in Table 3-2. Receptor subtypes for glutamate according to the selective agonist acting at that receptor as well as the specific molecular subunits that comprise that subtype are listed in Table 3-3. Subtype selective drugs for ionotropic glutamate receptors are under investigation but not currently used in clinical practice.

Table 3-3 Tetrameric ligand-gated ion channels

Three transmembrane regions and one re-entrant loop Four subunits	
Neurotransmitter	***Receptor subtype***
Glutamate	AMPA (e.g. GluR1–4 subunits)
	KAINATE (e.g. GluR5–7, KA1–2 subunits)
	NMDA (e.g. NMDAR1, NMDAR2A–D, NMDAR3A subunits)

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; NMDA, *N*-methyl-D-aspartate.

The Agonist Spectrum

The concept of an agonist spectrum for G-protein-linked receptors discussed extensively in Chapter 2 can also be applied to ligand-gated ion channels (Figure 3-4). Thus, *full agonists* change the conformation of the receptor to open the ion channel the maximal frequency allowed by that binding site (Figure 3-5). This then triggers the maximal amount of downstream signal transduction possible to be mediated by this binding site. The ion channel can open to an even greater extent (i.e., more frequently) than with a full agonist alone, but this requires the help of a second receptor site, that of a positive allosteric modulator (PAM) as will be shown later.

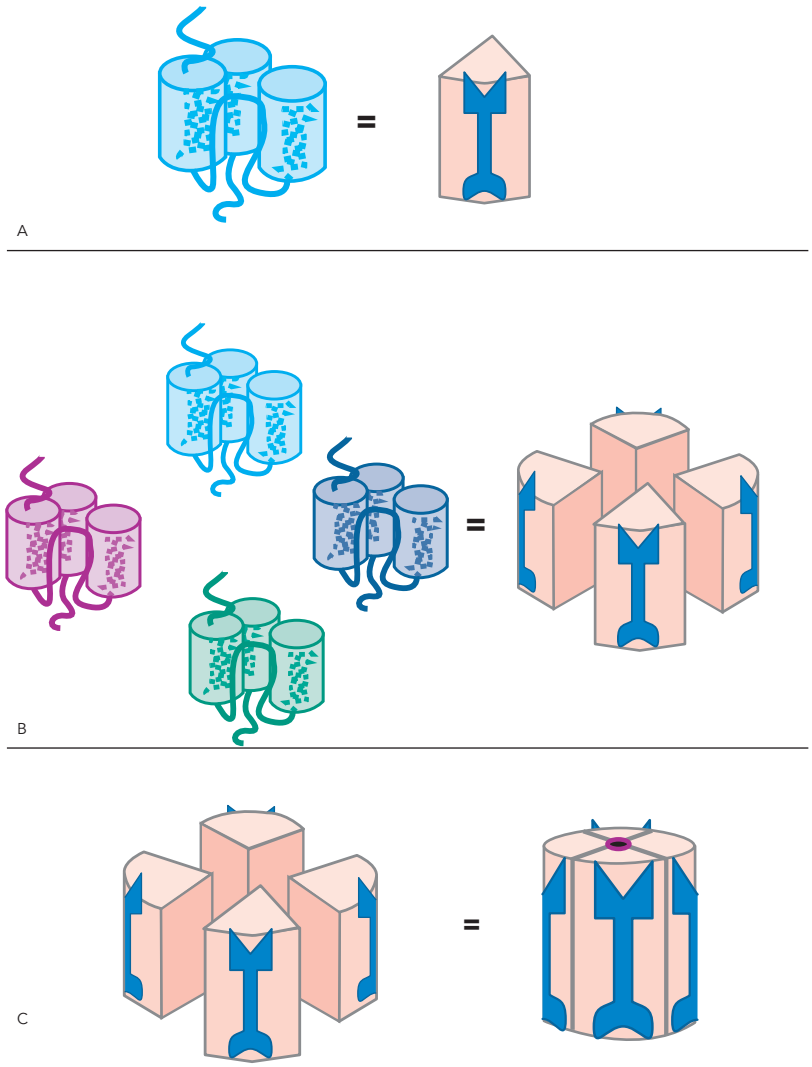


Figure 3-3 Tetrameric ligand-gated ion channel structure. A single subunit of a tetrameric ligand-gated ion channel is shown to form a cluster in panel A, with an icon for this subunit shown on the right in panel A. Four copies of these subunits come together in space (panel B) to form a functional ion channel in the middle (panel C). Ligand-gated ion channels have receptor binding sites located on all four subunits, both inside and outside the channel.

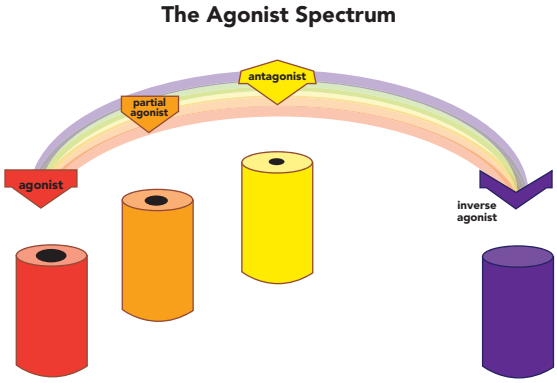


Figure 3-4 Agonist spectrum. The agonist spectrum and its corresponding effects on the ion channel are shown here. This spectrum ranges from agonists (on the far left), which open the channel the maximal frequency allowed by that binding site (depicted for simplicity's sake with a wider opening), through antagonists (middle of the spectrum), which retain the resting state with infrequent opening of the channel, to inverse agonists (on the far right), which put the ion channel into a closed and inactive state. Between the extremes of agonist and antagonist are partial agonists, which increase the degree and frequency of ion-channel opening as compared to the resting state, but not as much as a full agonist. Antagonists can block anything in the agonist spectrum, returning the ion channel to the resting state in each instance.

Antagonists stabilize the receptor in the resting state (Figure 3-6B), which is the same as the state of the receptor in the absence of agonist (Figure 3-6A). Since there is no difference between the presence and absence of the antagonist, the antagonist is said to be neutral or silent. The resting state is not a fully closed ion channel, so there is some degree of ion flow through the channel even in the absence of agonist (Figure 3-6A) and even in the presence of antagonist (Figure 3-6B). This is due to occasional and infrequent opening of the channel even when an agonist is not present and even when an antagonist is present. This is called constitutive activity and is also discussed in Chapter 2 for G-protein-linked receptors. Antagonists of ion-channel-linked receptors reverse the action of agonists (Figure 3-7) and bring the receptor conformation back to the resting baseline state, but do not block any constitutive activity.

Partial agonists produce a change in receptor conformation such that the ion channel opens to a greater extent and more frequently than in its resting state but less than in the presence of a full agonist (Figures 3-8 and 3-9). An antagonist reverses a partial agonist, just like it reverses a full agonist, returning the receptor to its resting state (Figure 3-10). Partial agonists thus produce

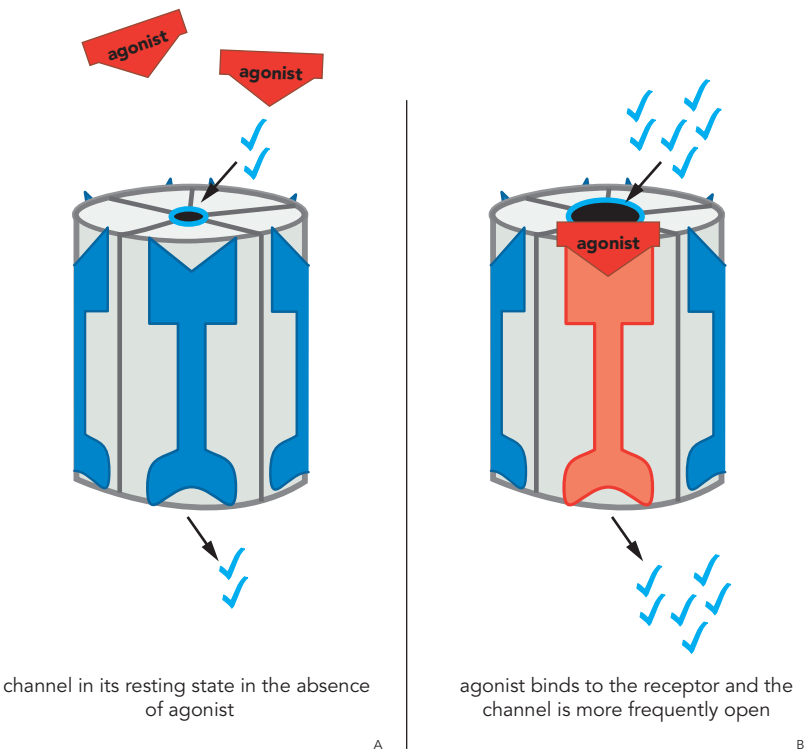
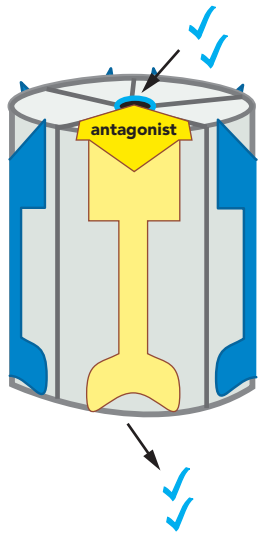


Figure 3-5 Actions of an agonist. In panel A, the ion channel is in its resting state, during which the channel opens infrequently (constitutive activity). In panel B, the agonist occupies its binding site on the ligand-gated ion channel, increasing the frequency at which the channel opens. This is represented as the red agonist turning the receptor red and opening the ion channel.



channel in its resting state

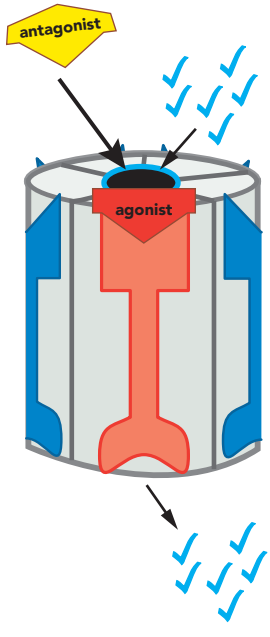
A



antagonist binds to the receptor, not affecting the frequency of opening of the channel compared to the resting state of no agonist

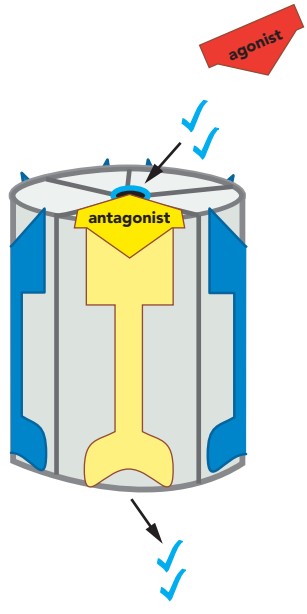
B

Figure 3-6 **Antagonists acting alone.** In panel A, the ion channel is in its resting state, during which the channel opens infrequently. In panel B, the antagonist occupies the binding site normally occupied by the agonist on the ligand-gated ion channel. However, there is no consequence to this, and the ion channel does not affect the degree or frequency of opening of the channel compared to the resting state. This is represented as the yellow antagonist docking into the binding site and turning the receptor yellow but not affecting the state of the ion channel.



the agonist causes the channel to become open more frequently

A



the antagonist takes over and puts the channel back into the resting state

B

Figure 3-7 **Antagonist acting in the presence of agonist.** In panel A, the ion channel is bound by an agonist, which causes it to open at a greater frequency than in the resting state. This is represented as the red agonist turning the receptor red and opening the ion channel as it docks into its binding site. In panel B, the yellow antagonist prevails and shoves the red agonist off the binding site, reversing the agonist's actions and restoring the resting state. Thus, the ion channel has returned to its status before the agonist acted.

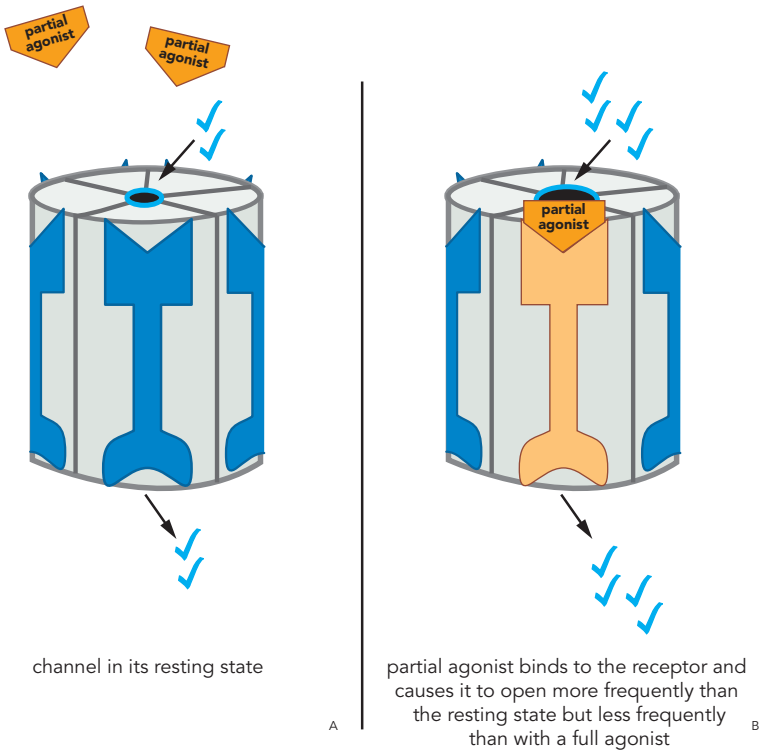


Figure 3-8 **Actions of a partial agonist.** In panel A, the ion channel is in its resting state and opens infrequently. In panel B, the partial agonist occupies its binding site on the ligand-gated ion channel and produces a conformational change such that the ion channel opens to a greater extent and at a greater frequency than in the resting state, though less than in the presence of a full agonist. This is depicted by the orange partial agonist turning the receptor orange and partially but not fully opening the ion channel.

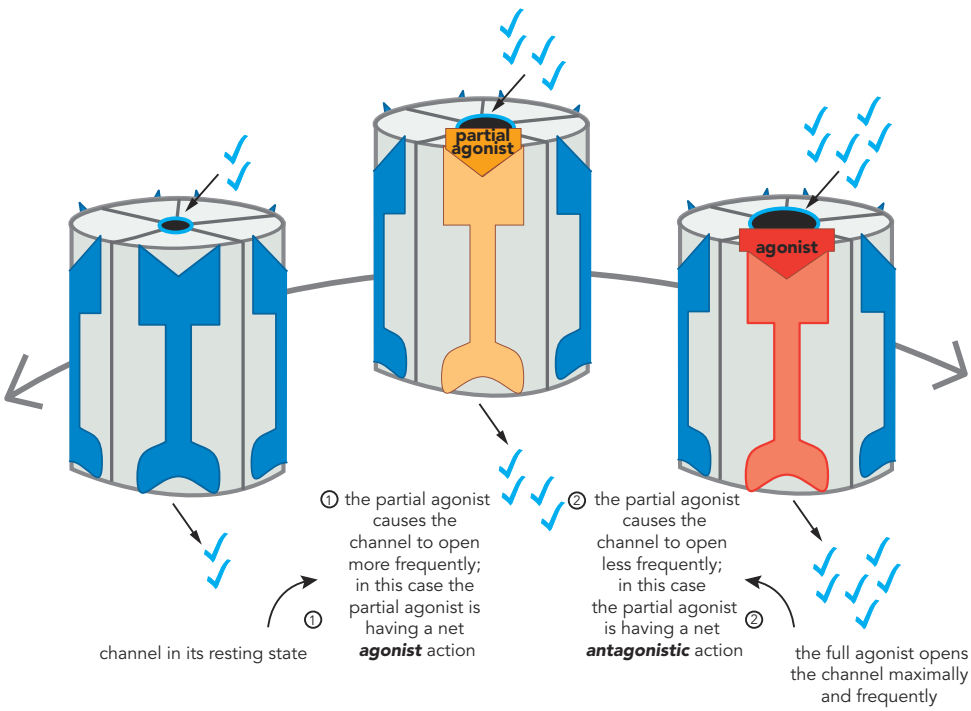


Figure 3-9 **Net effect of partial agonist.** Partial agonists act either as net agonists or as net antagonists, depending on the amount of agonist present. When full agonist is absent (on the far left), a partial agonist causes the channel to open more frequently as compared to the resting state; thus, the partial agonist is having a net agonist action (moving from left to right). However, in the presence of a full agonist (on the far right), a partial agonist decreases the frequency of channel opening in comparison to the full agonist and thus acts as a net antagonist (moving from right to left).

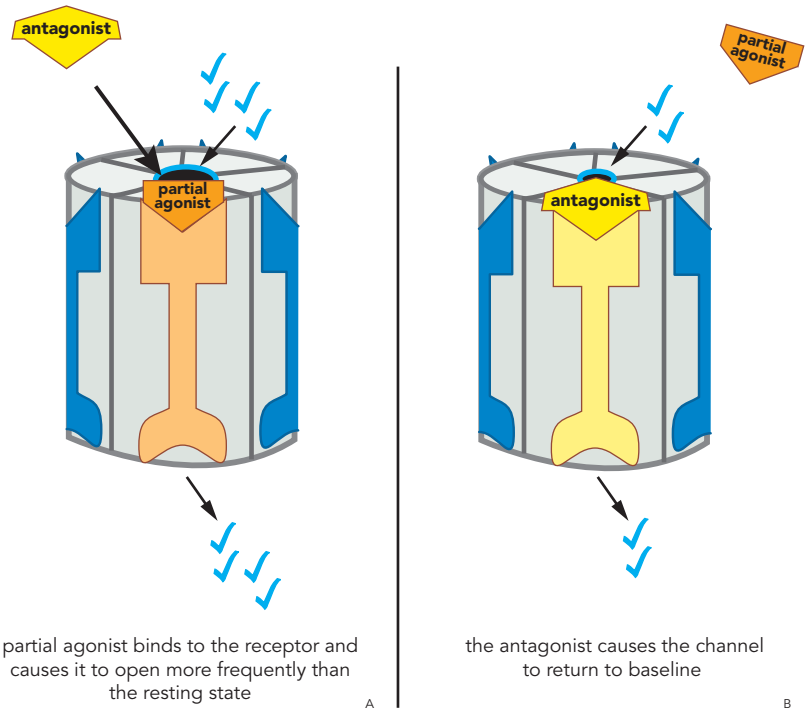


Figure 3-10 Antagonist acting in presence of partial agonist. In panel A, a partial agonist occupies its binding site and causes the ion channel to open more frequently than the resting state. This is represented as the orange partial agonist docking to its binding site, turning the receptor orange, and partially opening the ion channel. In panel B, the yellow antagonist prevails and shoves the orange partial agonist off the binding site, reversing the partial agonist's actions. Thus the ion channel is returned to its resting state.

ion flow and downstream signal transduction that is something more than the resting state in the absence of agonist, yet something less than a full agonist. Just as is the case for G-protein-linked receptors, depending upon how close this partial agonist is to a full agonist or to a silent antagonist on the agonist spectrum will determine the impact of a partial agonist on downstream signal transduction events.

The ideal therapeutic agent should have ion flow and signal transduction that is not too hot, yet not too cold, but just right, called the "Goldilocks" solution in Chapter 2, a concept that can apply here to ligand-gated ion channels as well. Such an ideal state may vary from one clinical situation to another, depending upon the balance between full agonism and silent antagonism that is desired. In cases where there is unstable neurotransmission throughout the brain, finding such a balance may stabilize receptor output somewhere between too much and too little downstream action. For this reason, partial agonists are also called "stabilizers," since they have the theoretical capacity to find the stable solution between the extremes of too much full agonist action and no agonist action at all (Figure 3-9).

Just as is the case for G-protein-linked receptors, partial agonists at ligand-gated ion channels can appear as net agonists, or as net antagonists, depending upon the amount of naturally occurring full agonist neurotransmitter which is present. Thus, when a full agonist neurotransmitter is absent, a partial agonist will be a net agonist (Figure 3-9). That is, from the resting state, a partial agonist initiates somewhat of an increase in the ion flow and downstream signal transduction cascade from the ion-channel-linked receptor. However, when full agonist neurotransmitter agonist is present, the same partial agonist will become a net antagonist (Figure 3-9). That is, it will decrease the level of full signal output to a lesser level, but not to zero. Thus, a partial agonist can simultaneously *boost* deficient neurotransmitter activity yet *block* excessive neurotransmitter activity, another reason that partial agonists are called stabilizers. An agonist and an antagonist in the same molecule acting at ligand-gated ion channels is quite an interesting new dimension to therapeutics. This concept has led to proposals that partial agonists could treat not only states which are theoretically deficient in full agonist, but also states that are theoretically in excess of full agonist. As mentioned in the discussion of G-protein-linked receptors in Chapter 2, a partial agonist at ligand-gated ion channels could also theoretically treat states that are mixtures of both

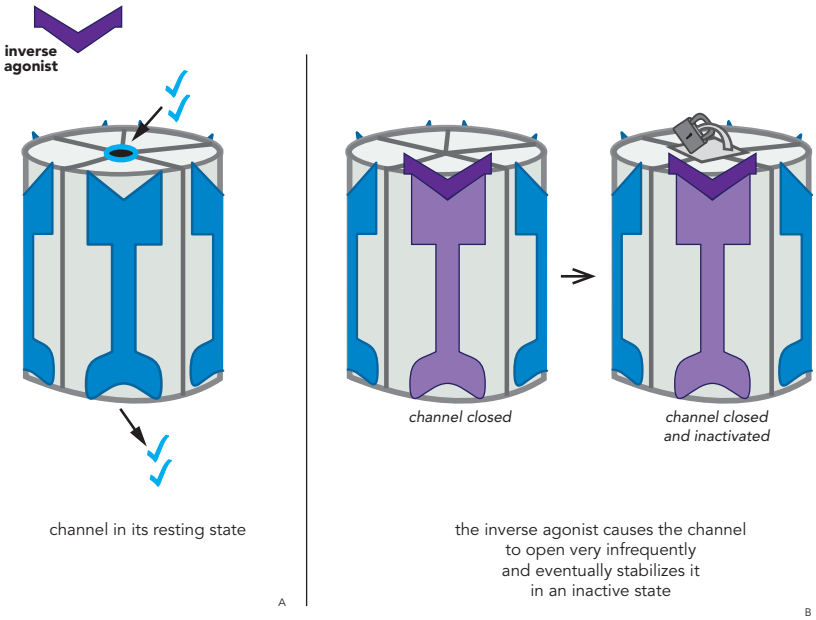


Figure 3-11 **Actions of an inverse agonist.** In panel A, the ion channel is in its resting state and opens infrequently. In panel B, the inverse agonist occupies the binding site on the ligand-gated ion channel and causes it to close. This is the opposite of what an agonist does and is represented by the purple inverse agonist turning the receptor purple and closing the ion channel. Eventually, the inverse agonist stabilizes the ion channel in an inactive state, represented by the padlock on the channel itself.

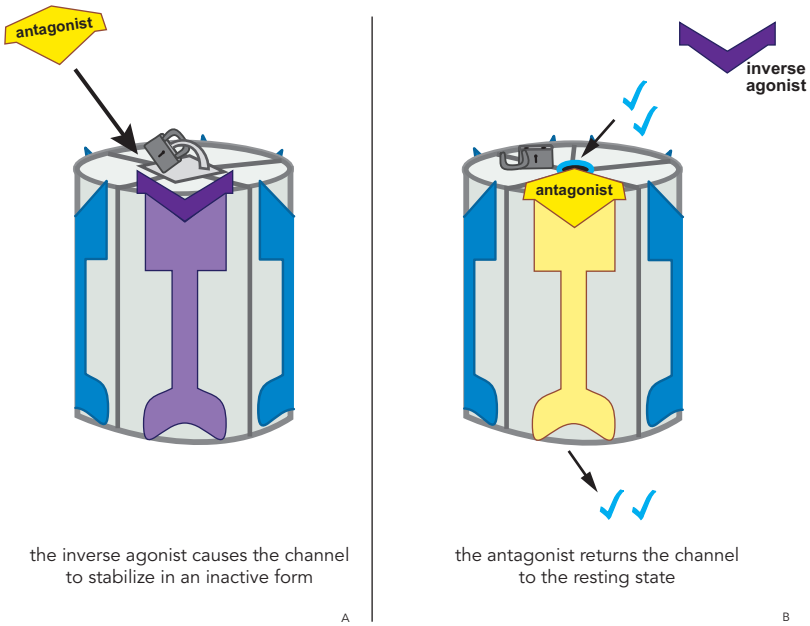


Figure 3-12 **Antagonist acting in the presence of inverse agonist.** In panel A, the ion channel has been stabilized in an inactive form by the inverse agonist occupying its binding site on the ligand-gated ion channel. This is represented as the purple inverse agonist turning the receptor purple and closing and padlocking the ion channel. In panel B, the yellow antagonist prevails and shoves the purple inverse agonist off the binding site, returning the ion channel to its resting state. In this way, the antagonist's effects on an inverse agonist's actions are similar to its effects on an agonist's actions; namely, it returns the ion channel to its resting state. However, in the presence of an inverse agonist, the antagonist increases the frequency of channel opening, whereas in the presence of an agonist, the antagonist decreases the frequency of channel opening. Thus an antagonist can reverse the actions of either an agonist or an inverse agonist despite the fact that it does nothing on its own.

excessive and deficient neurotransmitter activity. Partial agonists at ligand-gated ion channels are just beginning to enter into use in clinical practice (Table 3-2), and several more are in clinical development.

Inverse agonists at ligand-gated ion channels are different from simple antagonists, and are neither neutral nor silent. Inverse agonists are explained in Chapter 2 in relationship to G-protein-linked receptors. Inverse agonists at ligand-gated ion channels are thought to produce a conformational change in these receptors that first closes the channel and then stabilizes it in an inactive form (Figure 3-11). Thus, this inactive conformation (Figure 3-11B) produces a functional reduction in ion flow and in consequent signal transduction compared to the resting state (Figure 3-11A) that is even less than that produced when there is either no agonist present or when

a silent antagonist is present. Antagonists reverse this inactive state caused by inverse agonists, returning the channel to the resting state (Figure 3-12).

In many ways, therefore, an inverse agonist does the *opposite* of an agonist. If an agonist increases signal transduction from baseline, an inverse agonist decreases it, even below baseline levels. Also, in contrast to antagonists, which stabilize the resting state, inverse agonists stabilize an inactivated state (Figures 3-11 and 3-13). It is not yet clear if the inactivated state of the inverse agonist can be distinguished clinically from the resting state of the silent antagonist at ionotropic receptors. In the meantime, inverse agonists remain an interesting pharmacological concept.

In summary, ion-channel-linked receptors act along an agonist spectrum, and drugs have been described that can produce conformational changes in these receptors to create any state from full agonist, to partial agonist, to silent antagonist, to inverse agonist (Figure 3-4). When one considers the spectrum of signal transduction along this spectrum, it is easy to understand why agents at each point along the agonist spectrum differ so much from each other, and why their clinical actions are so different.

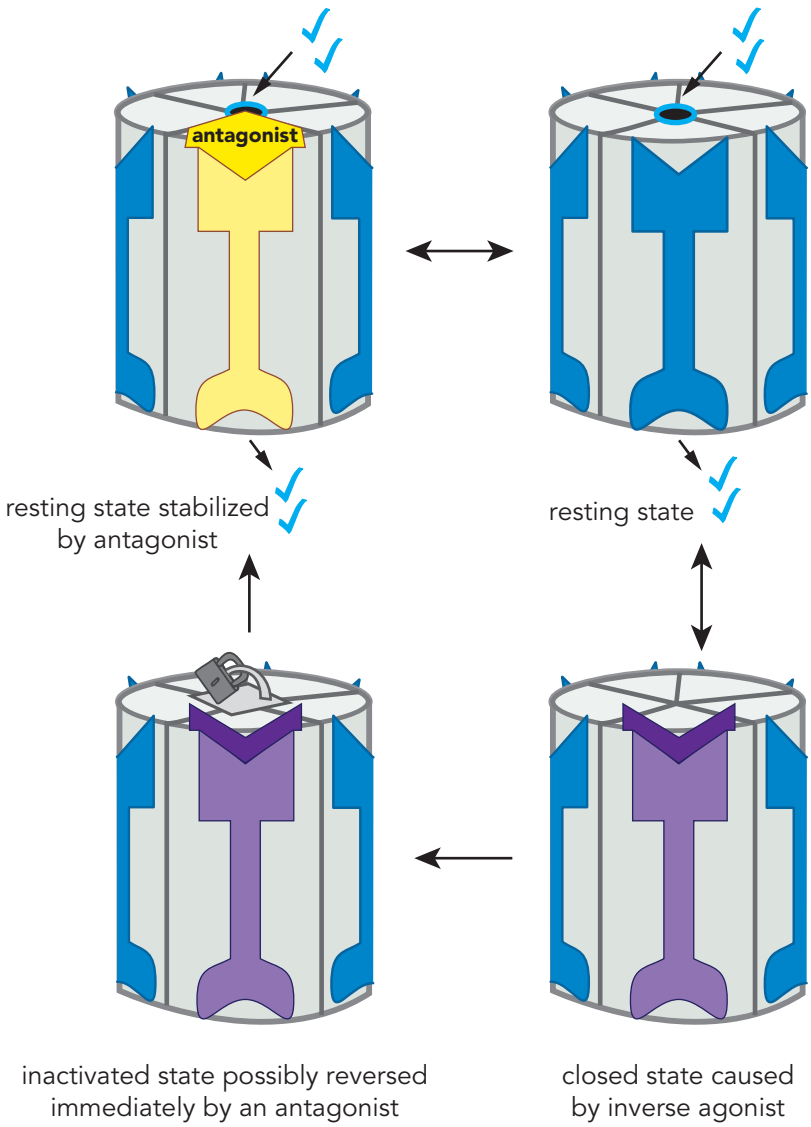


Figure 3-13 Inverse agonist actions reversed by antagonist. Antagonists cause conformational change in ligand-gated ion channels that stabilizes the receptors in the resting state (top left), the same state they are in when no agonist or inverse agonist is present (top right). Inverse agonists cause conformational change that closes the ion channel (bottom right). When an inverse agonist is bound over time, it may eventually stabilize the ion channel in an inactive conformation (bottom left). This stabilized conformation of an inactive ion channel can be quickly reversed by an antagonist, which restabilizes it in the resting state (top left).

Different States of Ligand-Gated Ion Channels

There are even more states of ligand-gated ion channels than those determined by the agonist spectrum discussed above and shown in Figures 3-4 through 3-13. The states discussed so far are those that occur predominantly with acute administration of agents that work across the agonist spectrum. These range from the maximal opening of the ion channel from conformational changes caused by a full agonist to the maximal closing of the ion channel caused by an inverse agonist. Such changes in conformation caused by the acute action of agents across this spectrum are subject to change over time since these receptors have the capacity to adapt, particularly when there is chronic or excessive exposure to such agents.

We have already discussed the resting state, the open state, and the closed state shown in Figure 3-14. The best-known adaptive states are those of desensitization and inactivation, also shown in Figure 3-14. We have also briefly discussed inactivation as a state that can be caused by acute administration of an inverse agonist, beginning with a rapid conformational change in the ion channel that first closes it, but over time stabilizes the channel in an inactive conformation that can relatively quickly be reversed by an antagonist, which then restabilizes the ion channel in the resting state (Figures 3-11 through 3-13).

Desensitization is yet another state of the ligand-gated ion channel shown in Figure 3-14. Ion-channel-linked receptor desensitization can be caused by prolonged exposure to agonists, and may be a way for receptors to protect themselves from overstimulation. An agonist acting at a ligand-gated ion channel first induces a change in receptor conformation that opens the channel, but with the continuous presence of the agonist, over time leads to another conformational change where the receptor essentially stops responding to the agonist even though the agonist is still present. This receptor is then considered to be desensitized (Figures 3-14 and 3-15). This state of desensitization can at first be reversed relatively quickly by removal of the agonist (Figure 3-15). However, if the agonist stays much longer, on the order of hours, the receptor converts from a state of simple desensitization to one of inactivation (Figure 3-15). This state does not reverse simply upon removal of the agonist, since it also takes hours in the absence of agonist to revert back to the resting state where the receptor is again sensitive to new exposure to agonist (Figure 3-15).

The state of inactivation may be best characterized for nicotinic cholinergic receptors, ligand-gated ion channels that are normally responsive to the endogenous neurotransmitter acetylcholine. Acetylcholine is quickly hydrolyzed by an abundance of the enzyme acetylcholinesterase, so it rarely gets the chance to desensitize and inactivate its nicotinic receptors. However, the drug nicotine is not hydrolyzed by

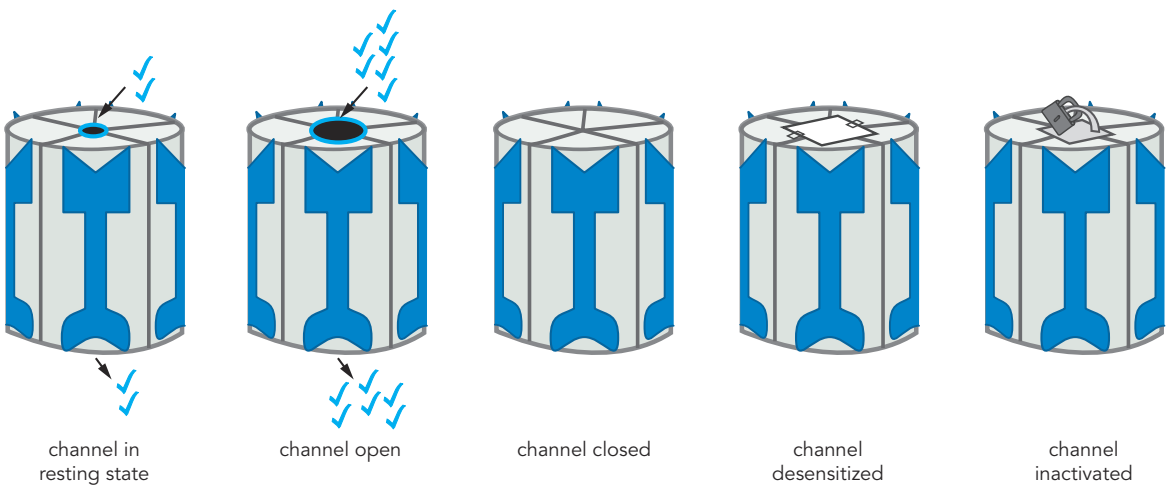


Figure 3-14 Five states of ligand-gated ion channels. Summarized here are five well-known states of ligand-gated ion channels. In the resting state, ligand-gated ion channels open infrequently, with consequent constitutive activity that may or may not lead to detectable signal transduction. In the open state, ligand-gated ion channels open to allow ion conductance through the channel, leading to signal transduction. In the closed state, ligand-gated ion channels are closed, allowing no ion flow to occur and thus reducing signal transduction to even less than is produced in the resting state. Channel desensitization is an adaptive state in which the receptor stops responding to agonist even if it is still bound. Channel inactivation is a state in which a closed ion channel over time becomes stabilized in an inactive conformation.

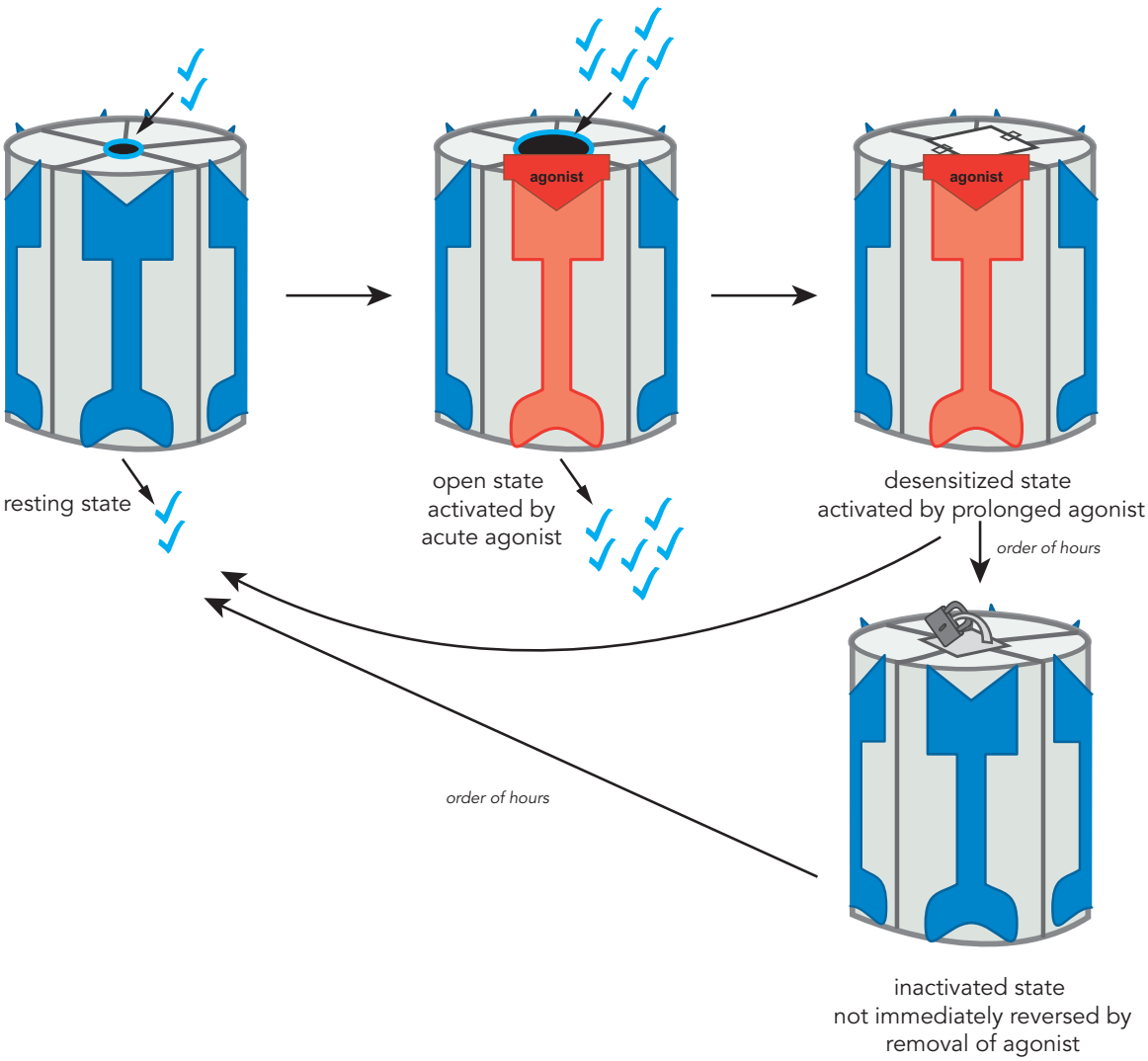


Figure 3-15 Opening, desensitizing, and inactivating by agonists. Agonists cause ligand-gated ion channels to open more frequently, increasing ion conductance in comparison to the resting state. Prolonged exposure to agonists can cause a ligand-gated ion channel to enter a desensitized state in which it no longer responds to the agonist even if it is still bound. Prompt removal of the agonist can reverse this state fairly quickly. However, if the agonist stays longer, it can cause a conformational change that leads to inactivation of the ion channel. This state is not immediately reversed when the agonist is removed.

acetylcholinesterase, and is famous for stimulating nicotinic cholinergic receptors so profoundly and so enduringly that the receptors are not only rapidly desensitized in about the time it takes to smoke a single cigarette, but enduringly inactivated for about the time most smokers take between cigarettes. Ever wonder why cigarettes are the length they are and why most smokers smoke about a pack a day (20 cigarettes) in about 16 waking hours? It all has to do with adjusting the dosing of nicotine to the nature of receptor action of nicotinic receptors described here. Addiction to nicotine and other substances is described in more detail in Chapter 13 on impulsivity and substance abuse. These transitions among various receptor states induced by agonists are shown in Figure 3-15.

Allosteric Modulation: PAMs and NAMs

Ligand-gated ion channels are regulated by more than the neurotransmitter(s) that bind to them. That is, there are other molecules that are not neurotransmitters but

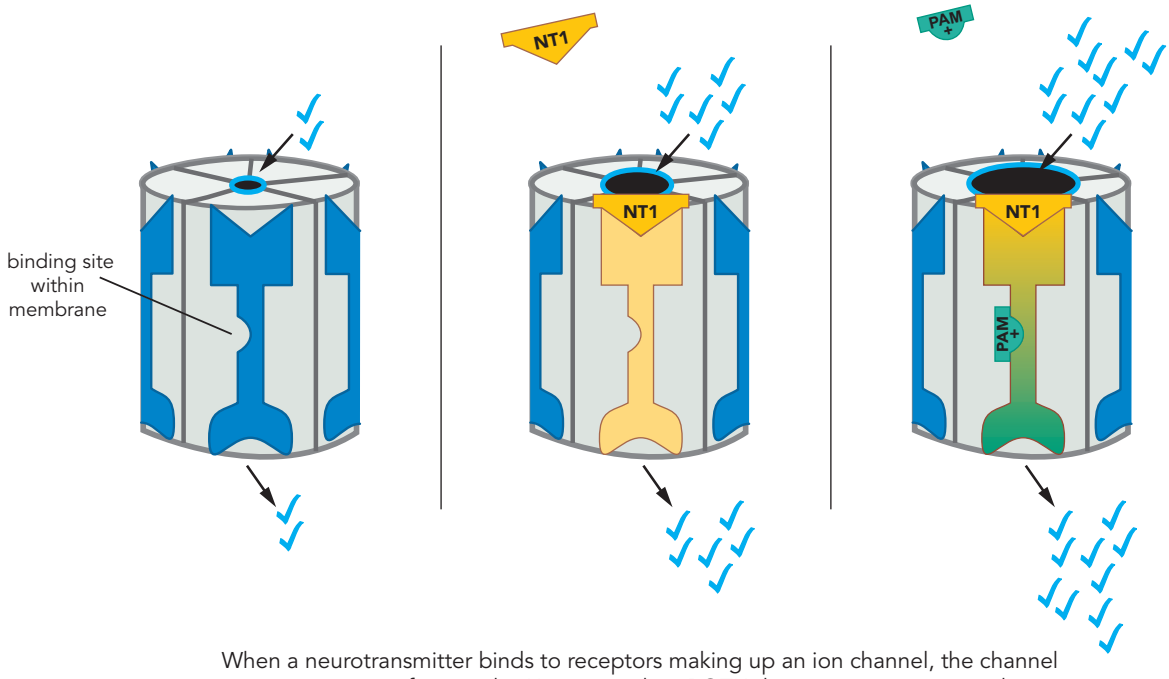


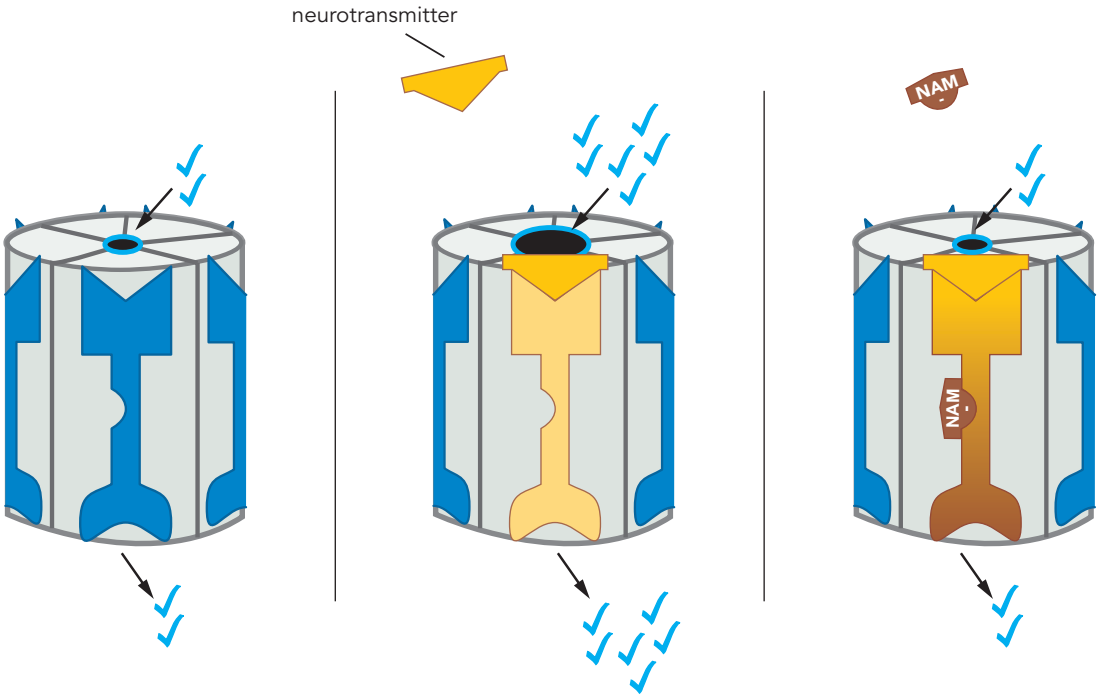
Figure 3-16 Positive allosteric modulators. Allosteric modulators are ligands that bind to sites other than the neurotransmitter site on an ion-channel-linked receptor. Allosteric modulators have no activity of their own but rather enhance (positive allosteric modulators, or PAMs) or block (negative allosteric modulators, or NAMs) the actions of neurotransmitters. When a PAM binds to its site while an agonist is also bound, the channel opens more frequently than when only the agonist is bound, therefore allowing more ions into the cell.

can bind to the receptor/ion channel complex at different sites from where neurotransmitter(s) bind. These sites are called *allosteric* (literally, "other site") and ligands that bind there are called allosteric modulators. These ligands are modulators rather than neurotransmitters because they have little or no activity on their own in the absence of the neurotransmitter. Allosteric modulators thus only work in the presence of the neurotransmitter.

There are two forms of allosteric modulators – those that boost what the neurotransmitter does and are thus called positive allosteric modulators (PAMs), and those that block what the neurotransmitter does and are thus called negative allosteric modulators (NAMs).

Specifically, when PAMs or NAMs bind to their allosteric sites while the neurotransmitter is *not* binding to its site, the PAM and the NAM do nothing. However, when a PAM binds to its allosteric site while the neurotransmitter is sitting in its site, the PAM causes conformational changes in the ligand-gated ion channel that open the channel even further and more frequently than happens with a full agonist by itself (Figure 3-16). That is why the PAM is called "positive." Good examples of PAMs are benzodiazepines. These ligands boost the action of GABA (γ-aminobutyric acid) at $GABA_A$ types of ligand-gated chloride ion channels. GABA binding to $GABA_A$ sites increases chloride ion flux by opening the ion channel, and benzodiazepines acting as agonists at benzodiazepine receptors elsewhere on the $GABA_A$ receptor complex cause the effect of GABA to be amplified in terms of chloride ion flux by opening the ion channel to a greater degree or more frequently. Clinically, this is exhibited as reducing anxiety, inducing sleep, blocking convulsions, blocking short-term memory, and relaxing muscles. In this example, benzodiazepines are acting as full agonists at the PAM site.

On the other hand, when a NAM binds to its allosteric site while the neurotransmitter resides at its agonist binding site, the NAM causes conformational changes in the ligand-gated ion channel that block or reduce the actions that normally occur when the neurotransmitter



When a neurotransmitter binds to receptors making up an ion channel, the channel opens more frequently. However, when BOTH the neurotransmitter and a negative allosteric modulator (NAM) are bound to the receptor, the channel opens much less frequently, allowing fewer ions into the cell.

Figure 3-17 Negative allosteric modulators. Allosteric modulators are ligands that bind to sites other than the neurotransmitter site on an ion-channel-linked receptor. Allosteric modulators have no activity of their own but rather enhance (positive allosteric modulators, or PAMs) or block (negative allosteric modulators, or NAMs) the actions of neurotransmitters. When a NAM binds to its site while an agonist is also bound, the channel opens less frequently than when only the agonist is bound, therefore allowing fewer ions into the cell.

acts alone (Figure 3-17). That is why the NAM is called "negative." One example of a NAM is a benzodiazepine inverse agonist. Although these are only experimental, as expected, they have the opposite actions of benzodiazepine full agonists and thus diminish chloride conductance through the ion channel so much that they cause panic attacks, seizures, and some improvement in memory – the opposite clinical effects of a benzodiazepine full agonist. Thus, the same allosteric site can either have NAM or PAM actions, depending upon whether the ligand is a full agonist or an inverse agonist. NAMs for NMDA receptors include phencyclidine (PCP, also called "angel dust") and its structurally related anesthetic agent ketamine, also used as a treatment for resistant depression and suicidal thoughts. These agents bind to a site inside the calcium channel, but can get into the channel to block it only when the channel is open. When either PCP or ketamine bind to their NAM site, they prevent glutamate/glycine cotransmission from opening the channel.

VOLTAGE-SENSITIVE ION CHANNELS AS TARGETS OF PSYCHOPHARMACOLOGICAL DRUG ACTION

Structure and Function

Not all ion channels are regulated by neurotransmitter ligands. Indeed, critical aspects of nerve conduction, action potentials, and neurotransmitter release are all mediated by another class of ion channels, known as *voltage-sensitive* or *voltage-gated* ion channels because their opening and closing are regulated by the ionic charge or voltage potential across the membrane in

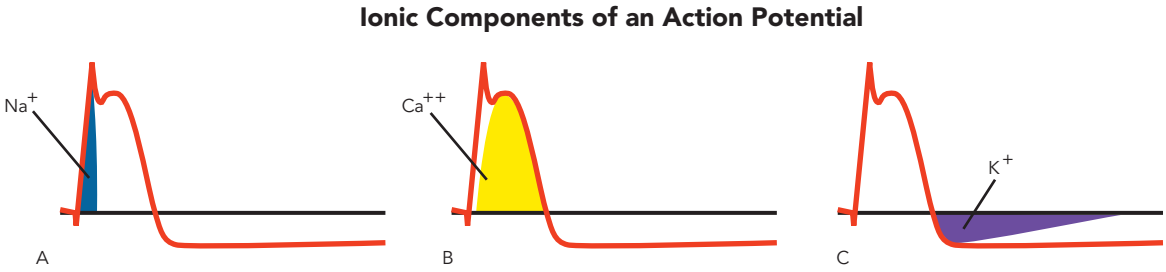


Figure 3-18 Ionic components of an action potential. The ionic components of an action potential are shown graphically here. First, voltage-sensitive sodium channels open to allow an influx of "downhill" sodium into the negatively charged internal milieu of the neuron (A). The change of voltage potential caused by the influx of sodium triggers voltage-sensitive calcium channels to open and allow calcium influx (B). Finally, after the action potential is gone, potassium enters the cell while sodium is pumped out, restoring the neuron's baseline internal electrical milieu (C).

which they reside. An electrical impulse in a neuron, also known as the action potential, is triggered by summation of the various neurochemical and electrical events of neurotransmission. These are discussed extensively in Chapter 1, which covers the chemical basis of neurotransmission and signal transduction.

Electrically, the action potential is shown in Figure 3-18. The first phase is sodium rushing "downhill" into the sodium deficient, negatively charged internal milieu of the neuron (Figure 3-18A). This is made possible when voltage-gated sodium channels open the gates and let the sodium in. A few milliseconds later, the calcium channels get the same idea, with their voltage-gated ion channels opened by the change in voltage potential caused by the sodium rushing in (Figure 3-18B). Finally, after the action potential is gone, during recovery of the neuron's baseline internal electrical milieu, potassium makes its way back into the cell through potassium channels as sodium is again pumped out (Figure 3-18C). It is now known or suspected that several psychotropic drugs work on voltage-sensitive sodium channels (VSSCs) and voltage-sensitive calcium channels (VSCCs). These classes of ion channels will be discussed here. Potassium channels are less well known to be targeted by psychotropic drugs and will thus not be emphasized.

VSSCs (Voltage-Sensitive Sodium Channels)

Many dimensions of ion-channel structure are similar for VSSCs and VSCCs. Both have a "pore" that is the channel itself, allowing ions to travel from one side of the membrane to the other. However, voltage-gated ion channels have a more complicated structure than just a hole or pore in the membrane. These channels are long strings of amino acids, comprising subunits, and four different subunits are connected to form the critical pore, known as an α subunit. In addition, other proteins are associated with the four subunits, and these appear to have regulatory functions.

Let us now build a voltage-sensitive ion channel from scratch, and describe the known functions for each part of the proteins that make up these channels. The subunit of a pore-forming protein has six transmembrane segments (Figure 3-19). Transmembrane segment 4 can detect the difference in charge across the membrane, and is thus the most electrically sensitive part of the voltage-sensitive channel. Transmembrane segment 4 thus functions like a voltmeter, and when it detects a change in ion charge across the membrane, it can alert the rest of the protein, and begin conformational changes of the ion channel, and either open it or close it. This same general structure exists for both VSSCs (Figure 3-19A) and for VSCCs (Figure 3-19B), but the exact amino acid sequence of the protein subunits are obviously different for VSSCs compared to VSCCs.

Each subunit of a voltage-sensitive ion channel has an extracellular amino acid loop between transmembrane segments 5 and 6 (Figure 3-19). This section of amino acids serves as an "ionic filter" and is located in a position so that it can cover the outside opening of the pore. This is illustrated as a colander configured molecularly to allow only sodium ions to filter through the sodium channel on the left and only calcium ions to filter through the calcium channel on the right (Figure 3-19).

Four copies of the sodium-channel version of this protein are strung together to form one complete ion channel pore of a VSSC (Figure 3-20A). The cytoplasmic loops of amino acids that tie these four subunits together are sites that regulate various functions of the sodium channel. For example, on the connector loop between the third and fourth subunits of a VSSC, there are amino acids that act as a "plug" to close the channel. Like a ball on an amino acid chain, this "pore inactivator" stops up the channel on the inner membrane surface of the pore

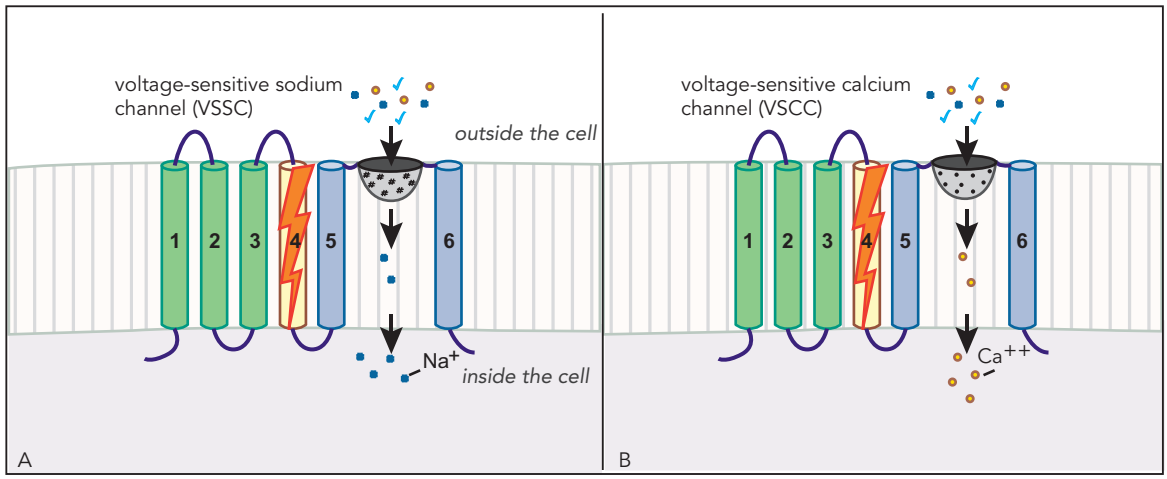


Figure 3-19 Ionic filter of voltage-sensitive sodium and calcium channels. The extracellular loop between transmembrane segments 5 and 6 of an α pore unit acts as an ionic filter (illustrated here as a colander). (A) Shown here is an α pore unit of a voltage-sensitive sodium channel, with the ionic filter allowing only sodium ions to enter the cell. (B) Shown here is an α pore unit of a voltage-sensitive calcium channel, with the ionic filter allowing only calcium ions to enter the cell.

(Figure 3-20A and B). This is a physical blocking of the hole in the pore, and reminiscent of an old-fashioned bathtub plug stopping up the drain in a bathtub. The pore-forming unit of the VSSC is also shown as an icon in Figure 3-20B with a hole in the middle of the pore, and a pore inactivator ready to plug the hole from the inside.

Many figures in textbooks represent voltage-gated ion channels with the outside of the cell on the top of a figure and this is the way the ion channel is shown in Figure 3-20A and B. Here, we also show what the channel looks like when the inside of the cell is at the top of the figure, since throughout this book these channels will often be shown on presynaptic membranes where the inside of the neuron is up and the outside of the neuron, namely its synapse, is down, like that orientation represented in Figure 3-20C). In either case, the sodium is kept out of the neuron when the channel is closed or inactivated, and the direction of sodium flow is into the neuron when the channel is open, activated, and the pore is not plugged up with the pore-inactivating amino acid loops.

Voltage-sensitive sodium channels may have one or more regulatory proteins, some called β units, located in the transmembrane area and flanking the α pore forming unit (Figure 3-20C). The function of these β subunits is not clearly established, but they may modify the actions of the α unit and thereby indirectly influence the opening and closing of the channel. It is possible that β units may be phosphoproteins, and that their state of phosphorylation or dephosphorylation could regulate how much influence they exert on ion-channel regulation. Indeed, the α unit itself may also be a phosphoprotein, with the possibility that its own phosphorylation state could be regulated by signal transduction cascades and thus increase or decrease the sensitivity of the ion channel to changes in the ionic environment. This is discussed in Chapter 1 as part of the signal transduction cascade, and ion channels in some cases may act as third, fourth, or subsequent messengers triggered by neurotransmission. Both β subunits and the α subunit itself may have various sites where various psychotropic drugs act, especially anticonvulsants, some of which are also useful as mood stabilizers or as treatments for chronic pain. Specific drugs will be discussed in further detail in the chapters on mood stabilizers and pain.

Three different states of a VSSC are shown in Figure 3-21. The channel can be open and active, a state allowing maximum ion flow through the α unit (Figure 3-21A). When a sodium channel needs to stop ion flow, it has two states that can do this. One state acts very quickly to flip the pore inactivator into place, stopping ion flow so fast that the channel has not yet even closed (Figure 3-21B). Another state of inactivation actually closes the channel with conformational changes in the ion channel's shape (Figure 3-21C). The pore inactivation mechanism may be for fast inactivation, and the channel closing mechanism may be for a more stable state of inactivation, but it is not entirely clear.

There are many subtypes of sodium channels, but the details of how they are differentiated from each other by differential location in the brain, by differential functions, and by differential drug actions are only beginning to

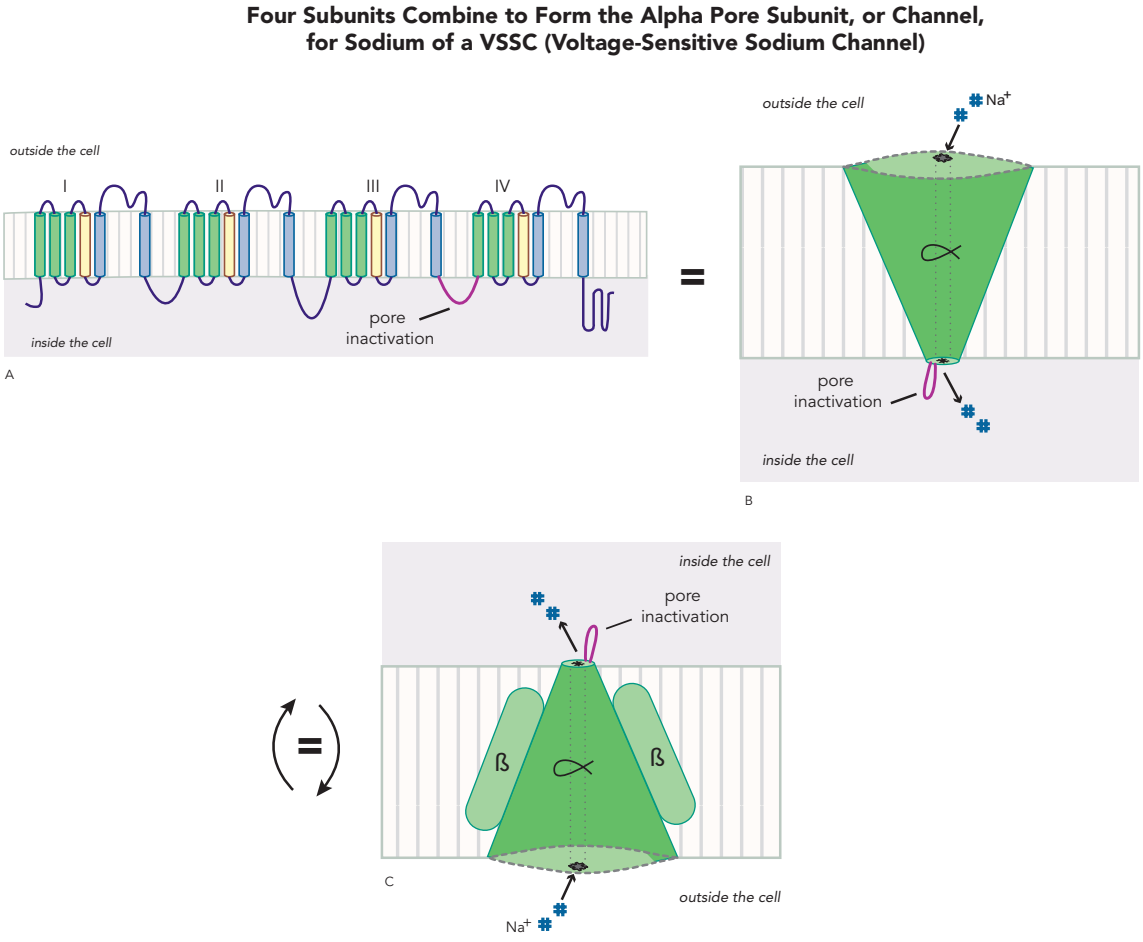


Figure 3-20 **Alpha pore of voltage-sensitive sodium channel.** The α pore of a voltage-sensitive sodium channel comprises four subunits (A). Amino acids in the intracellular loop between the third and fourth subunits act as a pore inactivator, "plugging" the channel. An iconic version of the α unit is shown here, with the extracellular portion on top (B) and with the intracellular portion on top (C).

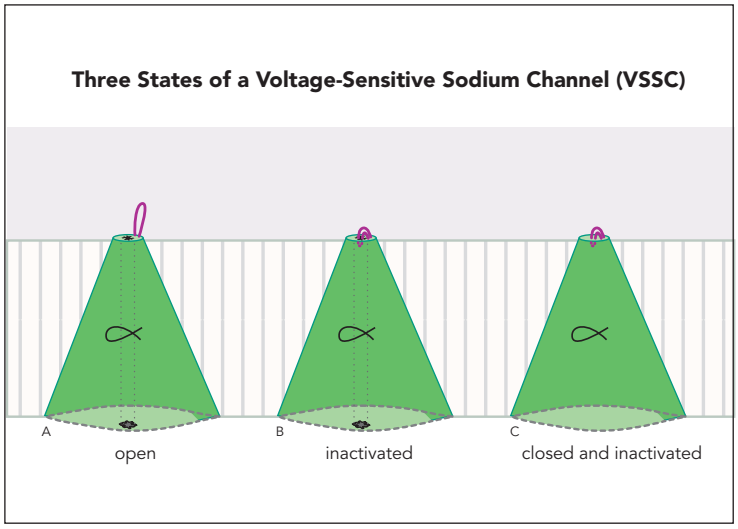


Figure 3-21 **States of voltage-sensitive sodium channel.** Such channels can be in the open state, in which the ion channel is open and active and ions flow through the α unit (A). Voltage-sensitive sodium channels may also be in an inactivated state, in which the channel is not yet closed but has been "plugged" by the pore inactivator, preventing ion flow (B). Finally, conformational changes in the ion channel can cause it to close, the third state (C).

be clarified. For the psychopharmacologist, what is now of interest is the fact that various sodium channels may be the sites of action of several anticonvulsants, some of which have mood-stabilizing and pain-reducing properties. Most currently available anticonvulsants probably have multiple sites of action, including multiple sites of action at multiple types of ion channels. The specific actions of specific drugs will be discussed in the chapters that cover specific disorders.

VSCCs (Voltage-Sensitive Calcium Channels)

Many aspects of VSCCs and VSSCs are similar – not just their names. Like their sodium-channel cousins, the VSCCs also have subunits with six transmembrane segments, with segment 4 a voltmeter, and with the extracellular amino acids connecting segments 5 and 6 acting as an ionic filter (Figure 3-19) – only this time as a colander allowing calcium to come into the cell, not sodium (see Figure 3-19B). Obviously, the exact sequence of amino acids differs between a sodium channel and a calcium channel, but they have a very similar overall organization and structure.

Just like voltage-gated sodium channels, VSCCs also string together four of their subunits to form a pore, called in the case of a calcium channel, an α_1 unit (Figure 3-22A and B). The connecting string of amino acids also has functional activities that can regulate calcium-channel functioning, but in this case the functions are different from that for sodium channels. That is, there is no pore inactivator working as a plug for

Four Subunits Combine to Form the Alpha1 Pore Subunit, or Channel, for Calcium of a VSCC (Voltage-Sensitive Calcium Channel)

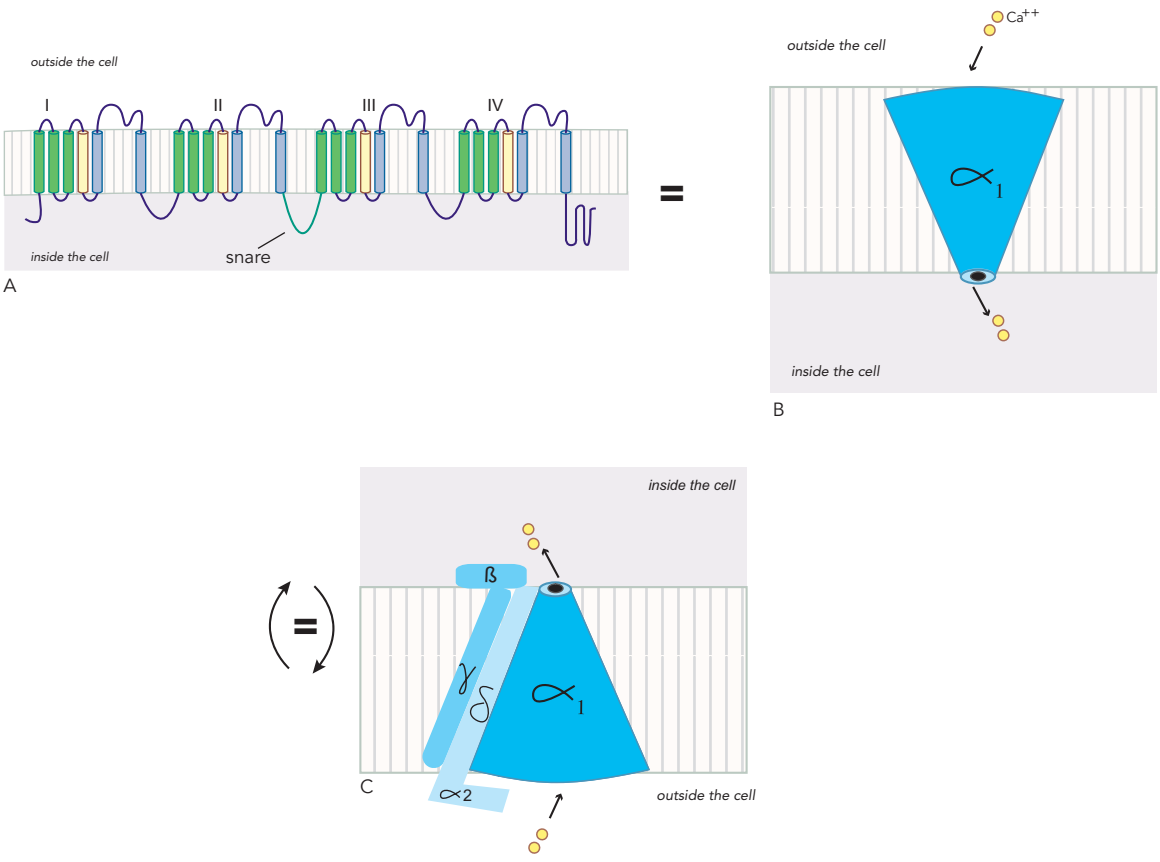


Figure 3-22 Alpha1 pore of voltage-sensitive calcium channel. The α pore of a voltage-sensitive calcium channel, termed an α_1 unit, comprises four subunits (A). Amino acids in the cytoplasmic loop between the second and third subunits act as a snare to connect with synaptic vesicles, thereby controlling neurotransmitter release (A). An iconic version of the α_1 unit is shown here, with the extracellular portion on top (B) and with the intracellular portion on top (C).

Opening a Presynaptic Voltage-Sensitive N or P/Q Calcium Channel: Triggers Neurotransmitter Release

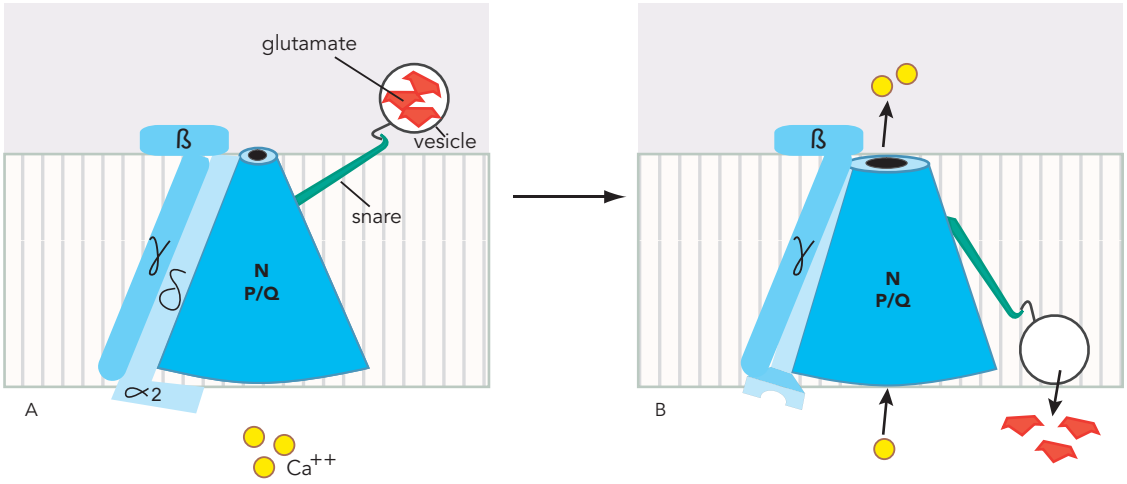


Figure 3-23 **N and P/Q voltage-sensitive calcium channels.** Voltage-sensitive calcium channels that are most relevant to psychopharmacology are termed N and P/Q channels. These ion channels are presynaptic and involved in the regulation of neurotransmitter release. The intracellular amino acids linking the second and third subunits of the α_1 unit form a snare that hooks onto synaptic vesicles (A). When a nerve impulse arrives, the snare "fires," leading to neurotransmitter release (B).

the VSCC, as was described above for the VSSC; instead, the amino acids connecting the second and third subunits of the VSCC work as a "snare" to hook up with synaptic vesicles and regulate the release of neurotransmitter into the synapse during synaptic neurotransmission (Figure 3-22A and Figure 3-23). The orientation of the calcium channel in Figure 3-22B is with the outside of the cell at the top of the page, and this is switched in Figure 3-22C so that the inside of the cell is now at the top of the page, so the reader can see how these channels might look in various configurations in space. In all cases, the direction of ion flow is from outside the cell to the inside when that channel opens to allow ion flow to occur.

Several proteins flank the α_1 pore-forming unit of a VSCC, called γ, β, and $\alpha_2\delta$ (Figure 3-22C). Shown here are γ units that span the membrane, cytoplasmic β units, and a curious protein called $\alpha_2\delta$, because it has two parts: a δ part that is transmembrane, and an α_2 part that is extracellular (Figure 3-22C). The functions of all these proteins associated with the α_1 pore-forming unit of a VSCC are just beginning to be understood, but already it is known that the $\alpha_2\delta$ protein is the target of certain psychotropic drugs, such as the anticonvulsants pregabalin and gabapentin, and that this $\alpha_2\delta$ protein may be involved in regulating conformational changes of the ion channel to change the way the ion channel opens and closes.

As would be expected, there are several subtypes of VSCCs (Table 3-4). The vast array of VSCCs indicates that the term "calcium channel" is much too general, and in fact can be confusing. For example, calcium channels associated with the *ligand-gated ion channels* discussed in the previous section, especially those associated with glutamate and nicotinic cholinergic ionotropic receptors, are members of an entirely different class of ion channels from the VSCCs under discussion here. As we have mentioned, calcium channels associated with this previously discussed class of ion channels are called ligand-gated ion channels, ionotropic receptors, or ion-channel-linked receptors, to distinguish them from VSCCs.

The specific subtypes of VSCCs of most interest to psychopharmacology are those that are presynaptic, that regulate neurotransmitter release, and that are targeted by certain psychotropic drugs. This subtype designation of VSCC is shown in Table 3-4 and such channels are known as N or P/Q channels.

Another well-known subtype of VSCC is the L channel. This channel exists not only in the central nervous system, where its functions are still being clarified, but also on vascular smooth muscle where it regulates blood pressure and where a group of drugs known as dihydropyridine "calcium channel blockers" interact as therapeutic antihypertensives to lower blood pressure. R and T

Table 3-4 Subtypes of voltage-sensitive calcium channels (VSCCs)

Type	Pore-forming	Location	Function
L	$Ca_v1.2$, 1.3	Cell bodies, dendrites	Gene expression, synaptic integration
N	Ca_v 2.2	*Nerve terminals* Dendrites, cell bodies	*Transmitter release* Synaptic integration
P/Q	Ca_v, 2.1	*Nerve terminals* Dendrites, cell bodies	*Transmitter release* Synaptic integration
R	Ca_v, 2.3	*Nerve terminals* Cell bodies, dendrites	*Transmitter release* Repetitive firing, synaptic integration
T	Ca_v, 3.1, 3.2, 3.3	Cell bodies, dendrites	Pacemaking, repetitive firing, synaptic integration

Docking of Synaptic Vesicle with Presynaptic Membrane, VSCC (Voltage-Sensitive Calcium Channel), and Snare Proteins

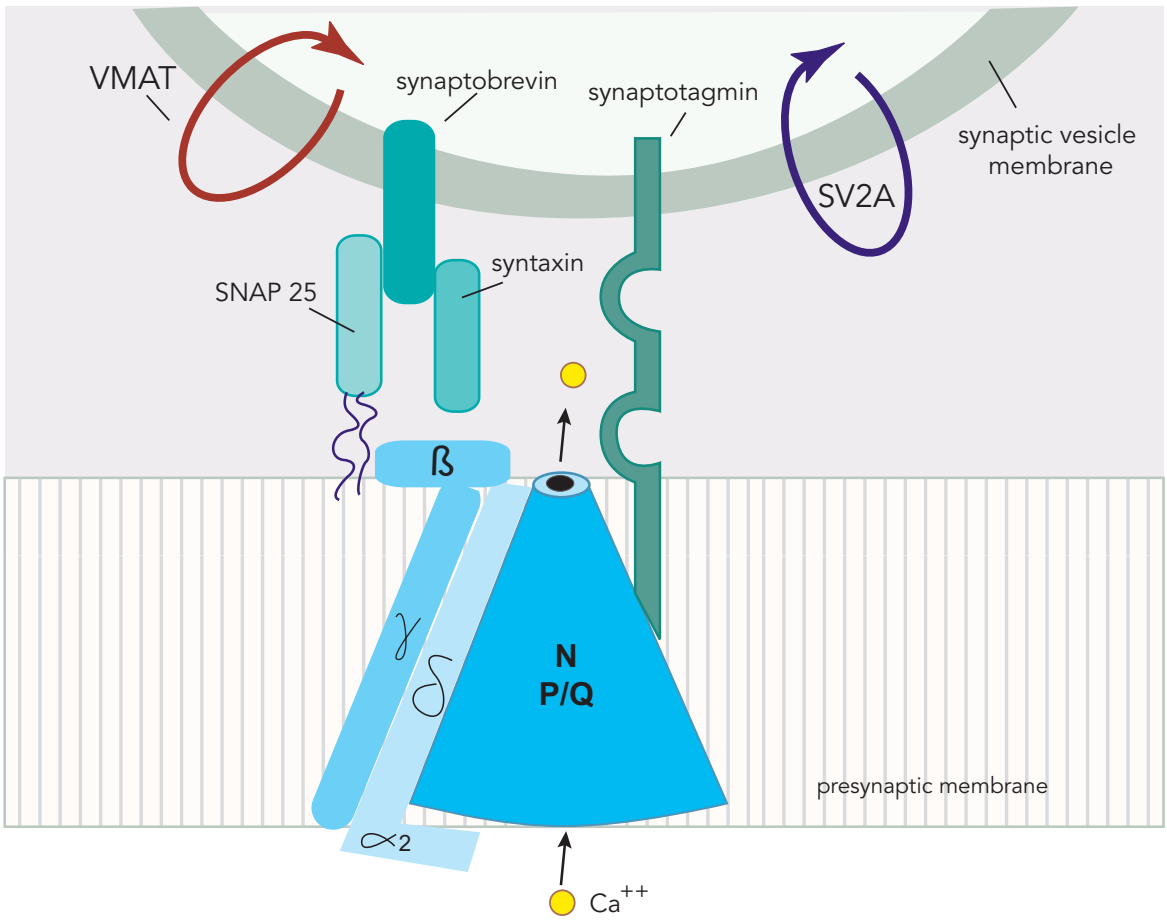


Figure 3-24 **Snare proteins.** Proteins that link the voltage-sensitive calcium channel to the synaptic vesicle, called snare proteins, are shown here; they include SNAP 25 (synaptosomal-associated protein 25), synaptobrevin, syntaxin, and synaptotagmin. A VMAT (vesicular monoamine transporter) is shown on the left. Another transporter, SV2A, is shown on the right. The mechanism of this transporter is not yet clear, but the anticonvulsant levetiracetam is known to bind to this site.

channels are also of interest, and some anticonvulsants and psychotropic drugs may also interact there, but the exact roles of these channels are still being clarified.

Presynaptic N and P/Q VSCCs have a specialized role in regulating neurotransmitter release because they are linked by molecular "snares" to synaptic vesicles (Figure 3-23). That is, these channels are literally hooked to synaptic vesicles. Some experts think of this as a cocked gun – loaded with neurotransmitters packed in a synaptic vesicle bullet (Figure 3-23A) ready to be fired at the postsynaptic neuron as soon as a nerve impulse arrives (Figure 3-23B). Some of the structural details of the molecular links – namely, with snare proteins – that connect the N, P/Q VSCC with the synaptic vesicle are shown in Figure 3-24. If a drug interferes with the ability of the channel to open and let in calcium, the synaptic vesicle stays tethered to the voltage-gated calcium channel. Neurotransmission can thus be prevented, and this may be desirable in states of excessive neurotransmission, such as pain, seizures, mania, or anxiety. This may explain the action of certain anticonvulsants.

Indeed, it is neurotransmitter release that is the *raison d'etre* for presynaptic voltage-sensitive N and P/Q channels. When a nerve impulse invades the presynaptic area, this causes the charge across the membrane to change, in turn opening the VSCC, allowing calcium to enter, and this makes the synaptic vesicle dock into and merge with the presynaptic membrane, spewing its neurotransmitter contents into the synapse to effect neurotransmission (Figures 3-25 and 3-26). This conversion of an electrical impulse into a chemical message is triggered by calcium and sometimes called excitation–secretion coupling.

Anticonvulsants are thought to act at various VSSCs and VSCCs and will be discussed in further detail in the relevant clinical chapters. Many of these anticonvulsants have several uses in psychopharmacology, from chronic pain to migraine, from bipolar mania to bipolar depression to bipolar maintenance, and possibly as agents for anxiety and sleep aids. These specific applications and more details about hypothetical mechanisms of action are explored in depth in the clinical chapters dealing with the various psychiatric disorders.

ION CHANNELS AND NEUROTRANSMISSION

Although the various subtypes of ligand-gated ion channels and voltage-gated ion channels are presented separately, the reality is that they work cooperatively during neurotransmission. When the actions of all these ion channels are well orchestrated, brain communication becomes a magical mix of electrical and chemical messages made possible by ion channels. The coordinated acts of ion channels during neurotransmission are illustrated in the Figures 3-25 and 3-26.

The initiation of chemical neurotransmission by a neuron's ability to integrate all of its inputs, and then translate them into an electrical impulse is presented in Chapter 1. We now show how ion channels are involved in this process (Figure 3-26). After a neuron receives and integrates its inputs from other neurons, it then encodes them into an action potential, and that nerve impulse is next sent along the axon via VSSCs that line the axon (Figure 3-25).

The action potential could be described as lighting a fuse, with the fuse burning from the initial segment of the axon to the axon terminal. Movement of the burning edge of the fuse is carried out by a sequence of VSSCs that open one after the other, allowing sodium to pass into the neuron, and then carrying the electrical impulse so generated along to the next VSSC in line (Figure 3-25). When the electrical impulse reaches the axon terminal, it meets VSCCs in the presynaptic neuronal membrane, already loaded with synaptic vesicles and ready to fire (see axon terminal of neuron A in Figure 3-25).

When the electrical impulse is detected by the voltmeter in the VSCC, it opens the calcium channel, allowing calcium to enter, and bang!, the neurotransmitter is released in a cloud of synaptic chemicals from the presynaptic axon terminal via excitation–secretion coupling (see axon terminal of neuron A in Figure 3-25 and enlarged illustrations of this in Figure 3-26). Details of this process of excitation–secretion coupling are shown in Figure 3-26, beginning with the action potential about to invade the presynaptic terminal, and with a closed VSSC sitting next to a closed but poised VSCC snared to its synaptic vesicle (Figure 3-26A). As the nerve impulse arrives in the axon terminal, it first hits the VSSC as a wave of positive sodium charges delivered by the openings of upstream sodium channels, which are detected by the sodium channel's voltmeter (Figure 3-26B). This opens the last sodium channel shown, allowing sodium to enter (Figure 3-26C). The consequence of this sodium entry is to change the electrical charge nearby the calcium channel, and then this is detected by the VSCC's voltmeter (Figure 3-26D). Next, the calcium channel opens (Figure 3-26E). At this point, chemical neurotransmission has now been irreversibly triggered,

and the translation of an electrical message into a chemical message has begun. Calcium entry from the VSCC now increases the local concentrations of this ion in the vicinity of the VSCC, the synaptic vesicle, and the neurotransmitter release machinery (Figure 3-26F). This causes the synaptic vesicle to dock into the inside of the presynaptic membrane, then merge with it, spewing its neurotransmitter contents out of the membrane and into the synapse (Figure 3-26G). This amazing process occurs almost instantaneously and simultaneously from many VSCCs releasing neurotransmitter from many synaptic vesicles.

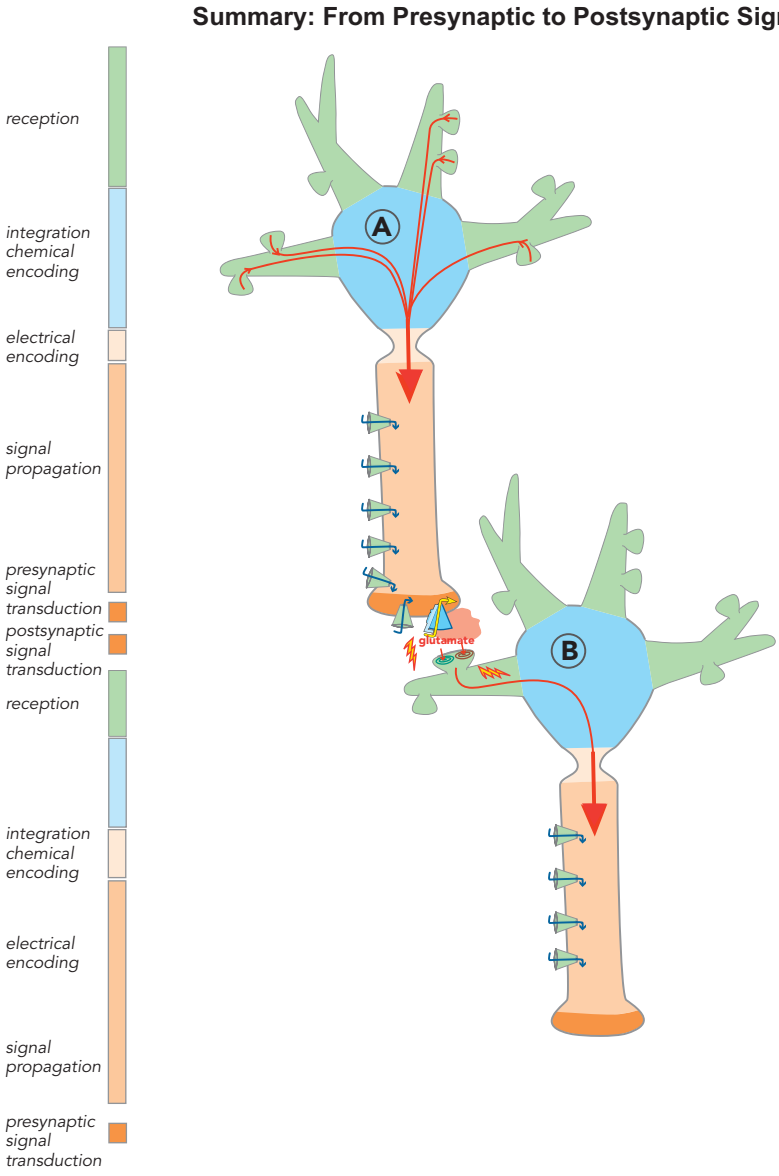


Figure 3-25 Signal propagation. Summary of signal propagation from presynaptic to postsynaptic neuron. A nerve impulse is generated in neuron A, and the action potential is sent along the axon via voltage-sensitive sodium channels until it reaches voltage-sensitive calcium channels linked to synaptic vesicles full of neurotransmitters in the axon terminal. Opening of the voltage-sensitive calcium channel and consequent calcium influx causes neurotransmitter release into the synapse. Arrival of neurotransmitter at postsynaptic receptors on the dendrite of neuron B triggers depolarization of the membrane in that neuron and, consequently, postsynaptic signal propagation.

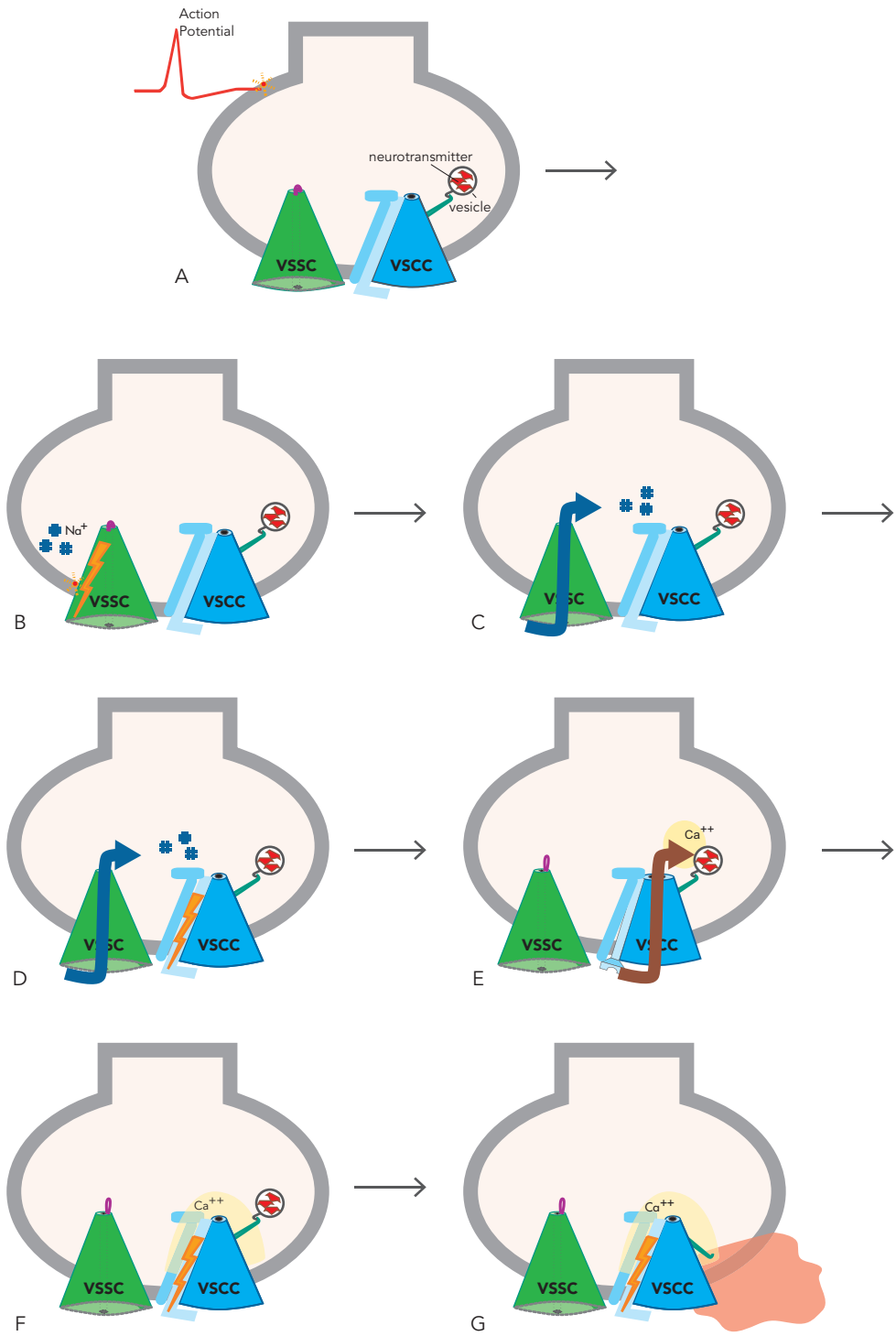


Figure 3-26 **Excitation–secretion coupling.** Details of excitation–secretion coupling are shown here. An action potential is encoded by the neuron and sent to the axon terminal via voltage-sensitive sodium channels along the axon (A). The sodium released by those channels triggers a voltage-sensitive sodium channel at the axon terminal to open (B), allowing sodium influx into the presynaptic neuron (C). Sodium influx changes the electrical charge of the voltage-sensitive calcium channel (D), causing it to open and allow calcium influx (E). As the intraneuronal concentration of calcium increases (F), the synaptic vesicle is caused to dock and merge with the presynaptic membrane, leading to neurotransmitter release (G).

By now, only about half of the sequential phenomena of chemical neurotransmission have been described. The other half occurs on the other side of the synapse. That is, reception of the released neurotransmitter now occurs in neuron B (Figure 3-25), which can set up another nerve impulse in neuron B. This whole process, from nerve impulse generation and propagation of it along neuron A to its nerve terminal, then sending chemical neurotransmission to neuron B, and finally propagating this second nerve impulse along neuron B, is summarized in Figure 3-25. VSSCs in presynaptic neuron A propagate the impulse there, and then VSCCs in presynaptic neuron A release the neurotransmitter glutamate. Ligand-gated ion channels on dendrites in postsynaptic neuron B next receive this chemical input, and translate this chemical message back into a nerve impulse propagated in neuron B by VSSCs in that neuron. Also, ligand-gated ion channels in postsynaptic neuron B translate the glutamate chemical signal into another type of electrical phenomenon called long-term potentiation, to cause changes in the function of neuron B.

SUMMARY

Ion channels are key targets of many psychotropic drugs. This is not surprising because these targets are key regulators of chemical neurotransmission and the signal transduction cascade.

There are two major classes of ion channels: ligand-gated ion channels and voltage-sensitive ion channels. The opening of ligand-gated ion channels is regulated by neurotransmitters whereas the opening of voltage-gated ion channels is regulated by the charge across the membrane in which they reside.

Ligand-gated ion channels are both ion channels and receptors. They are also commonly called ionotropic receptors as well as ion-channel-linked receptors. One subclass of ligand-gated ion channels has a pentameric structure, and includes $GABA_A$ receptors, nicotinic cholinergic receptors, $5HT_3$ receptors, and certain glycine receptors. The other subclass of ligand-gated ion channels has a tetrameric structure, and includes many glutamate receptors, including the AMPA, kainate, and NMDA subtypes.

Ligands act at ligand-gated ion channels across an agonist spectrum, from full agonist, to partial agonist, to antagonist, to inverse agonist. Ligand-gated ion channels can be regulated not only by neurotransmitters acting as agonists, but also by molecules interacting at other sites on the receptor, either boosting the action of neurotransmitter agonists as positive allosteric modulators (PAMs), or diminishing the action of neurotransmitter agonists as negative allosteric modulators (NAMs). In addition, these receptors exist in several states, from open, to resting, to closed, to inactivated, to desensitized.

The second major class of ion channels is called either voltage-sensitive ion channels or voltage-gated ion channels, since they are opened and closed by the voltage charge across the membrane. The major channels from this class of interest to psychopharmacologists are the voltage-sensitive sodium channels (VSSCs) and the voltage-sensitive calcium channels (VSCCs). Numerous anticonvulsants bind to various sites on these channels, and may exert their anticonvulsant actions by this mechanism, as well as their actions as mood stabilizers, treatments for chronic pain, drugs for anxiety, and sleep effects.

4 Psychosis, Schizophrenia, and the Neurotransmitter Networks Dopamine, Serotonin, and Glutamate

Symptoms of Psychosis 77
The Three Major Hypotheses of Psychosis and Their Neurotransmitter Networks 78
The Classic Dopamine Hypothesis of Psychosis and Schizophrenia 79
The Dopamine Neurotransmitter Network 79
The Classic Dopamine Hypothesis of the Positive Symptoms of Psychosis: Mesolimbic HyperDopaminergia 90
Corollary to the Classic Dopamine Hypothesis of Schizophrenia: Mesocortical HypoDopaminergia and the Cognitive, Negative, and Affective Symptoms of Schizophrenia 95
The Glutamate Hypothesis of Psychosis and Schizophrenia 95
The Glutamate Neurotransmitter Network 96
The NMDA Glutamate Hypofunction Hypothesis of Psychosis: Faulty NMDA Neurotransmission at Glutamate Synapses on GABA Interneurons in Prefrontal Cortex 105
The Serotonin Hypothesis of Psychosis and Schizophrenia 111
The Serotonin Neurotransmitter Network 113
The Serotonin Hyperfunction Hypothesis of Psychosis 131
Summary and Conclusions Regarding Dopamine, NMDA, and Serotonin Neurotransmission in Psychosis 141
Schizophrenia as the Prototypical Psychotic Disorder 141
Beyond the Positive and Negative Symptoms of Schizophrenia 143
What Is the Cause of Schizophrenia? 148
Other Psychotic Illnesses 156
Mood-Related Psychosis, Psychotic Depression, Psychotic Mania 157
Parkinson's Disease Psychosis 157
Dementia-Related Psychosis 157
Summary 158

Psychosis is a difficult term to define and is frequently misused not only in the media, but unfortunately among mental health professionals as well. Stigma and fear surround the concept of psychosis, sometimes using the pejorative term "crazy." This chapter gives a general description of psychotic symptoms and explores the major theories of how all forms of psychosis are linked to the neurotransmitter systems dopamine, serotonin, and glutamate. An overview of specific psychotic disorders, with an emphasis on schizophrenia, is presented here but does not list the diagnostic criteria for all the disorders in which psychosis is either a defining feature or an associated feature. The reader is referred to standard reference sources such as the DSM (*Diagnostic and Statistical Manual of the American Psychiatric Association*) and the ICD (*International Classification of Diseases*) for that information. Although schizophrenia is emphasized here, we will approach psychosis as a syndrome associated with a variety of disorders that are all targets for the various drugs that treat psychosis and that will be discussed in Chapter 5.

SYMPTOMS OF PSYCHOSIS

Psychosis is a syndrome – that is, a mixture of symptoms – that can be associated with many different psychiatric disorders, but is not a specific disorder itself in diagnostic schemes such as the DSM or ICD. At a minimum, psychosis means delusions and hallucinations. *Delusions* are fixed beliefs – often bizarre – that have an inadequate rational basis and can't be changed by rational arguments or evidence to the contrary. *Hallucinations* are perceptual experiences of any sensory modality – especially auditory – that occur without a real external stimulus, yet are vivid and clear, just like normal perceptions, but not under voluntary control. Delusions and hallucinations are the hallmarks of psychosis and are often called the "positive symptoms" of psychosis. Psychosis can also include other symptoms such as disorganized speech, disorganized behavior, gross distortions of reality testing, and so-called "negative symptoms" of psychosis, such as diminished emotional expression and decreased motivation.

Psychosis itself, whether part of schizophrenia or another disorder, can be paranoid, disorganized/excited, or depressive. In addition, perceptual distortions and motor disturbances can be associated with any type of psychosis. *Perceptual distortions* include being distressed by hallucinatory voices; hearing voices that accuse, blame, or threaten punishment; seeing visions; reporting hallucinations of touch, taste, or odor; or reporting that familiar things and people seem changed. *Motor disturbances* are peculiar, rigid postures; overt signs of tension; inappropriate grins or giggles; peculiar repetitive gestures; talking, muttering, or mumbling to oneself; or glancing around as if hearing voices.

In *paranoid psychosis*, the patient has paranoid projections, hostile belligerence, and grandiose expansiveness. This type of psychosis often occurs in schizophrenia and in many drug-induced psychoses. *Paranoid projection* includes preoccupation with delusional beliefs; believing that people are talking about oneself; believing one is being persecuted, or being conspired against; and believing people or external forces control one's actions. A particular type of paranoid delusion may be seen in Parkinson's disease psychosis; namely, the belief that one's spouse is being unfaithful or that one's spouse or loved ones are stealing from them. *Hostile belligerence* is verbal expression of feelings of hostility; expressing an attitude of disdain; manifesting a hostile, sullen attitude; manifesting irritability and grouchiness; tending to blame others for problems; expressing feelings of resentment; complaining and finding fault; as well as expressing suspicion of people. This, too may be seen especially in schizophrenia and drug-induced psychoses. *Grandiose expansiveness* is exhibiting an attitude of superiority; hearing voices that praise and extol; believing one has unusual powers or is a well-known personality, or that one has a divine mission, which is often seen in schizophrenia and in manic psychosis

In a *disorganized/excited psychosis*, there is conceptual disorganization, disorientation, and excitement. *Conceptual disorganization* can be characterized by giving answers that are irrelevant, or incoherent; drifting off the subject; using neologisms; or repeating certain words or phrases. Any psychotic disorder may exhibit disorganization. *Disorientation* is not knowing where one is, the season of the year, the calendar year, or one's own age and is common in psychoses associated with dementias and in drug-induced states. *Excitement* is expressing feelings without restraint; manifesting speech that is hurried; exhibiting an elevated mood; an attitude of superiority; dramatizing oneself or one's symptoms; manifesting loud and boisterous speech; exhibiting overactivity or restlessness; and exhibiting excess of speech. Excitement can be especially characteristic of mania or schizophrenia.

Depressive psychosis is characterized by psychomotor retardation, apathy, and anxious self-punishment and blame. *Psychomotor retardation* and *apathy* are manifested by slowed speech; indifference to one's future; fixed facial expression; slowed movements; deficiencies in recent memory; manifesting blocking in speech; apathy toward oneself or one's problems; slovenly appearance; low or whispered speech; and failure to answer questions. It can be hard to distinguish from negative symptoms of psychosis. *Anxious self-punishment* and *blame* is the tendency to blame or condemn oneself; anxiety about specific matters; apprehensiveness regarding vague future events; an attitude of self-deprecation, manifesting depressed mood; expressing feelings of guilt and remorse; preoccupation with suicidal thoughts, unwanted ideas, and specific fears; and feeling unworthy or sinful, seen often in psychotic depression

In summary, the term "psychosis" can be considered to be a set of symptoms in which a person's mental capacity, affective response, and capacity to recognize reality, communicate, and relate to others is impaired. This brief discussion of clusters of psychotic symptoms does not constitute diagnostic criteria for any psychotic disorder. It is given merely as a description of several types of symptoms that can occur as a part of many different types and causes of psychosis in order to give the reader an overview of the nature of behavioral disturbances associated with the various psychotic illnesses.

THE THREE MAJOR HYPOTHESES OF PSYCHOSIS AND THEIR NEUROTRANSMITTER NETWORKS

The dopamine (DA) hypothesis of psychosis is well known and has in fact become a classic, and one of the most enduring ideas in psychopharmacology. However, DA is not the only neurotransmitter linked to psychosis. Increasing evidence implicates both glutamate and serotonin neuronal networks as well in the pathophysiology and treatment of some forms of psychosis, not only schizophrenia, but psychoses associated with Parkinson's disease, with various forms of dementia, and with numerous psychotomimetic drugs. Thus, there are

Table 4-1 Pharmacological models link dopamine and serotonin receptor agonists and NMDA glutamate receptor antagonists to psychosis symptoms

	Psychostimulants (cocaine, amphetamine)	Dissociative anesthetics (PCP, ketamine)	Psychedelics (LSD, psilocybin)
Proposed mechanism	Dopamine D_2 agonist	NMDA antagonist	Serotonin $5HT_{2A}$ agonist (and to a lesser extent $5HT_{2C}$)
Main type of hallucinations	Auditory	Visual	Visual
Most frequently associated delusions	Paranoid	Paranoid	Mystical
Insightfulness	No	No	Yes

D_2, dopamine 2; PCP, phencyclidine NMDA, *N*-methyl-D-aspartate; LSD, lysergic acid diethylamide; 5HT, 5-hydroxytryptamine (serotonin).

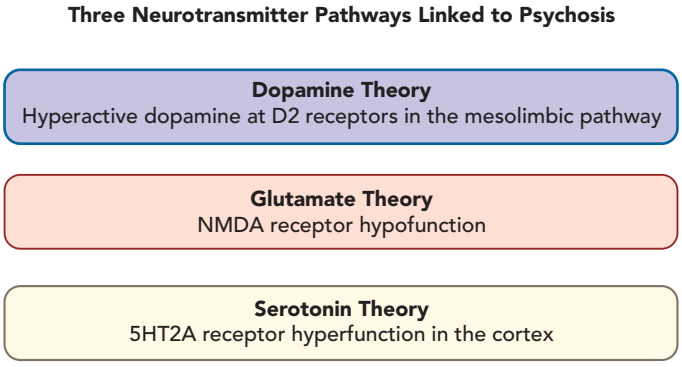


Figure 4-1 Neurotransmitter pathways linked to psychosis. Psychosis has been theoretically linked to three major neurotransmitter pathways. The longstanding dopamine theory centers around the concept of hyperactive dopamine 2 (D_2) receptors in the mesolimbic pathway. The glutamate theory proposes that *N*-methyl-D-aspartate (NMDA) receptors are hypoactive at critical synapses in the prefrontal cortex, which could lead to downstream hyperactivity in the mesolimbic dopamine pathway. The serotonin theory posits that there is serotonergic hyperactivity particularly at serotonin 2A ($5HT_{2A}$) receptors in the cortex, which also could result in hyperactivity in the mesolimbic dopamine pathway. It is likely that one or more of these three pathways is involved in the development of psychosis.

now three major neurotransmitter systems hypothetically linked to psychosis (Figure 4-1 and Table 4-1). What follows is a discussion of each of these three hypotheses accompanied by an extensive presentation of the neuronal pathways and receptors for the three neurotransmitter networks for DA, glutamate, and serotonin.

THE CLASSIC DOPAMINE HYPOTHESIS OF PSYCHOSIS AND SCHIZOPHRENIA

If one had asked any mental health clinician or researcher over the past 50 years what neurotransmitter was linked to psychosis, the resounding answer would have been DA, and specifically DA hyperactivity at D_2 DA receptors in the mesolimbic pathway. This so-called DA hypothesis of psychosis makes sense because release of DA by amphetamine causes a paranoid psychosis similar to the psychosis in schizophrenia (see Table 4-1), and drugs that block DA D_2 receptors have been the mainstay of treatment for essentially all forms of psychosis for over 50 years. Furthermore, this DA theory has proven so powerful that some may still assume (wrongly) that all positive symptoms of psychosis are caused by excessive DA in the mesolimbic pathway and that all treatments must therefore block DA D_2 receptors in this pathway. As it turns out, however, there is much more to psychosis than mesolimbic DA, and much more to the treatment of psychosis than D_2 antagonists, as will be discussed in Chapter 5. Before reviewing the classic and the updated DA hypothesis, not only of psychosis but of drugs that treat psychosis, it is important to understand fully DA neurotransmission, so we will begin with a discussion of DA receptors and brain circuits.

The Dopamine Neurotransmitter Network

To understand the potential role of DA in schizophrenia, we will first review how DA is synthesized, metabolized, and regulated, then show the functions of DA receptors, and finally show the localization of key DA pathways in the brain.

Synthesis and Inactivation of Dopamine in Dopaminergic Neurons

Dopaminergic neurons utilize the neurotransmitter DA, which is synthesized in dopaminergic nerve terminals from the amino acid tyrosine after it is taken up into the neuron from the extracellular space and bloodstream by

a tyrosine pump, or transporter (Figure 4-2). Tyrosine is converted into DA first by the rate-limiting enzyme tyrosine hydroxylase (TOH) and then by the enzyme DOPA decarboxylase (DDC) (Figure 4-2). DA is then taken up into synaptic vesicles by a vesicular monoamine transporter (VMAT2) and stored there until it is used during neurotransmission. Excess DA that escapes storage in synaptic vesicles can be destroyed within the neuron by the enzymes monoamine oxidase A (MAO-A) or monoamine oxidase B (MAO-B) (Figure 4-3A).

In the striatum and some other brain regions, DA terminals have a presynaptic transporter (reuptake pump) called DAT (DA transporter), which is unique for DA and which terminates DA's synaptic action by whisking it out of the synapse back into the presynaptic nerve terminal where it can be re-stored in synaptic vesicles for subsequent reuse in another neurotransmission (Figure 4-3A). DATs are the principle pathway of inactivation for DA at synapses where DATs are present, with secondary inactivation extracellularly by catechol-*O*-methyltransferase (COMT).

DATs are not in high density at the axon terminals of all DA neurons (Figure 4-3B). For example, in the prefrontal cortex, DATs are relatively sparse, and thus DA is inactivated in these synapses by other mechanisms, principally COMT (Figure 4-3B). When DATs are not present, DA can also diffuse away from synapses where it is released until it eventually reaches a neighboring norepinephrine (NE) neuron and confronts its NE transporters (NETs) that then inactivate this DA by transporting it into NE neurons as a "false" substrate (Figure 4-3B).

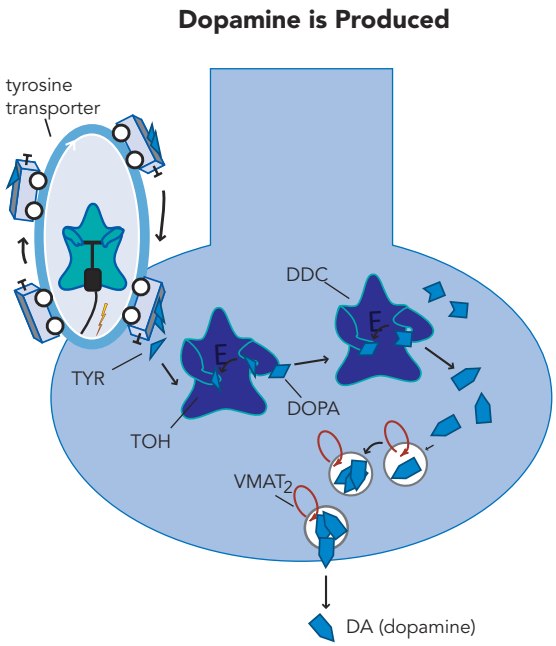


Figure 4-2 Dopamine synthesis. Tyrosine (TYR), a precursor to dopamine, is taken up into dopamine nerve terminals via a tyrosine transporter and converted into DOPA by the enzyme tyrosine hydroxylase (TOH). DOPA is then converted into dopamine by the enzyme DOPA decarboxylase (DDC). After synthesis, dopamine is packaged into synaptic vesicles via the vesicular monoamine transporter (VMAT2) and stored there until its release into the synapse during neurotransmission.

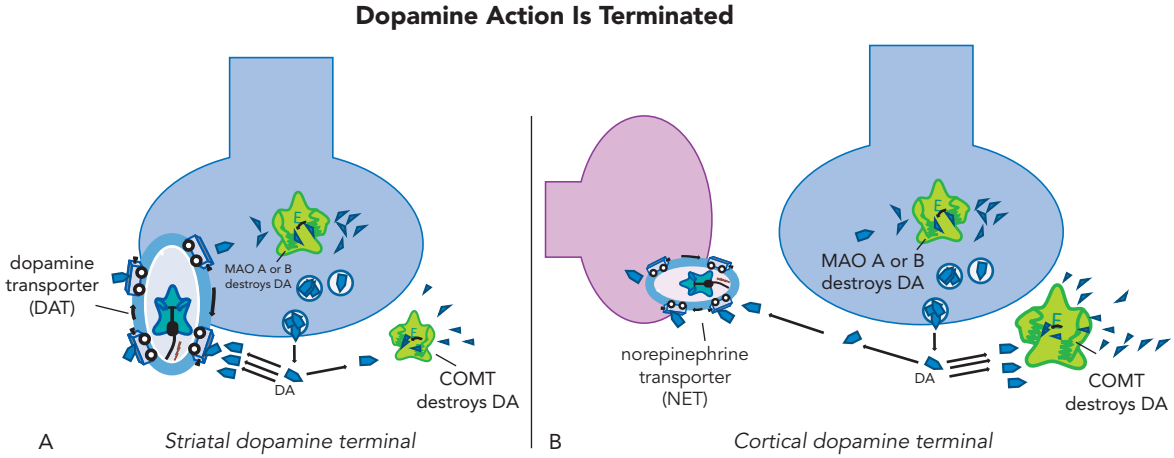


Figure 4-3 Dopamine's action is terminated. Dopamine's action can be terminated through multiple mechanisms. (A) Dopamine can be transported out of the synaptic cleft and back into the presynaptic neuron via the dopamine transporter (DAT), where it may be repackaged for future use. Alternatively, dopamine may be broken down extracellularly via the enzyme catechol-*O*-methyltransferase (COMT). Other enzymes that break down dopamine are monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B), which are present in mitochondria within the presynaptic neuron and in other cells such as glia. (B) In the prefrontal cortex, DATs are relatively sparse; thus, the predominant method of dopamine inactivation is via MAO-A or MAO-B intracellularly, and COMT extracellularly. Dopamine can also diffuse away from the synapses and be taken up by the norepinephrine transporter (NET) at neighboring neurons.

Dopamine Receptors

Receptors for DA are the key regulators of dopaminergic neurotransmission (Figure 4-4). We have already mentioned the DA transporter DAT and the vesicular monoamine transporter VMAT2, which are both types of receptors. A plethora of additional DA receptors exist, including at least five pharmacological subtypes and several more molecular isoforms (Figure 4-4). Currently, DA receptors are divided into two groups. The first group is the D_1-like receptors, including both D_1 and D_5 receptors. D_1-like receptors are excitatory, and positively linked to adenylate cyclase (Figure 4-4, left). The second group is the D_2-like receptors, including D_2, D_3, and D_4 receptors. D_2-like receptors are inhibitory and negatively linked to adenylate cyclase (Figure 4-4, right). Thus, the neurotransmitter DA can be either excitatory or

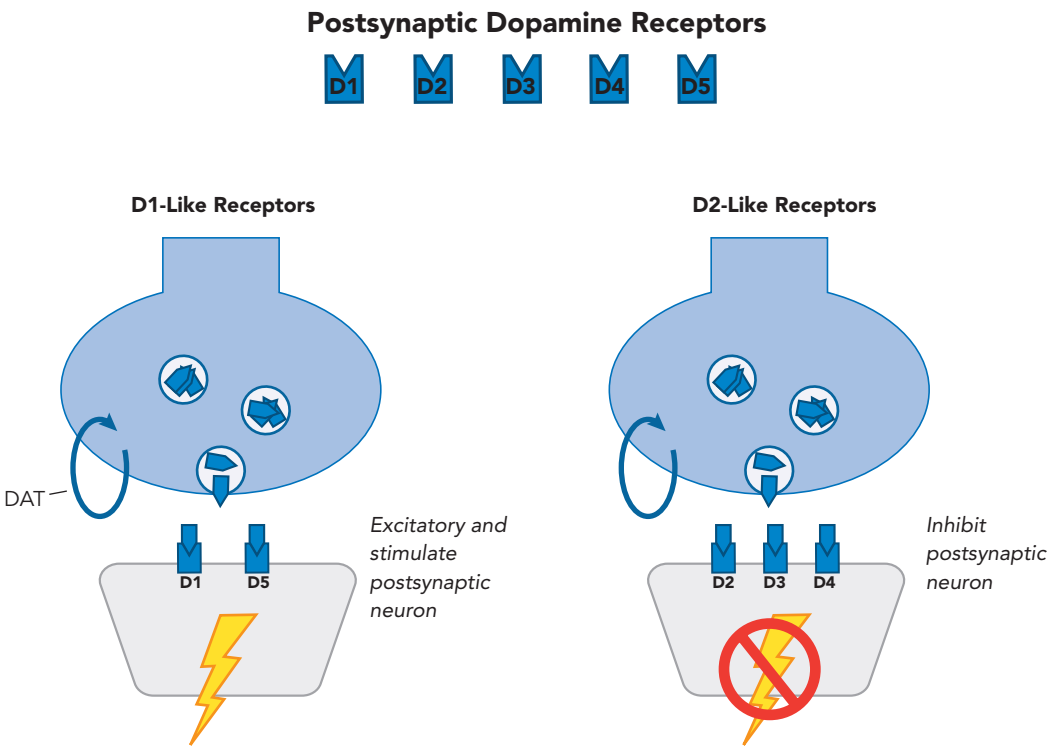


Figure 4-4 Postsynaptic dopamine receptors. There are two groups of postsynaptic dopamine receptors. D_1-like receptors, which include both D_1 and D_5 receptors, are excitatory and thus stimulate the postsynaptic neuron. D_2-like receptors, which include D_2, D_3, and D_4, are inhibitory and thus inhibit the postsynaptic neuron.

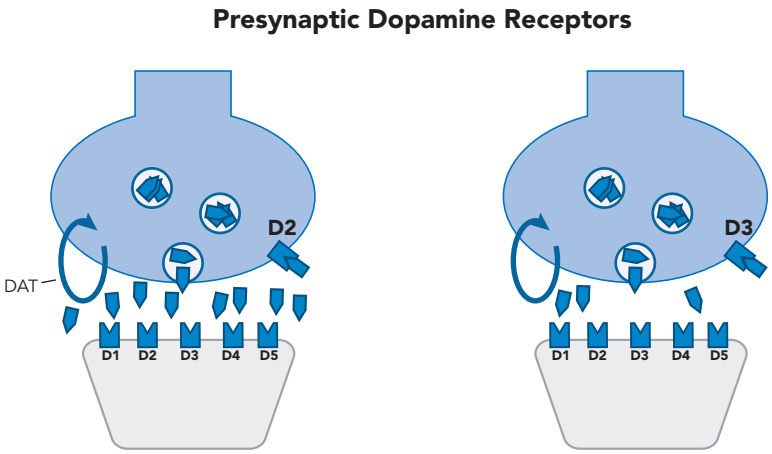


Figure 4-5 Presynaptic dopamine receptors. Dopamine 2 and 3 are also located presynaptically, where, due to their inhibitory actions, they act as autoreceptors to inhibit further dopamine release. The D_2 autoreceptor is less sensitive to dopamine than the D_3 autoreceptor and thus it takes a higher concentration of synaptic dopamine for the D_2 autoreceptor to become activated (left) than it does for the D_3 autoreceptor to become activated (right).

inhibitory, depending upon which DA receptor subtype it binds.

All five DA receptors can be located postsynaptically (Figure 4-4), but D_2 and D_3 receptors can also both be located presynaptically, where, due to their inhibitory actions, they act as autoreceptors to inhibit further DA release (Figure 4-5). Note in Figure 4-5 that more DA has accumulated in the synapse with a D_2 presynaptic autoreceptor (on the left) than in the synapse with a D_3 presynaptic autoreceptor (on the right). This is because the D_3 receptor is more sensitive to DA and thus it takes a lesser concentration of synaptic DA to activate the D_3 receptor and turn off further DA release compared to neurons having the D_2 presynaptic receptor.

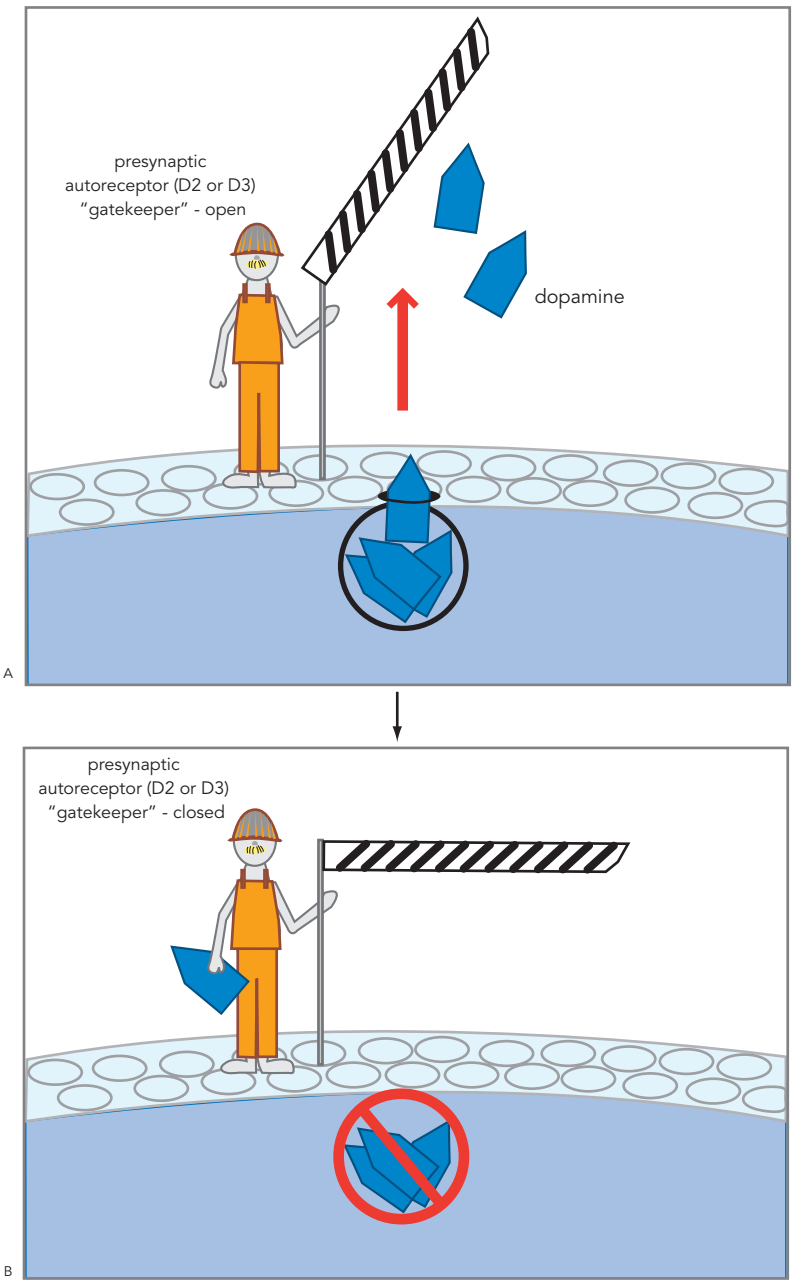


Figure 4-6 Presynaptic dopamine autoreceptors. Presynaptic D_2 and D_3 autoreceptors are "gatekeepers" for dopamine. (A) When dopamine autoreceptors are not bound by dopamine (no dopamine in the gatekeeper's hand), the molecular gate is open and allows dopamine release. (B) When dopamine binds to the dopamine autoreceptor (now the gatekeeper has dopamine in his hand), the molecular gate closes and prevents dopamine from being released.

Presynaptic D_2/D_3 receptors act as "gatekeepers" either allowing DA release when they are not occupied by DA (Figure 4-6A) or inhibiting DA release when DA builds up in the synapse and occupies the gatekeeping presynaptic autoreceptor (Figure 4-6B). Such receptors are located either on the axon terminal (Figure 4-7) or on the other end of the neuron in the somatodendritic area of the DA neuron (Figure 4-8). In both cases, they are considered presynaptic and occupancy of these D_2 or D_3 autoreceptors provides negative feedback input, or a braking action upon the release of DA from the DA neuron (Figures 4-7B and 4-8B).

Thus, DA neurons can be regulated quite differently depending upon which DA receptors are present. This is exemplified not only by synapses with D_3 presynaptic autoreceptors having their DA release regulated in a different manner than synapses with D_2 presynaptic autoreceptors (Figure 4-5), but also when comparing mesocortical DA neurons with mesolimbic and nigrostriatal (mesostriatal) neurons side by side (Figure 4-9). Mesocortical DA neurons arising from the ventral tegmental area (VTA) in the brainstem and projecting to prefrontal cortex have either D_2 or D_3 autoreceptors on their cell bodies in the VTA, but there are only sparse D_2/D_3 receptors in the prefrontal cortex pre- or postsynaptically (Figure 4-9A). Without autoreceptors on axon terminals in the prefrontal cortex, DA release is not shut off by this mechanism and thus is freer to diffuse away from the synapse where it is released, as shown by the large blue cloud of DA. Moreover, as already mentioned, mesocortical DA neurons have few if any DATs on their presynaptic nerve terminals in the

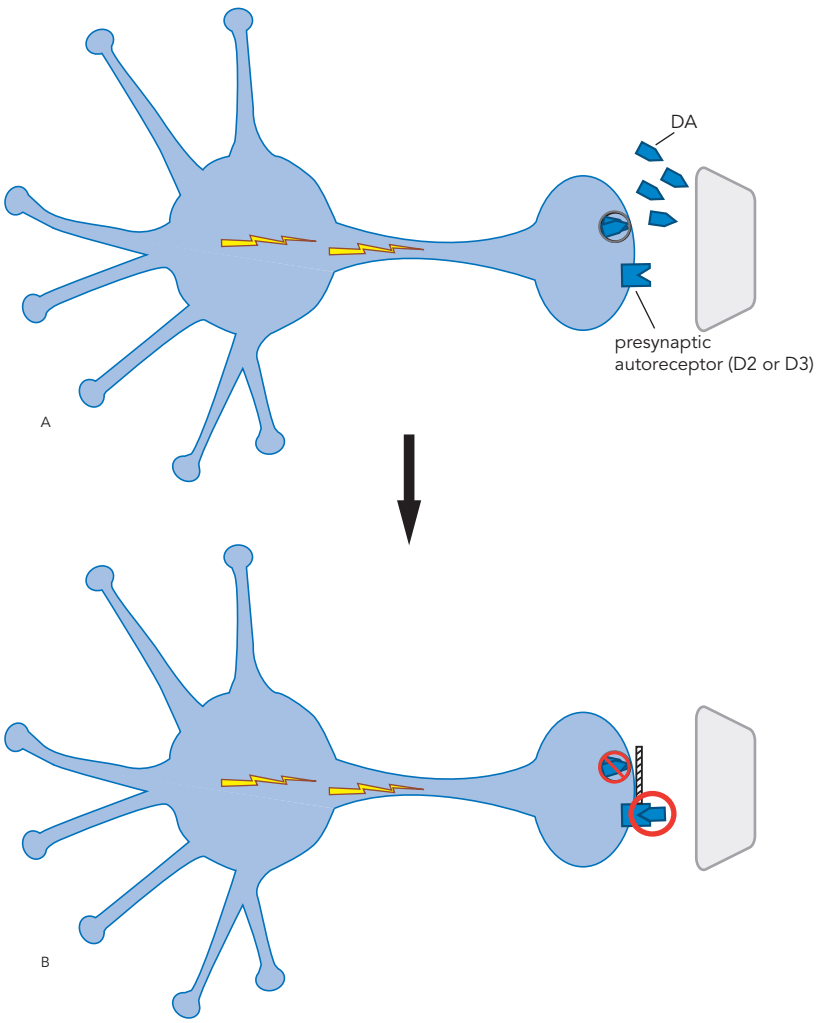


Figure 4-7 Presynaptic dopamine autoreceptors. Presynaptic D_2 and D_3 autoreceptors can be located on the axon terminal, as shown here. When dopamine builds up in the synapse (A), it is available to bind to the autoreceptor, which then inhibits dopamine release (B).

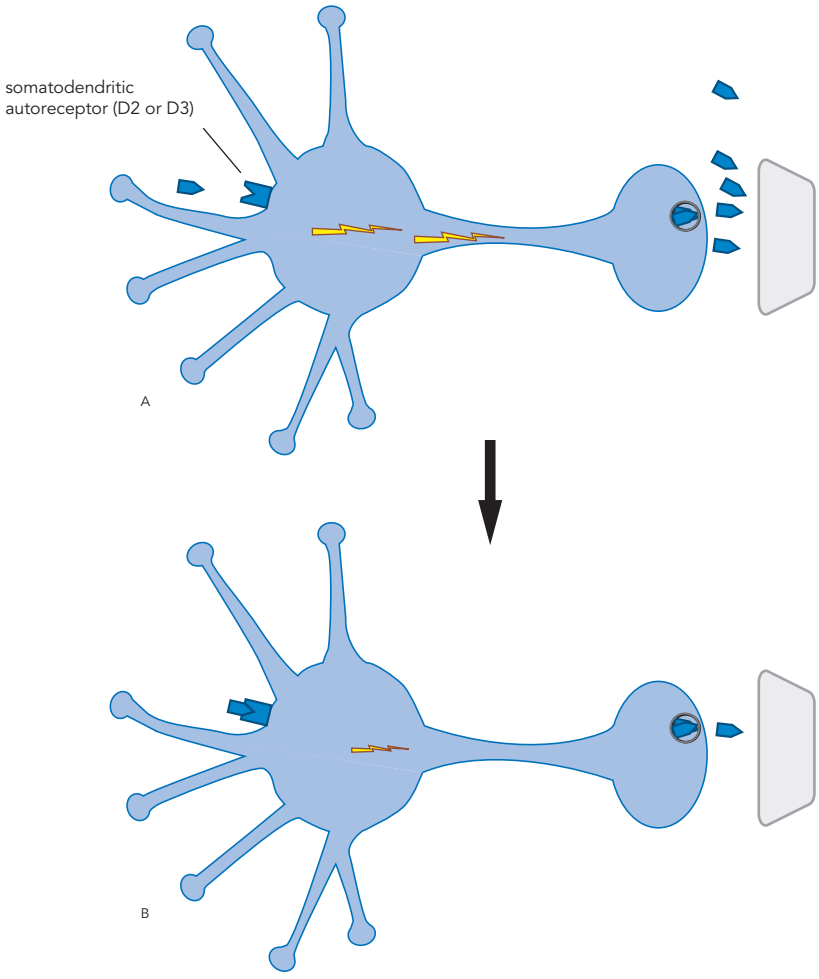


Figure 4-8 Somatodendritic dopamine autoreceptors. D_2 and D_3 autoreceptors can also be located in the somatodendritic area, as shown here. When dopamine binds to the receptor here, it shuts off neuronal impulse flow in the dopamine neuron (see loss of lightning bolts in the neuron in B), and this stops further dopamine release.

prefrontal cortex. Without DATs to whisk synaptic DA back into the presynaptic neuron, or D_2/D_3 presynaptic autoreceptors to turn off DA release as synaptic DA accumulates, this allows a larger diffusion radius of DA away from presynaptic terminals (Figure 4-9A) compared to terminals that have DATs and D_2/D_3 autoreceptors present (Figure 4-9B – note the sizes of the blue clouds in these figures). That is a good thing perhaps, since the predominant postsynaptic receptor in the prefrontal cortex is the D_1 receptor, and the D_1 receptor is the least sensitive to DA and thus requires a higher concentration of DA to be present to be activated compared to D_2 or D_3 receptors. Greater diffusion of DA also means the possibility of volume neurotransmission (see Chapter 1 and Figures 1-6 and 1-7) so that DA from one presynaptic terminal can communicate with D_1 receptors anywhere within its diffusion radius in the prefrontal cortex and thus beyond the synapse from where it was released. On the other hand, mesostriatal DA neurons have either presynaptic D_2 or D_3 receptors present, not only on the cell bodies in the VTA and substantia nigra, but also on presynaptic nerve terminals and postsynaptic sites in the striatum (Figure 4-9B). Furthermore, DATs are present on presynaptic nerve terminals in the striatum of these DA neurons. As mentioned, neurons with D_2 autoreceptors have a wider diffusion radius compared to those with D_3 autoreceptors, providing a range of possibilities for regulation of DA release in the striatum (Figure 4-9B).

Classic Dopamine Pathways and Key Brain Regions

The five classic DA pathways in the brain are shown in Figure 4-10. They include the tuberoinfundibular DA pathway, a thalamic DA pathway, the nigrostriatal DA pathway, and most importantly for the DA hypothesis,

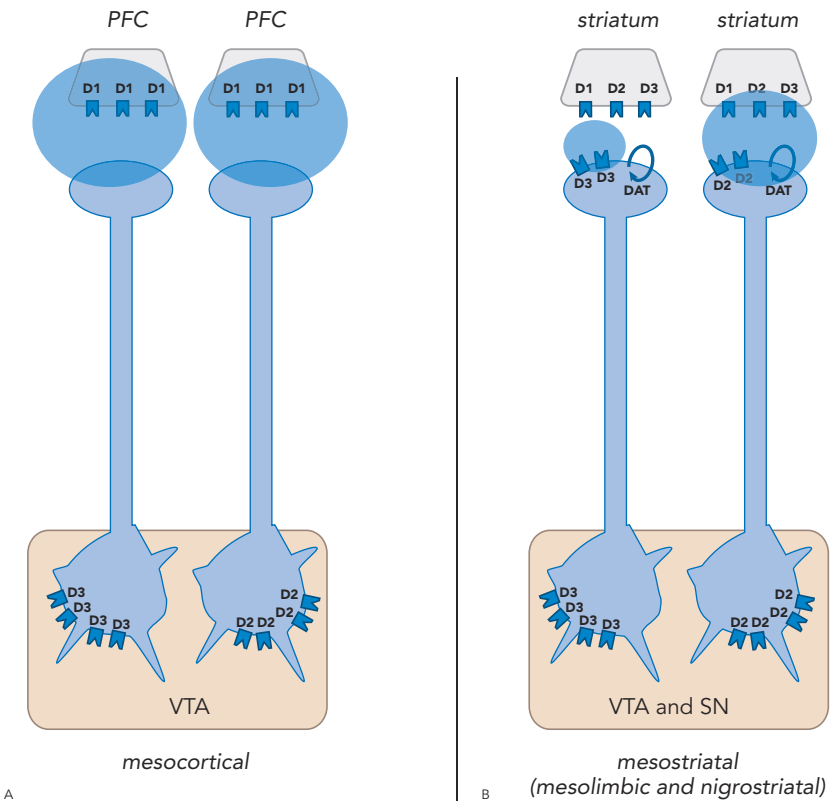


Figure 4-9 Mesocortical vs. mesostriatal neurons. (A) Mesocortical neurons project from the ventral tegmental area (VTA) to the prefrontal cortex (PFC). In the VTA, dopamine release is regulated by somatodendritic D_2 and D_3 autoreceptors. In the PFC, however, there are few D_2 or D_3 presynaptic autoreceptors to inhibit dopamine release, as well as few dopamine transporters (DATs) to remove dopamine from the synapse. Thus, dopamine is more freely able to diffuse away from the synapse (indicated by the large blue cloud). Postsynaptically, the predominant dopamine receptor is D_1, which is excitatory. (B) Dopamine release from mesolimbic neurons (projecting from the VTA to the striatum) is regulated by somatodendritic D_3 autoreceptors in the VTA and by presynaptic D_3 autoreceptors and DATs in the striatum (left). Dopamine release from nigrostriatal neurons (projecting from the substantia nigra [SN] to the striatum) is regulated by somatodendritic D_2 autoreceptors in the SN and by presynaptic D_2 autoreceptors and DATs in the striatum (right). D_2 autoreceptors are less sensitive to dopamine than D_3 autoreceptors, thus allowing for a wider diffusion radius (indicated by the comparative sizes of the blue clouds). Postsynaptically, D_1, D_2, and D_3 receptors are all present in the striatum.

the mesocortical and the mesolimbic DA pathways. Advances in neuroscience propose some more recent and sophisticated ways to view these pathways in schizophrenia, but first we will consider the classic approach.

Tuberoinfundibular Dopamine Pathway

The DA neurons that project from hypothalamus to anterior pituitary gland are known as the tuberoinfundibular DA pathway (Figure 4-11). Normally, these neurons are tonically active and *inhibit* prolactin release. In the postpartum state, however, the activity of these DA neurons is decreased. Prolactin levels can therefore rise during breast feeding so that lactation will occur. If the functioning of tuberoinfundibular DA neurons is disrupted by lesions or drugs, prolactin levels can also rise. Elevated prolactin levels are associated with galactorrhea (breast secretions), gynecomastia (enlarged breasts especially in men), amenorrhea (loss of ovulation and menstrual periods), and possibly other problems such as sexual dysfunction. Such problems can occur after treatment with many drugs for psychosis that block DA D_2 receptors, and will be discussed further in Chapter 5. In untreated schizophrenia, the function of the tuberoinfundibular pathway may be relatively preserved (Figure 4-11).

Thalamic Dopamine Pathway

Recently, a DA pathway that innervates the thalamus in primates has been described. It arises from multiple sites,

Classic Dopamine Pathways and Key Brain Regions

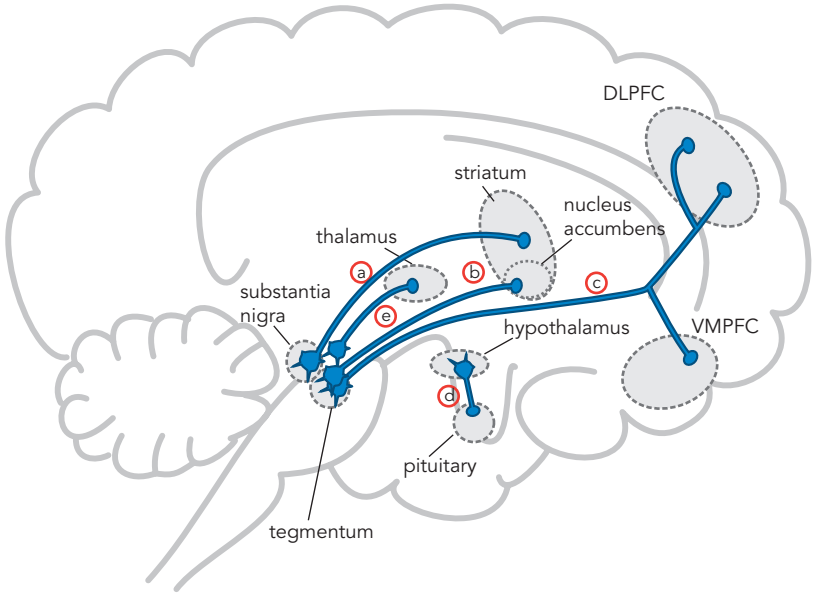


Figure 4-10 **Five dopamine pathways in the brain.** (a) The nigrostriatal dopamine pathway, which projects from the substantia nigra to the basal ganglia or striatum, is part of the extrapyramidal nervous system and controls motor function and movement. (b) The mesolimbic dopamine pathway projects from the midbrain ventral tegmental area (VTA) to the nucleus accumbens, a part of the limbic system of the brain thought to be involved in many behaviors such as pleasurable sensations, the powerful euphoria of drugs of abuse, and delusions and hallucinations of psychosis. (c) The mesocortical dopamine pathway also projects from the midbrain VTA but sends its axons to areas of the prefrontal cortex, where they may have a role in mediating cognitive symptoms (dorsolateral prefrontal cortex or DLPFC) and affective symptoms (ventromedial prefrontal cortex or VMPFC) of schizophrenia. (d) The tuberoinfundibular dopamine pathway projects from the hypothalamus to the anterior pituitary gland and controls prolactin secretion. (e) The fifth dopamine pathway arises from multiple sites, including the periaqueductal gray, ventral mesencephalon, hypothalamic nuclei, and lateral parabrachial nucleus, and projects to the thalamus. Its function is not currently well known.

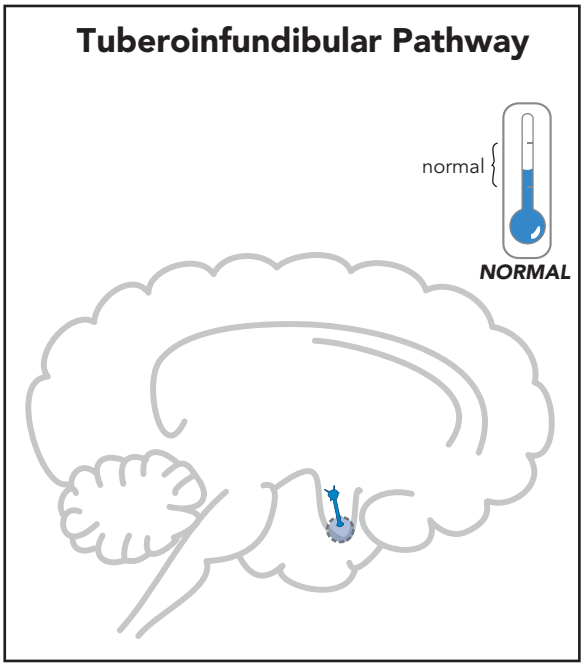


Figure 4-11 **Tuberoinfundibular dopamine pathway.** The tuberoinfundibular dopamine pathway from the hypothalamus to the anterior pituitary gland regulates prolactin secretion into the circulation. Dopamine inhibits prolactin secretion. In untreated schizophrenia, activation of this pathway is believed to be "normal."

including the periaqueductal gray matter, the ventral mesencephalon, from various hypothalamic nuclei, and from the lateral parabrachial nucleus (Figure 4-10). Its function is still under investigation, but may be involved in sleep and arousal mechanisms by gating information passing through the thalamus to the cortex and other brain areas. There is no evidence at this point for abnormal functioning of this DA pathway in schizophrenia.

Nigrostriatal Dopamine Pathway

Another key DA pathway is the nigrostriatal DA pathway, which projects from DA cell bodies in the brainstem substantia nigra via axons terminating in the striatum (Figure 4-12). Classically, the nigrostriatal DA pathway has been considered to be part of the extrapyramidal nervous system, and to control motor movements via its connections with the thalamus and cortex in cortico-striato-thalamo-cortical (CSTC) circuits or loops (Figure 4-13A). A more sophisticated anatomical model of how DA regulates CSTC loops and motor movements in the striatum is shown in Figures 4-13B through Figure 4-13F as the "direct" and "indirect" DA pathways. The so-called direct pathway (shown in Figure 4-13B on the left and in Figures 4-13C and 4-13E) is populated with D_1 dopamine receptors that are excitatory (Figure 4-13E; see also Figure 4-4, left) and projects directly from the striatum to the globus pallidus interna to *stimulate* movements ("go" pathway) (Figure 4-13C). The so-called indirect pathway (shown in Figure 4-13B on the right and in Figures 4-13D and 4-13F) is populated with D_2 dopamine receptors that are inhibitory (Figure 4-13F; see also Figure 4-4, right) and projects indirectly to the globus pallidus interna via the globus pallidus externa and subthalamic nucleus. Normally, this pathway *blocks* motor movements ("stop" pathway) (see Figure 4-13D). Dopamine inhibits this action at D_2 receptors in the indirect pathway (Figure 4-13F) and this says "don't stop" to the stop pathway, or "go more." The bottom line is that dopamine stimulates motor movements in both the direct and indirect motor pathways. Synchronizing the outputs of these pathways is thought to lead to the smooth execution of motor movements.

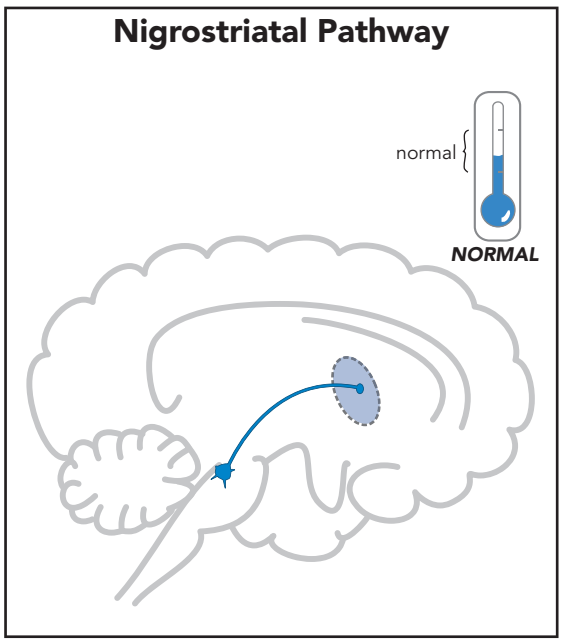
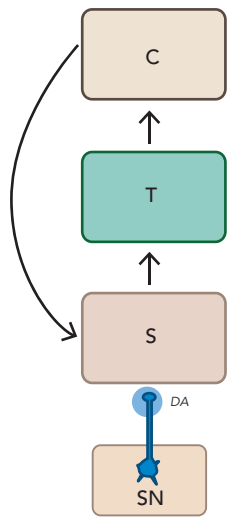


Figure 4-12 Nigrostriatal dopamine pathway. The nigrostriatal dopamine pathway projects from the substantia nigra to the basal ganglia or striatum. It is part of the extrapyramidal nervous system and plays a key role in regulating movements. When dopamine is deficient, it can cause parkinsonism with tremor, rigidity, and akinesia/bradykinesia. When dopamine is in excess, it can cause hyperkinetic movements such as tics and dyskinesias. In untreated schizophrenia, activation of this pathway is believed to be "normal."

Classic CSTC (Cortico-Striato-Thalamo-Cortical) Loop



C = cortex
T = thalamus
S = striatum
SN = substantia nigra

Figure 4-13A Cortico-striato-thalamo-cortical (CSTC) loop. In the most simple terms, the nigrostriatal dopamine pathway is considered to control motor movements via its connections with the thalamus and cortex in a circuit known as the cortico-striato-thalamo-cortical loop.

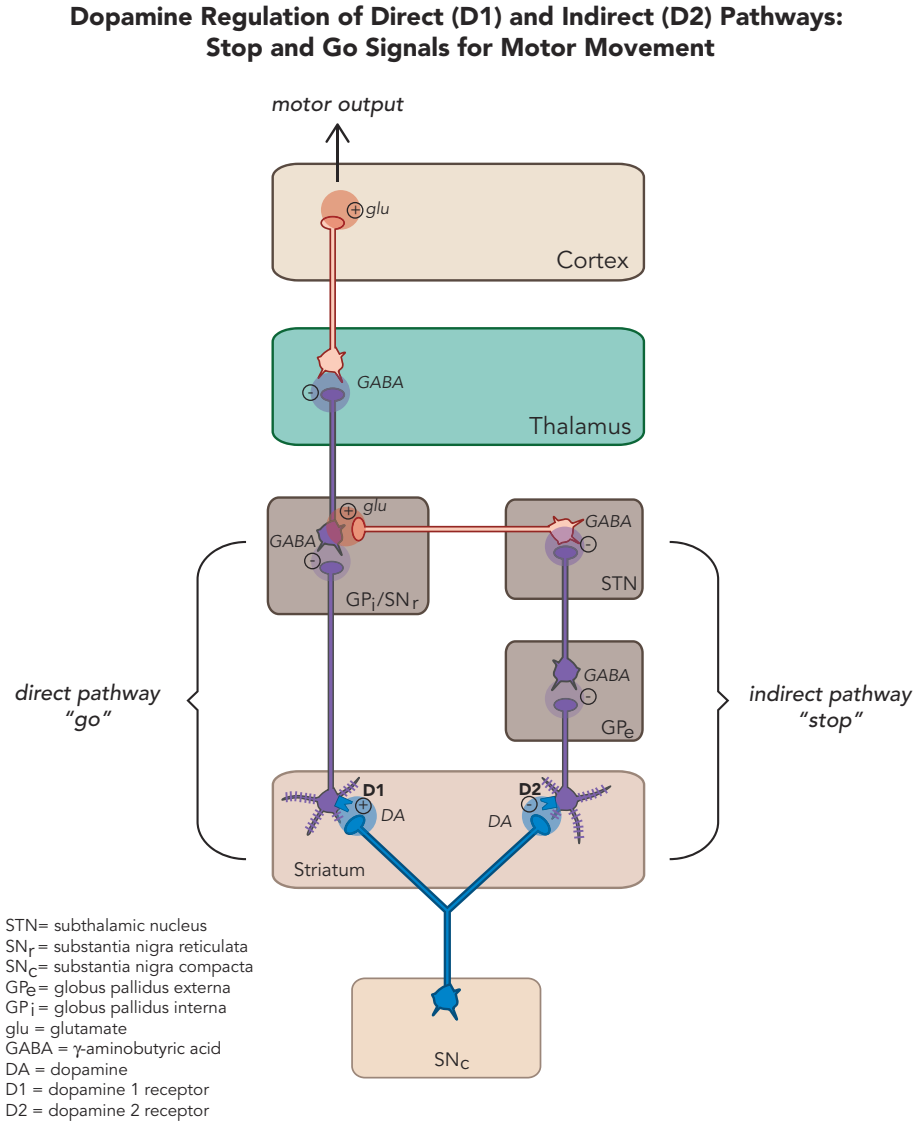


Figure 4-13B Direct and indirect dopamine pathways for motor control. Populated with excitatory D_1 receptors, the direct pathway for dopamine regulation of motor movements (left) projects from the striatum to the globus pallidus interna and results in the stimulation of movement. The indirect pathway for dopamine regulation of motor movements (right) projects to the globus pallidus interna via the globus pallidus externa and subthalamic nuclei. This pathway is populated with inhibitory D_2 receptors and normally blocks motor movements.

Although there is no evidence at this point for abnormal functioning of this DA pathway in schizophrenia (Figures 4-12 and 4-13), deficiencies of DA in these motor pathways cause movement disorders including Parkinson's disease, characterized by rigidity, akinesia/bradykinesia (i.e., lack of movement or slowing of movement), and tremor. DA deficiency in the striatum can hypothetically also be involved in the mechanism that produces akathisia (a type of restlessness) and dystonia (twisting movements especially of the face and

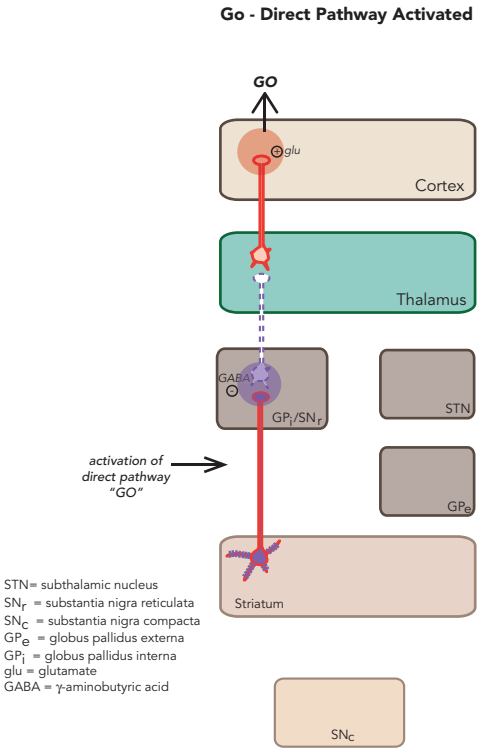


Figure 4-13C Activation of the direct (go) dopamine pathway. A γ-aminobutyric acid (GABA) neuron projecting from the striatum to the globus pallidus interna is activated. The released GABA inhibits activity of another GABAergic neuron that projects to the thalamus. In the absence of GABA release in the thalamus, a glutamatergic neuron is activated and releases glutamate into the cortex, stimulating movement.

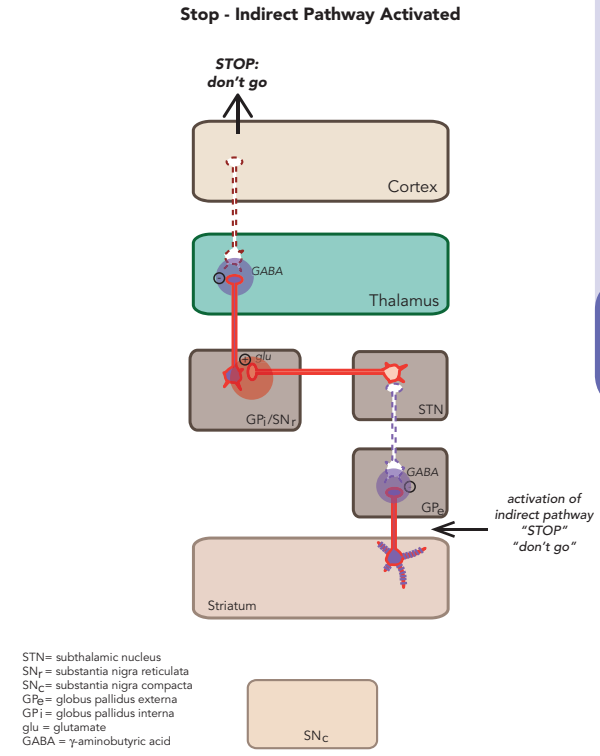


Figure 4-13D Activation of the indirect (stop) dopamine pathway. A γ-aminobutyric acid (GABA) neuron projecting from the striatum to the globus pallidus externa is activated. The released GABA inhibits activity of another GABAergic neuron that projects to the subthalamic nucleus (STN). In the absence of GABA release in the STN, a glutamatergic neuron is activated and releases glutamate into the globus pallidus interna, which in turn stimulates a GABAergic neuron to release GABA into the thalamus. GABA then binds to a glutamatergic neuron, inhibiting it from releasing glutamate into the cortex and thus inhibiting movement.

neck). These same movement disorders can be replicated by drugs that block D_2 DA receptors in this pathway, causing drug-induced parkinsonism (sometimes called by its better-known but much less accurate name extrapyramidal symptoms or EPS). This will be discussed in more detail in Chapter 5 on drugs for the treatment of psychosis.

Not only can too little DA activity cause movement disorders, so can too much. Thus, hyperactivity of DA in the nigrostriatal pathway is thought to underlie various hyperkinetic movement disorders such as chorea, dyskinesias, and tics (in conditions such as Huntington's disease, Tourette syndrome, and others). Chronic stimulation of D_2 DA receptors in the nigrostriatal pathway by treatment of Parkinson's disease with levodopa is hypothesized to underlie the emergence of abnormal hyperkinetic and dyskinetic movements (called levodopa-induced dyskinesias or LID). Chronic blockade of these same D_2 DA receptors in the nigrostriatal pathway is hypothesized to cause another hyperkinetic movement disorder known as tardive dyskinesia. Tardive dyskinesia and its treatment will be discussed further in Chapter 5 on drugs for psychosis.

The Mesolimbic Dopamine Pathway

The mesolimbic DA pathway projects from DA cell bodies in the VTA of the brainstem (i.e., mesencephalon) to the nucleus accumbens in the ventral striatum, which is part of the limbic system (thus, mesolimbic) (Figures 4-10 and 4-14 A–D). DA release from this pathway is thought to have an important role in several

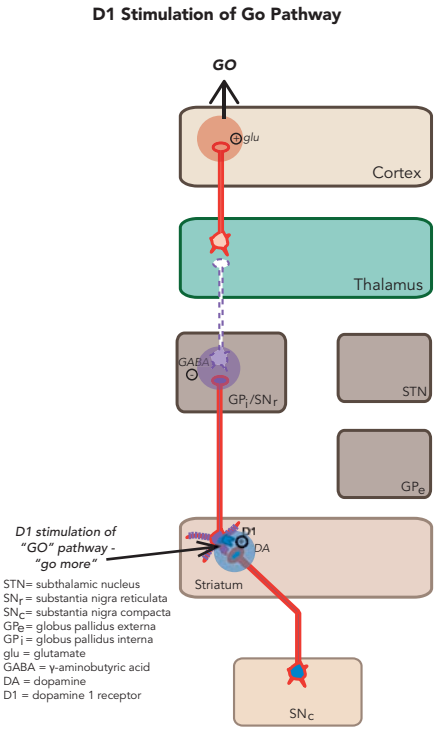


Figure 4-13E Dopamine-1 receptor stimulation of the go pathway. Dopamine released from the nigrostriatal pathway binds to postsynaptic D_1 receptors on a γ-aminobutyric acid (GABA) neuron projecting to the globus pallidus interna. This causes phasic activation of the direct (go) pathway, essentially telling it to "go more."

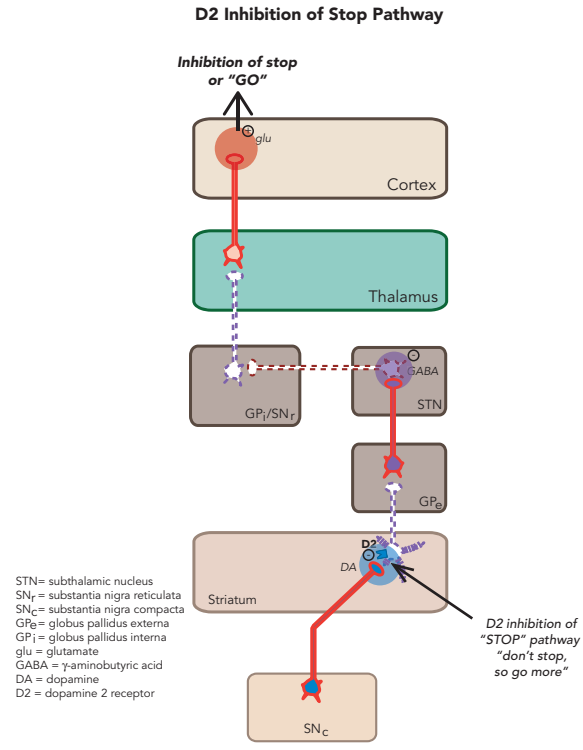


Figure 4-13F Dopamine-2 receptor inhibition of the stop pathway. Dopamine released from the nigrostriatal pathway binds to postsynaptic D_2 receptors on a γ-aminobutyric acid (GABA) neuron projecting to the globus pallidus externa. This causes inhibition of the indirect (stop) pathway, thus instead telling it to "go."

normal emotional behaviors, including motivation, pleasure, and reward (Figure 4-14A). Although this may be an oversimplification, the mesolimbic dopamine pathway may in fact be the final common pathway of all reward and reinforcement, including not only normal reward (such as the pleasure of eating good food, orgasm, listening to music) (Figure 4-14A), but also emotions experienced when rewards are too high (Figures 4-14B and C) or too low (Figure 4-14D). Too much DA in this pathway classically is thought to cause the positive symptoms of psychosis (Figure 4-14C) as well as the artificial reward (drug-induced "high") of substance abuse (Figure 4-14B) (see also discussion on drugs of abuse in Chapter 13). On the other hand, too little DA in this pathway hypothetically causes the symptoms of anhedonia, apathy, and lack of energy seen in conditions such as unipolar and bipolar depression and in the negative symptoms of schizophrenia (Figure 4-14D).

The Classic Dopamine Hypothesis of the Positive Symptoms of Psychosis: Mesolimbic HyperDopaminergia

As mentioned above, hyperactivity of this mesolimbic DA pathway ("hyperdopaminergia") hypothetically accounts for positive psychotic symptoms (that is, delusions and hallucinations) as a final common pathway for psychosis, whether those symptoms are part of the illness of schizophrenia, of drug-induced psychosis, or whether positive psychotic symptoms accompany mania, depression, Parkinson's disease, or dementia. Hyperactivity of mesolimbic DA neurons may also play a role in causing impulsive, agitated, aggressive, and hostile symptoms in any of the illnesses associated with positive symptoms of psychosis (Figure 4-15). Although mesolimbic DA hyperactivity can be a direct pharmacological consequence of psychostimulants such as cocaine and methamphetamine, mesolimbic DA hyperactivity in psychosis associated with schizophrenia, mania,

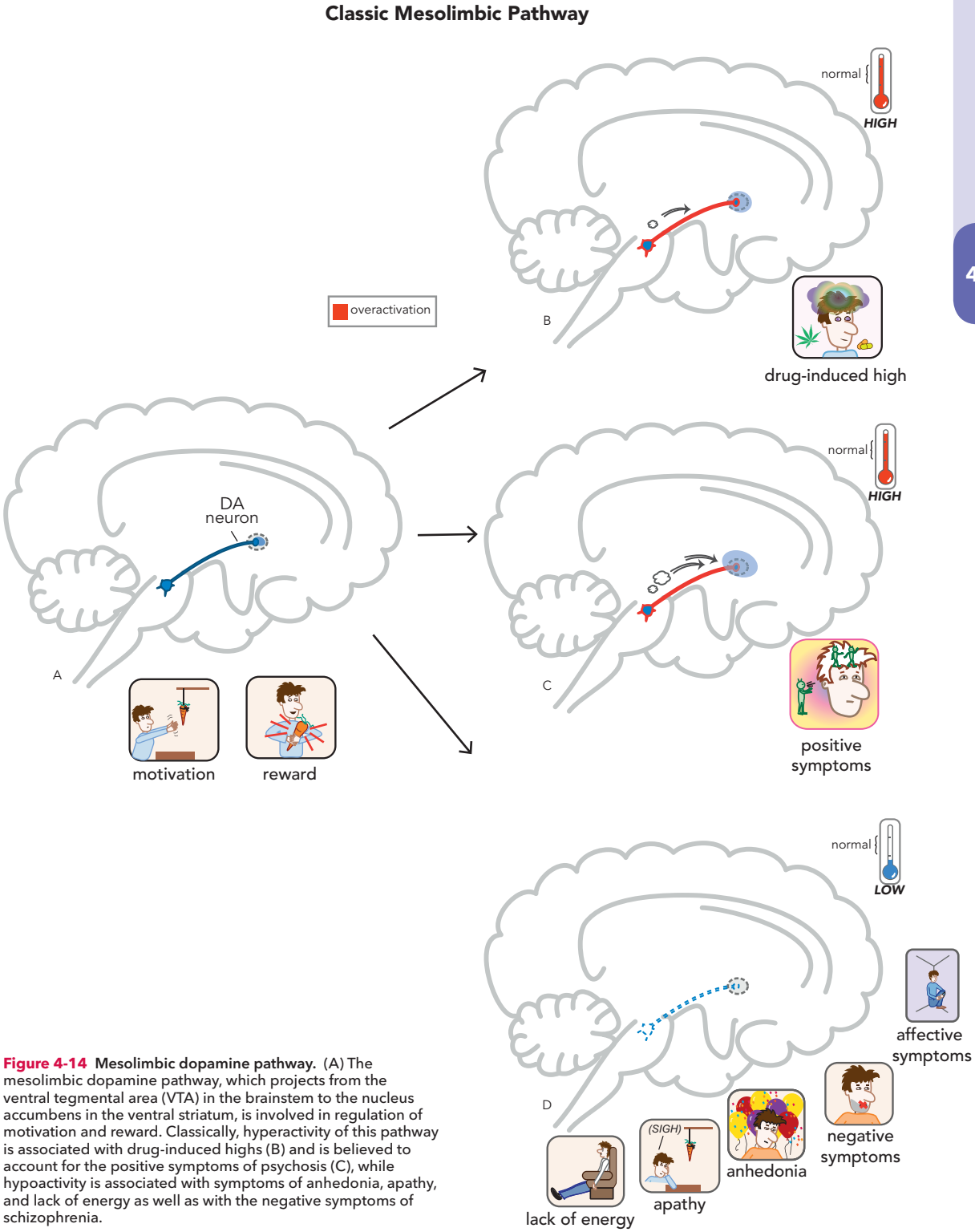


Figure 4-14 Mesolimbic dopamine pathway. (A) The mesolimbic dopamine pathway, which projects from the ventral tegmental area (VTA) in the brainstem to the nucleus accumbens in the ventral striatum, is involved in regulation of motivation and reward. Classically, hyperactivity of this pathway is associated with drug-induced highs (B) and is believed to account for the positive symptoms of psychosis (C), while hypoactivity is associated with symptoms of anhedonia, apathy, and lack of energy as well as with the negative symptoms of schizophrenia.

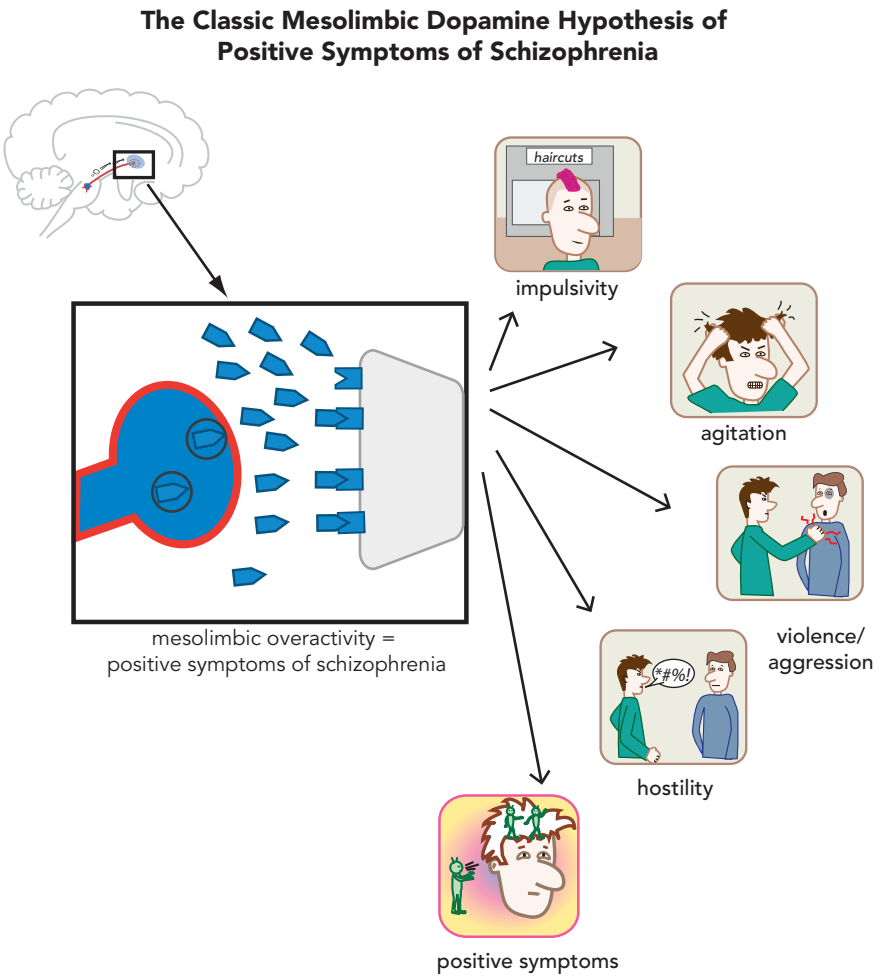


Figure 4-15 Mesolimbic dopamine hypothesis. Hyperactivity of dopamine neurons in the mesolimbic dopamine pathway theoretically mediates the positive symptoms of psychosis such as delusions and hallucinations. Mesolimbic overactivity may also be associated with impulsivity, agitation, violence/aggression, and hostility.

depression, Parkinson's disease, or Alzheimer disease and other dementias may be the indirect consequence of dysregulation in prefrontal circuits and their glutamate and serotonin neurons as well as dopamine neurons. These brain circuits are discussed in detail in the following sections on glutamate and serotonin.

New Developments in the Dopamine Hypothesis of Positive Symptoms of Psychosis in Schizophrenia

Classically, DA projections from the substantia nigra to the dorsal striatum (Figure 4-12) have been considered to regulate motor movements and to be in parallel with pathways from the VTA to the ventral striatum (nucleus accumbens) that regulate emotions (Figure 4-14A). A simplistic notion is that there is a dorsal or "upper" striatum for motor movements (the "neurologists' striatum") and a ventral or "lower" striatum for emotions (the "psychiatrists' striatum") (Figure 4-16A). These concepts have been derived largely from anatomical and pharmacological studies in rodents combined with drug studies in humans. Although heuristically valuable, recent results from human neuroimaging studies show that the idea of separate dedicated pathways where anatomical differences correlate with function (motor vs. emotion) may need to be modified. That is, neuroimaging of DA activity in the striatum of living, unmedicated patients with schizophrenia does not show the expected hyperdopaminergia uniquely in the ventral striatum. Instead, the hyperdopaminergia may be especially present in an intermediate part of the striatum

called the associative striatum, which receives input from the substantia nigra but not from the VTA (Figure 4-16B). These findings suggest that a more sophisticated formulation of DA pathways may be necessary in order to understand the hyperdopaminergia of schizophrenia. That is, hyperdopaminergia in projections not only from the VTA but perhaps especially from the medial and lateral substantia nigra may also be important in mediating the positive symptoms of schizophrenia (Figure 4-16B). These findings indicate a remarkable development in thinking about the dorsal striatum and nigrostriatal pathways as having emotional as well as motor components. Compulsions and habits are also theoretically localized to the dorsal striatum (discussed

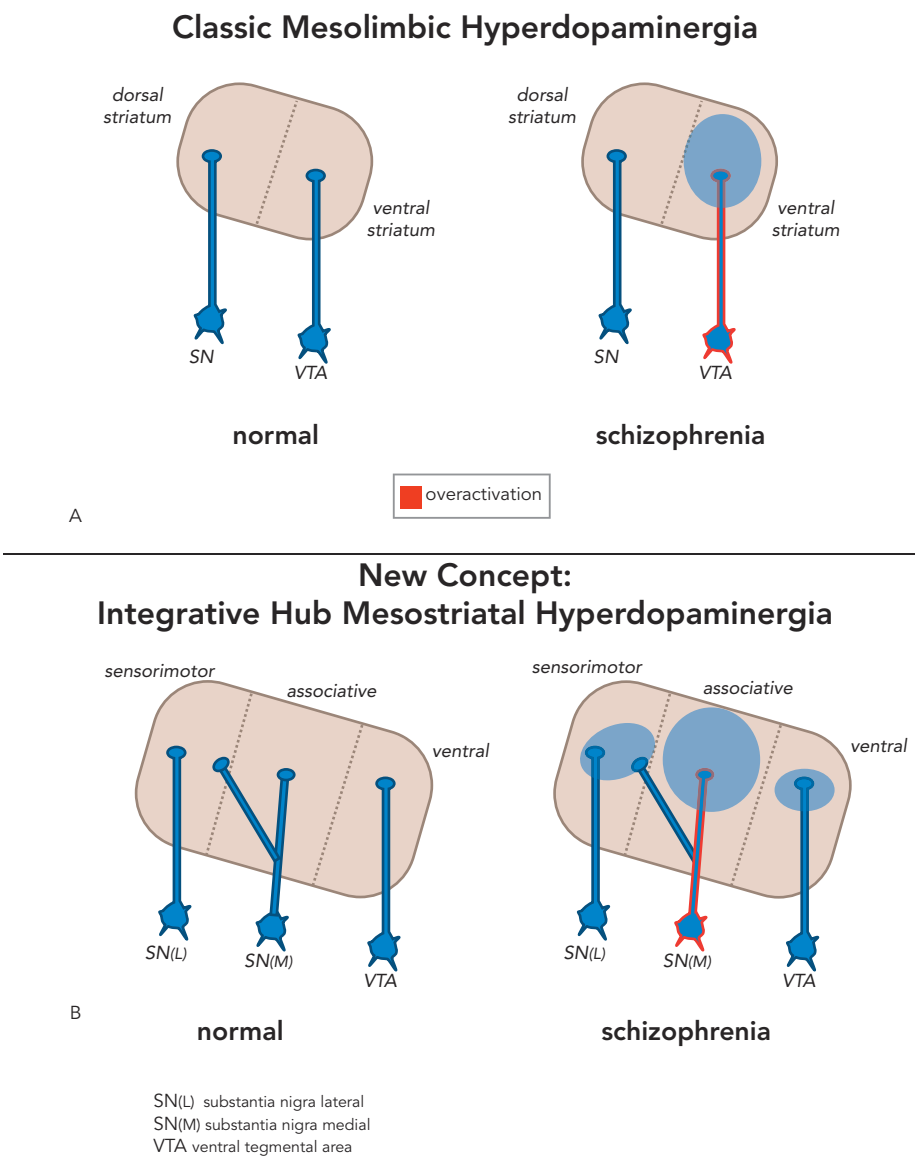


Figure 4-16 Integrative hub mesostriatal hyperdopaminergia. (A) A classic understanding of striatal functioning has been that the dorsal striatum regulates motor movement and the ventral striatum regulates emotions, with overactivity of dopamine in the ventral striatum associated with the positive symptoms of schizophrenia. (B) Neuroimaging data in unmedicated patients with schizophrenia suggest that dopaminergic activity may be unaltered in the ventral striatum, but may instead be overactive in an intermediate part of the striatum called the associative striatum, which receives input from the substantia nigra rather than the ventral tegmental area (VTA). Rather than separate nigrostriatal and mesolimbic projections, a better conception may be that of a mesostriatal pathway.

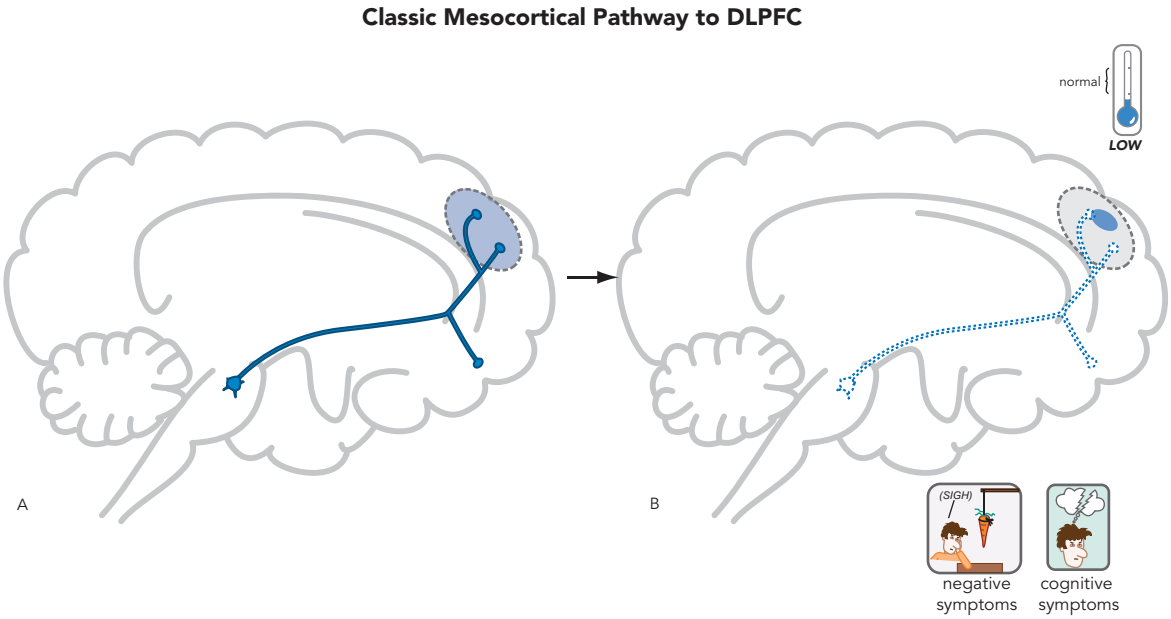


Figure 4-17 Mesocortical pathway to the dorsolateral prefrontal cortex (DLPFC). The mesocortical dopamine pathway projects from the ventral tegmental area (VTA) to the prefrontal cortex. Projections specifically to the DLPFC are associated with cognitive and executive functioning (A), with hypoactivity in this pathway classically believed to be involved in the cognitive and some negative symptoms of schizophrenia (B).

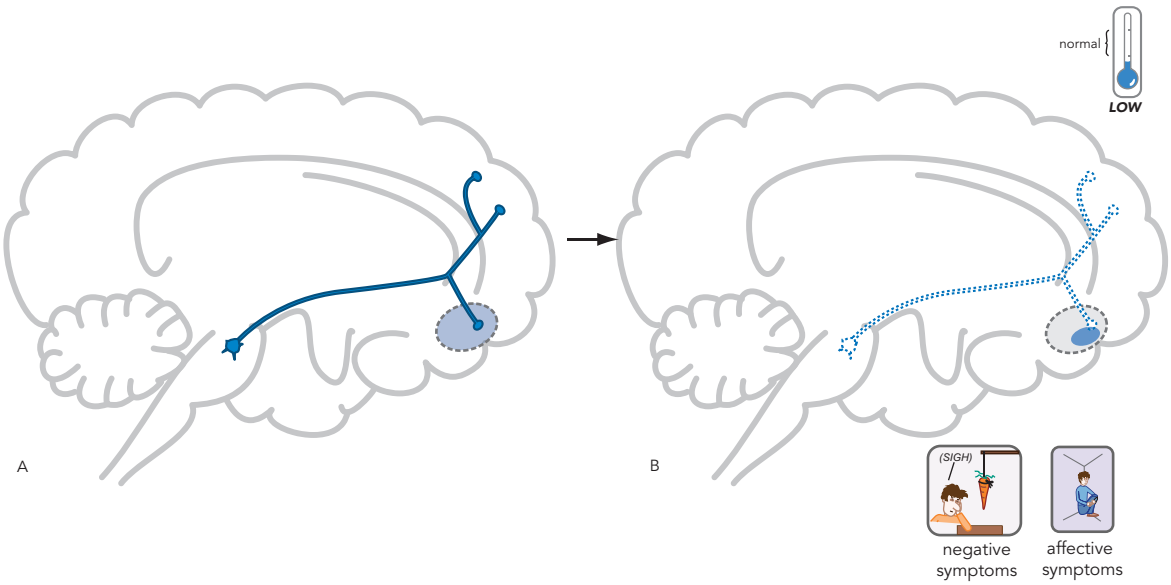


Figure 4-18 Mesocortical pathway to the ventromedial prefrontal cortex (VMPFC). The mesocortical dopamine pathway projects from the ventral tegmental area (VTA) to the prefrontal cortex. Projections specifically to the VMPFC are associated with emotions and affect (A), with hypoactivity in this pathway classically believed to be involved in the negative and affective symptoms of schizophrenia (B).

in Chapter 13). Thus, the dorsal striatum may not be all motor and only the neurologists' striatum! It may also have an important role in emotional regulation. The bottom line is that rather than thinking of the projections from the midbrain to the striatum as parallel pathways with separate and distinct functions (as in Figure

The Classic Mesocortical Dopamine Hypothesis of Cognitive, Negative, and Affective Symptoms of Schizophrenia

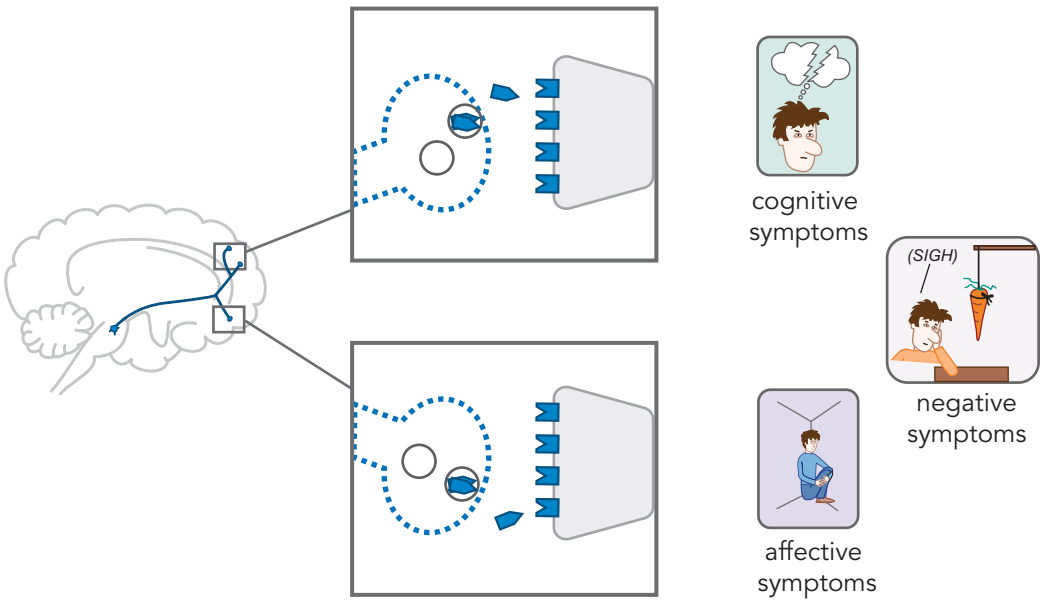


Figure 4-19 Mesocortical dopamine hypothesis. Hypoactivity of dopamine neurons in the mesocortical dopamine pathway theoretically mediates the cognitive, negative, and affective symptoms of schizophrenia.

4-16A), the new notion from neuroimaging is that the VTA–substantia nigra complex is instead an integrative hub and its pathways can be thought of as mesostriatal rather than nigrostriatal/mesolimbic (Figure 4-16B). Hyperdopaminergia of schizophrenia in this sense is mesostriatal rather than purely mesolimbic.

Corollary to the Classic Dopamine Hypothesis of Schizophrenia: Mesocortical HypoDopaminergia and the Cognitive, Negative, and Affective Symptoms of Schizophrenia

Another DA pathway also arising from cell bodies in the VTA but projecting to areas of the prefrontal cortex is known as the *mesocortical DA pathway* (Figures 4-17 through 4-19). Branches of this pathway into the dorsolateral prefrontal cortex are hypothesized to regulate cognition and executive functions (Figure 4-17), whereas branches of this pathway into the ventromedial parts of prefrontal cortex are hypothesized to regulate emotions and affect (Figure 4-18). The exact role of the mesocortical DA pathway in mediating symptoms of schizophrenia is still a matter of debate, but many researchers believe that cognitive and some negative symptoms of schizophrenia may be due to a deficit of DA activity in mesocortical projections to the dorsolateral prefrontal cortex (Figure 4-17) whereas affective and other negative symptoms of schizophrenia may be due to a deficit of DA activity in mesocortical projections to ventromedial prefrontal cortex (Figure 4-18). The behavioral deficit state suggested by negative symptoms certainly implies underactivity or lack of proper functioning of mesocortical DA projections, and a leading theory is that this is the consequence of neurodevelopmental abnormalities in the *N*-methyl-D-aspartate (NMDA) glutamate system, as described in the following section on glutamate.

THE GLUTAMATE HYPOTHESIS OF PSYCHOSIS AND SCHIZOPHRENIA

The glutamate theory of psychosis proposes that the NMDA (*N*-methyl-D-aspartate) subtype of glutamate receptor is hypofunctional at critical synapses in the prefrontal cortex (Table 4-1 and Figure 4-1). Disruption of NMDA glutamate functioning can be hypothetically due to the neurodevelopmental abnormalities in schizophrenia, to the neurodegenerative abnormalities in Alzheimer disease and other dementias, and to the NMDA receptor blocking actions of drugs such as the dissociative anesthetics

ketamine and phencyclidine (PCP) (Figure 4-1 and Table 4-1). In order to understand how glutamate dysfunction could lead to the positive, negative, and cognitive symptoms of psychosis in various disorders, and also how glutamate dysfunction might cause the downstream hyperdopaminergia discussed in the previous section, we will first review glutamate and its receptors and pathways.

The Glutamate Neurotransmitter Network

Glutamate is the major excitatory neurotransmitter in the central nervous system and is sometimes considered to be the "master switch" of the brain, since it can excite and turn on virtually all central nervous system neurons. In recent years, glutamate has attained a key theoretical role in the hypothesized pathophysiology of schizophrenia, of positive symptoms of psychosis in general, and also in a number of other psychiatric disorders, including depression. It is also now a key target of novel psychopharmacological agents for the treatment of schizophrenia and depression. The synthesis, metabolism, receptor regulation, and key pathways of glutamate are therefore critical to the functioning of the brain and will be reviewed here.

Glutamate Synthesis

Glutamate, or glutamic acid, is a neurotransmitter that is an amino acid. Its predominant use is not as a neurotransmitter, but as an amino acid building block for protein biosynthesis. When used as a neurotransmitter, it is synthesized from glutamine in glia, which also assist in the recycling and regeneration of more glutamate following glutamate release during neurotransmission. When glutamate is released from synaptic vesicles of glutamate neurons, it interacts with receptors in the synapse and is then transported into neighboring glia by a reuptake pump known as an excitatory amino acid transporter (EAAT) (Figure 4-20A). The presynaptic glutamate neuron and the postsynaptic site of glutamate neurotransmission may also have EAATs (not shown in the figures) but these EAATs do not appear to play as important a role in glutamate recycling and regeneration as the EAATs in glia (Figure 4-20A).

After reuptake into glia, glutamate is converted into glutamine inside the glia by an enzyme known as glutamine synthetase (arrow 3 in Figure 4-20B). It is possible that glutamate is not simply reused but rather converted into glutamine, to keep it in a pool for neurotransmitter use, rather than being lost into the pool for protein synthesis. Glutamine is released from glia by reverse transport via a pump or transporter known as a specific neutral amino acid transporter (SNAT, arrow 4 in Figure 4-20C). Glutamine may also be transported out of glia by a second transporter known as a glial alanine–serine–cysteine transporter or ASC-T (not shown). When

Glutamate Is Recycled and Regenerated: Part 1

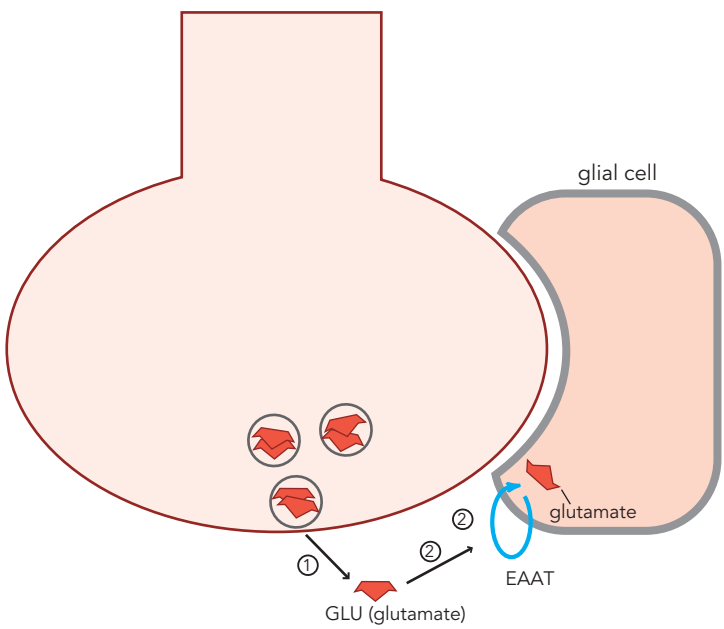


Figure 4-20A Glutamate is recycled and regenerated, part 1. After release of glutamate from the presynaptic neuron (1), it is taken up into glial cells via the excitatory amino acid transporter (EAAT) (2).

Glutamate Is Recycled and Regenerated: Part 2

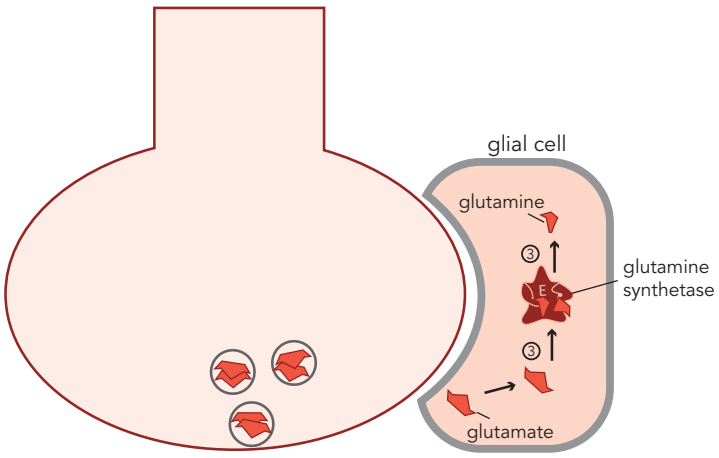


Figure 4-20B Glutamate is recycled and regenerated, part 2. Once inside the glial cell, glutamate is converted into glutamine by the enzyme glutamine synthetase (3).

Glutamate Is Recycled and Regenerated: Part 3

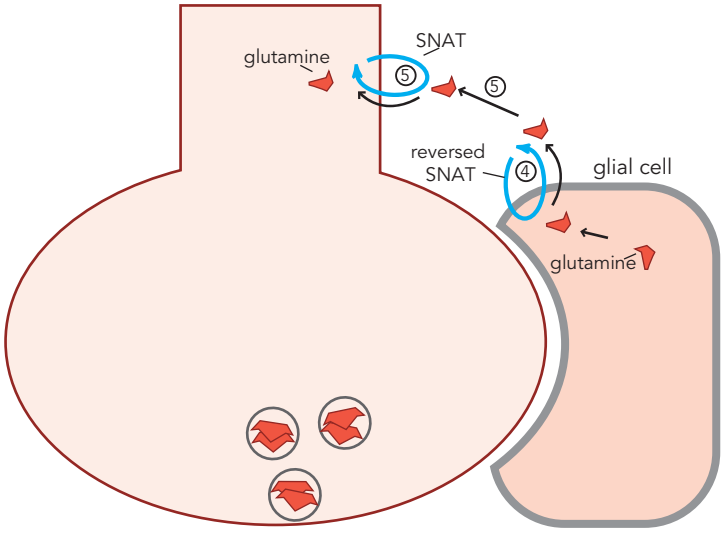


Figure 4-20C Glutamate is recycled and regenerated, part 3. Glutamine is released from glial cells by a specific glial neutral amino acid transporter (SNAT) through the process of reverse transport (4), and then taken up by SNATs on glutamate neurons (5).

glial SNATs and ASC-Ts operate in the inward direction, they transport glutamine and other amino acids into glia. Here, they are reversed so that glutamine can get out of the glia and hop a ride into a neuron via a different type of neuronal SNAT, operating inwardly in a reuptake manner (arrow 5 in Figure 4-20C).

Once inside the neuron, glutamine is converted back into glutamate for use as a neurotransmitter by an enzyme in mitochondria called glutaminase (arrow 6 in Figure 4-20D). Glutamate is then transported into synaptic vesicles via a vesicular glutamate transporter (vGluT, arrow 7 in Figure 4-20D), where it is stored for subsequent release during neurotransmission. Once released, glutamate's actions are stopped not by enzymatic breakdown, as in other neurotransmitter systems, but by removal by EAATs on neurons or glia, and the whole cycle is started again (Figures 4-20A–D).

Synthesis of Glutamate Cotransmitters Glycine and D-Serine

Glutamate systems are curious in that one of the key receptors for glutamate requires a cotransmitter in addition to glutamate in order to function. That receptor is the NMDA receptor, described below, and

Glutamate Is Recycled and Regenerated: Part 4

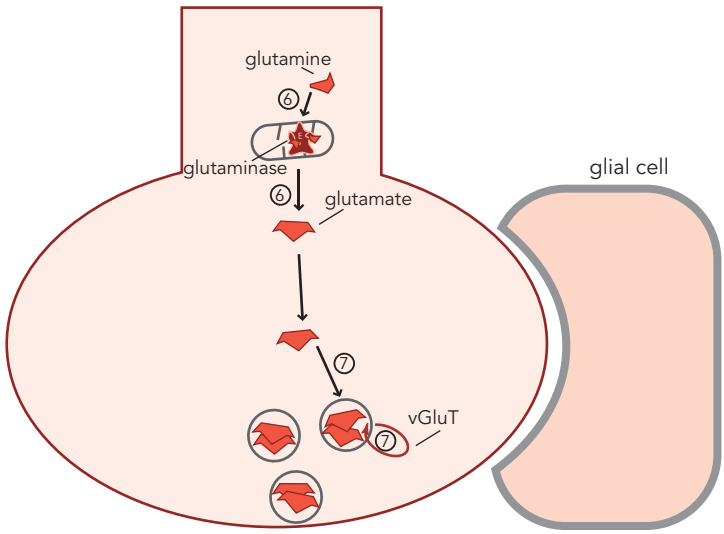


Figure 4-20D Glutamate is recycled and regenerated, part 4. Glutamine is converted into glutamate within the presynaptic glutamate neuron by the enzyme glutaminase (6) and taken up into synaptic vesicles by the vesicular glutamate transporter (vGluT), where it is stored for future release.

the cotransmitter is either the amino acid glycine (Figure 4-21), or another amino acid, closely related to glycine, known as D-serine (Figure 4-22).

Glycine is not known to be synthesized by glutamate neurons, so glutamate neurons must get the glycine they need for their NMDA receptors either from glycine neurons or from glia (Figure 4-21). Glycine neurons contribute only a small amount of glycine to glutamate synapses, since much of the glycine they release is taken back up into those neurons by a type of glycine reuptake pump known as the type 2 glycine transporter (GlyT2) (Figure 4-21).

Thus, neighboring glia are thought to be the source of most of the glycine available for glutamate synapses. Glycine itself can be taken up into glia as well as into glutamate neurons from the synapse by a type 1 glycine transporter (GlyT1) (Figure 4-21). Glycine can also be taken up into glia by a glial SNAT (specific neutral amino acid transporter). Glycine is not known to be stored within synaptic vesicles of glia, but as we will learn below, the companion neurotransmitter D-serine is thought possibly to be stored within some type of storage vesicle within glia. Glycine in the cytoplasm of glia is nevertheless somehow available for release into synapses, and it escapes from glial cells by riding outside them and into the glutamate synapse on a reversed GlyT1 transporter (Figure 4-21). Once outside, glycine can get right back into the glia by an inwardly directed GlyT1, which functions as a reuptake pump and is the main mechanism responsible for terminating the action of synaptic glycine (Figure 4-21). GlyT1 transporters are probably also located on the glutamate neuron, but any release or storage from the glutamate neuron is not well characterized (Figure 4-21). Glycine can also be synthesized from the amino acid L-serine, derived from the extracellular space, bloodstream, and diet, transported into glia by an L-serine transporter (L-SER-T), and converted from L-serine into glycine by the glial enzyme serine hydroxymethyl-transferase (SHMT) (Figure 4-21). This enzyme works in both directions, either converting L-serine into glycine, or glycine into L-serine.

How is the cotransmitter D-serine produced? D-serine is unusual in that it is a D-amino acid, whereas the 20 known essential amino acids are all L-amino acids, including D-serine's mirror image amino acid L-serine. It just so happens that D-serine has high affinity for the glycine site on NMDA receptors, and that glia are equipped with an enzyme that can convert regular L-serine into the neurotransmitting amino acid D-serine by means of an enzyme that can go back and forth between D- and L-serine known as D-serine racemase (Figure 4-22). Thus, D-serine can be derived either from glycine or from L-serine, both of which can be transported into glia by their own transporters, and then glycine converted to L-serine by the enzyme SHMT, and finally L-serine converted into D-serine by the enzyme D-serine racemase (Figure 4-22). Interestingly, the D-serine so

NMDA Receptor Cotransmitter Glycine Is Produced

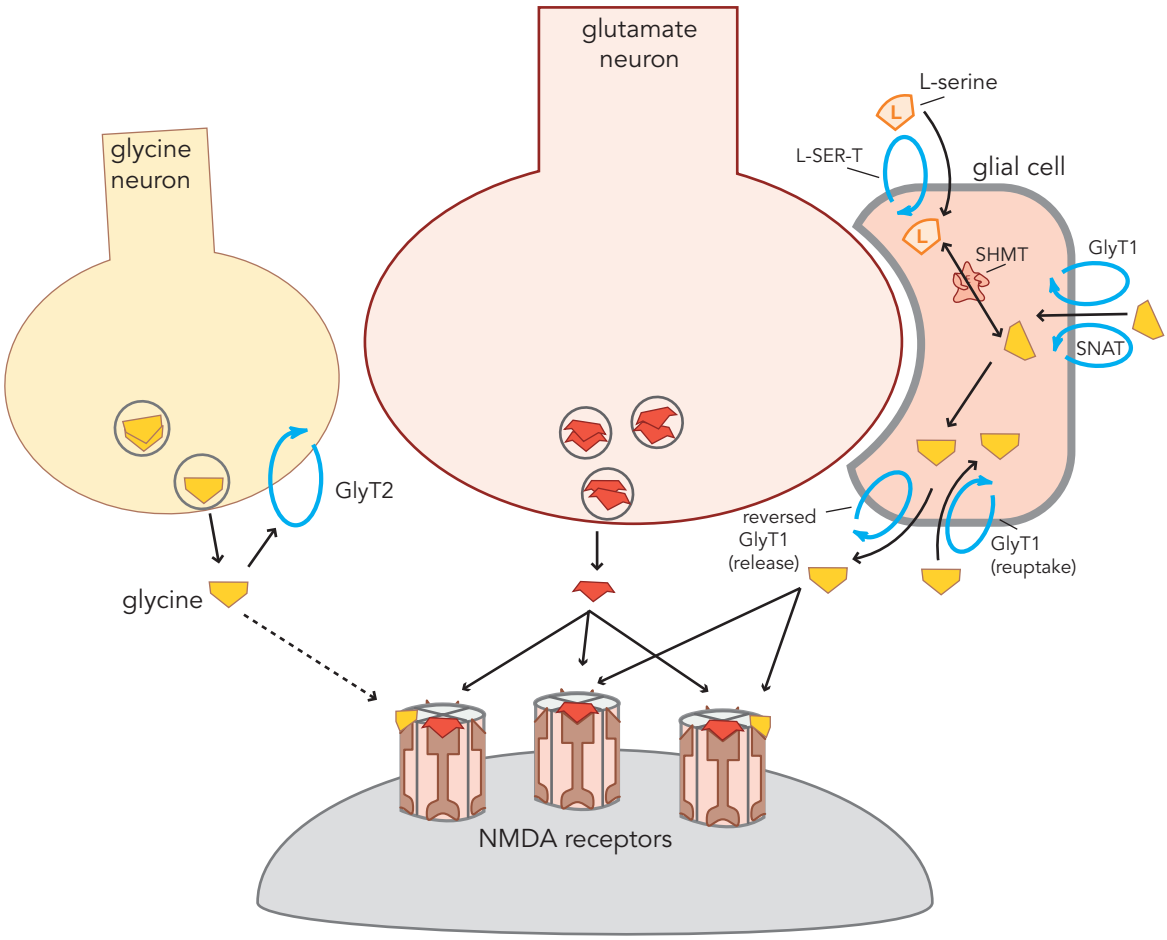


Figure 4-21 NMDA receptor cotransmitter glycine is produced. Glutamate's actions at NMDA receptors are dependent in part upon the presence of a cotransmitter, either glycine or D-serine. Glycine can be derived directly from dietary amino acids and transported into glial cells either by a glycine transporter (GlyT1) or by a specific neutral amino acid transporter (SNAT). Glycine can also be produced both in glycine neurons and in glial cells. Glycine neurons provide only a small amount of the glycine at glutamate synapses, because most of the glycine released by glycine neurons is used only at glycine synapses and then taken back up into presynaptic glycine neurons via the glycine 2 transporter (GlyT2) before much glycine can diffuse to glutamate synapses. Glycine produced by glial cells plays a larger role at glutamate synapses. Glycine is produced in glial cells when the amino acid L-serine is taken up into glial cells via the L-serine transporter (L-SER-T), and then converted into glycine by the enzyme serine hydroxymethyl-transferase (SHMT). Glycine from glial cells is released into the glutamate synapse through reverse transport by GlyT1. Extracellular glycine is then transported back into glial cells via GlyT1.

produced may be stored in some sort of vesicle in glia for subsequent release on a reversed glial D-serine transporter (D-SER-T) for neurotransmitting purposes at glutamate synapses containing NMDA receptors. D-serine's actions are not only terminated by synaptic reuptake via the inwardly acting glial D-SER-T, but also by an enzyme D-amino acid oxidase (DAO) that converts D-serine into inactive hydroxypyruvate (Figure 4-22). Below, we will discuss how the brain makes an activator of DAO, known not surprisingly as D-amino acid oxidase activator or DAOA.

Glutamate Receptors

There are several types of glutamate receptors (Figure 4-23 and Table 4-2), including the neuronal presynaptic reuptake pump (EAAT) and the vesicular transporter for glutamate into synaptic vesicles (vGluT), both of which are types of receptors. The general pharmacological

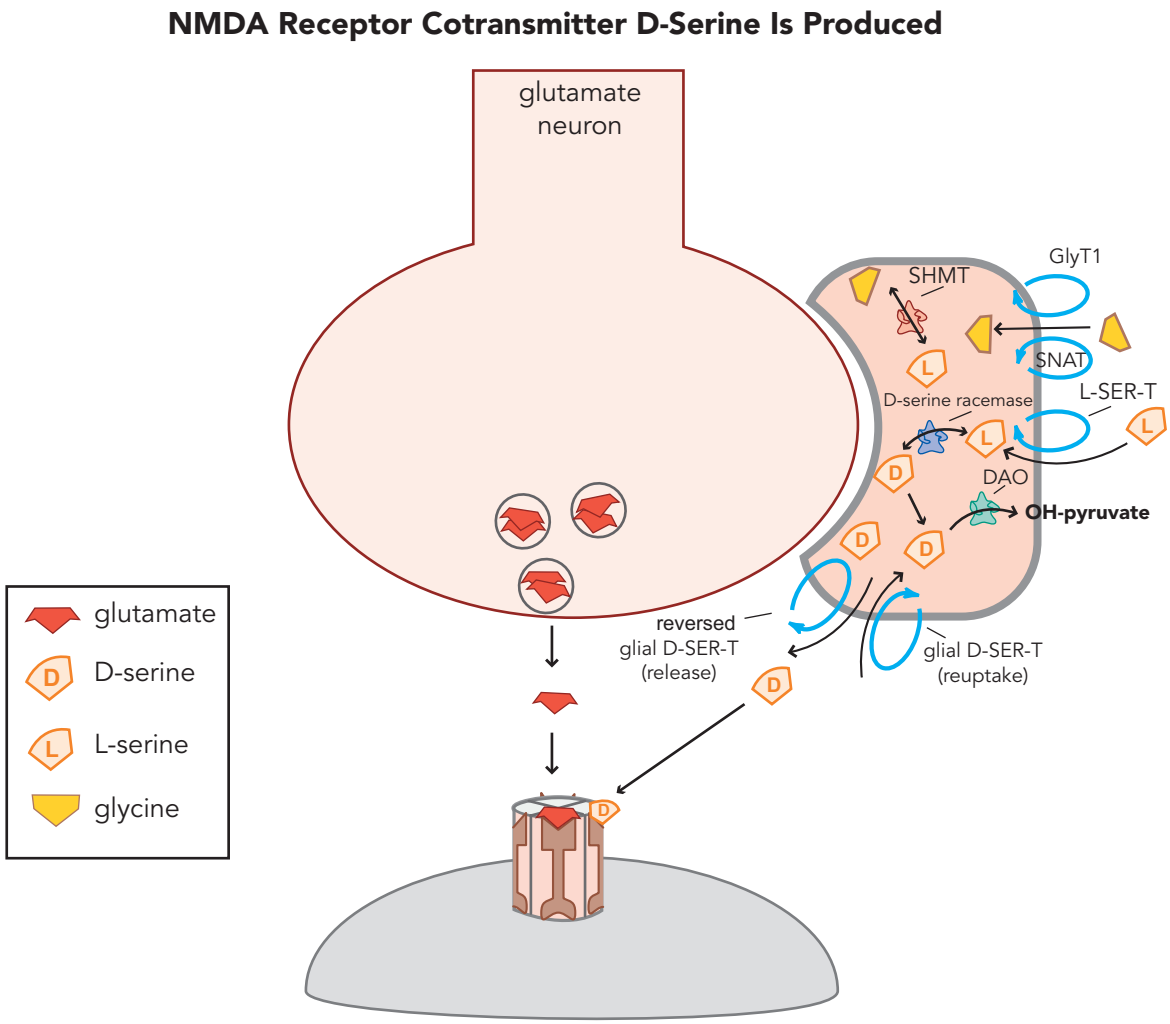


Figure 4-22 NMDA receptor cotransmitter D-serine is produced. Glutamate requires the presence of either glycine or D-serine at NMDA receptors in order to exert some of its effects there. In glial cells, the enzyme serine racemase converts L-serine into D-serine, which is then released into the glutamate synapse via reverse transport on the glial D-serine transporter (glial D-SER-T). L-serine's presence in glial cells is a result of either its transport there via the L-serine transporter (L-SER-T) or its conversion into L-serine from glycine via the enzyme serine hydroxymethyl-transferase (SHMT). Once D-serine is released into the synapse, it is taken back up into the glial cell by a reuptake pump called D-SER-T. Excess D-serine within the glial cell can be destroyed by the enzyme D-amino acid oxidase (DAO), which converts D-serine into hydroxypyruvate (OH-pyruvate).

properties of various transporters are discussed in Chapter 2. Shown also on the presynaptic neuron as well as the postsynaptic neuron are metabotropic glutamate receptors (Figure 4-23). Metabotropic glutamate receptors are those glutamate receptors that are linked to G proteins. The general pharmacological properties of G-protein-linked receptors are also discussed in Chapter 2.

There are at least eight subtypes of metabotropic glutamate receptors, organized into three separate groups (Table 4-2). Research suggests that Group II and Group III metabotropic receptors can occur presynaptically, where they function as autoreceptors to block glutamate release (Figures 4-23 and 4-24). Drugs that stimulate these presynaptic autoreceptors as agonists may therefore *reduce* glutamate release. Group I metabotropic glutamate receptors on the other hand may be located predominantly postsynaptically, where they hypothetically interact with other postsynaptic glutamate receptors to facilitate and strengthen responses mediated by ligand-gated ion-channel receptors for glutamate during excitatory glutamatergic neurotransmission (Figure 4-23).

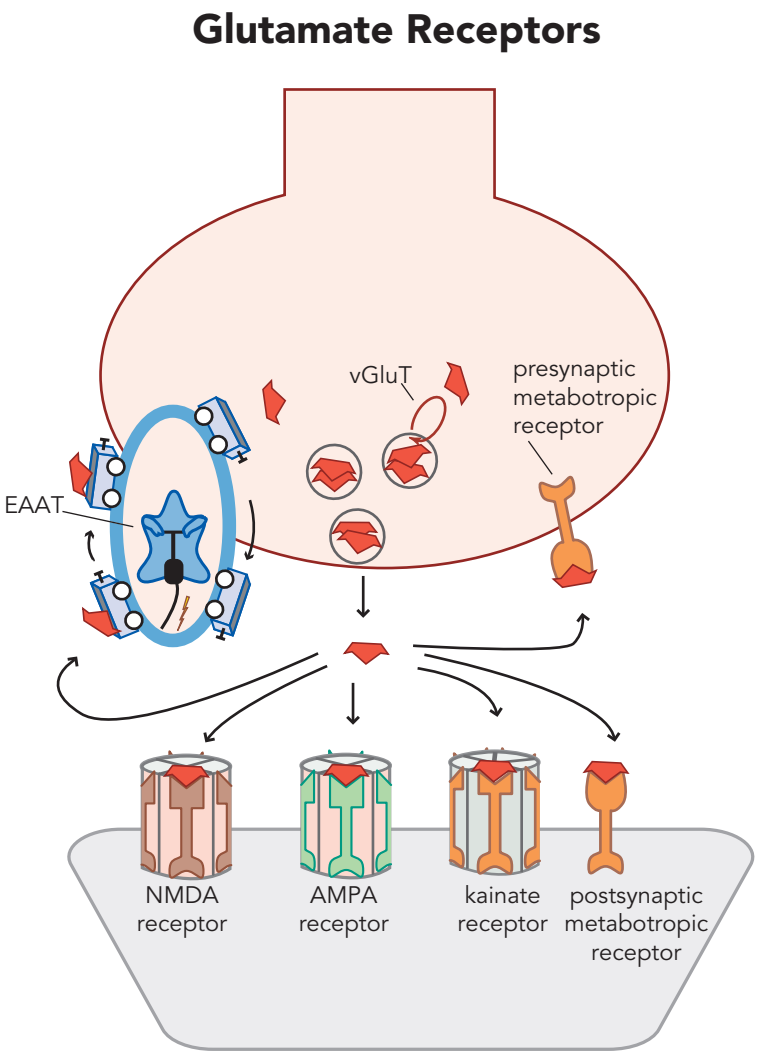


Figure 4-23 Glutamate receptors. Shown here are receptors for glutamate that regulate its neurotransmission. The excitatory amino acid transporter (EAAT) exists presynaptically and is responsible for clearing excess glutamate out of the synapse. The vesicular transporter for glutamate (vGluT) transports glutamate into synaptic vesicles, where it is stored until used in a future neurotransmission. Metabotropic glutamate receptors (linked to G proteins) can occur either pre- or postsynaptically. Three types of postsynaptic glutamate receptors are linked to ion channels, and are known as ligand-gated ion channels: *N*-methyl-D-aspartate (NMDA) receptors, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors, and kainate receptors, all named for the agonists that bind to them.

NMDA (*N*-methyl-D-asparate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid), and kainate receptors for glutamate, named after the agonists that selectively bind to them, are all members of the ligand-gated ion-channel family of receptors (Figure 4-23 and Table 4-2). These ligand-gated ion channels are also known as ionotropic receptors and also as ion-channel-linked receptors. The general pharmacological properties of ligand-gated ion channels are discussed in Chapter 3. They tend to be postsynaptic and work together to modulate excitatory postsynaptic neurotransmission triggered by glutamate. Specifically, AMPA and kainate receptors may mediate fast, excitatory neurotransmission, allowing sodium to enter the neuron to depolarize it (Figure 4-25). NMDA receptors in the resting state are normally blocked by magnesium, which plugs its calcium channel (Figure 4-26). NMDA receptors are an interesting type of "coincidence detector" that can open to let calcium into the neuron to trigger postsynaptic actions from glutamate neurotransmission only when three things occur at the same time (Figures 4-26 and 4-27):

(1) glutamate occupies its binding site on the NMDA receptor
(2) glycine or D-serine binds to its site on the NMDA receptor
(3) depolarization occurs, allowing the magnesium plug to be removed

Some of the many important signals by NMDA receptors that are activated when NMDA calcium channels are opened include long-term potentiation and synaptic plasticity, as will be explained later in this chapter.

Table 4-2 Glutamate receptors

Metabotropic			
Group I	mGluR1		
	mGluR5		
Group II	mGluR2		
	mGluR3		
Group III	mGluR4		
	mGluR6		
	mGluR7		
	mGluR8		
Ionotropic (ligand-gated ion channels; ion-channel-linked receptors)			
Functional class	**Gene family**	**Agonists**	**Antagonists**
AMPA	GluR1	Glutamate	
	GluR2	AMPA	
	GluR3	Kainate	
	GluR4		
Kainate	GluR5	Glutamate	
	GluR6	Kainate	
	GluR7		
	KA1		
	KA2		
NMDA	NR1	Glutamate	
	NR2A	Aspartate	
	NR2B	NMDA	MK801
	NR2C		Ketamine
	NR2D		PCP (phencyclidine)

Key Glutamate Pathways in the Brain

Glutamate is a ubiquitous excitatory neurotransmitter that seems to be able to excite nearly any neuron in the brain. That is why it is sometimes called the "master switch." Nevertheless, there are about a half-dozen specific glutamatergic pathways that are of particular relevance to psychopharmacology and especially to the pathophysiology of schizophrenia (Figure 4-28). They are:

(a) Cortico-brainstem
(b) Cortico-striatal
(c) Hippocampal-striatal
(d) Thalamo-cortical
(e) Cortico-thalamic
(f) Cortico-cortical (direct)
(g) Cortico-cortical (indirect)

(a) **Cortico-brainstem glutamate pathways.** A very important descending glutamatergic pathway projects from glutamatergic cortical pyramidal neurons to brainstem neurotransmitter centers, including the raphe for serotonin, the ventral tegmental area (VTA) and substantia nigra for dopamine, and the locus coeruleus for norepinephrine (pathway a in Figure 4-28). This pathway is the cortico-brainstem glutamate pathway, and is a key regulator of neurotransmitter release. Direct innervation of monoamine neurons in the brainstem by these excitatory cortico-brainstem glutamate neurons *stimulates* neurotransmitter release, whereas indirect innervation of monoamine neurons by

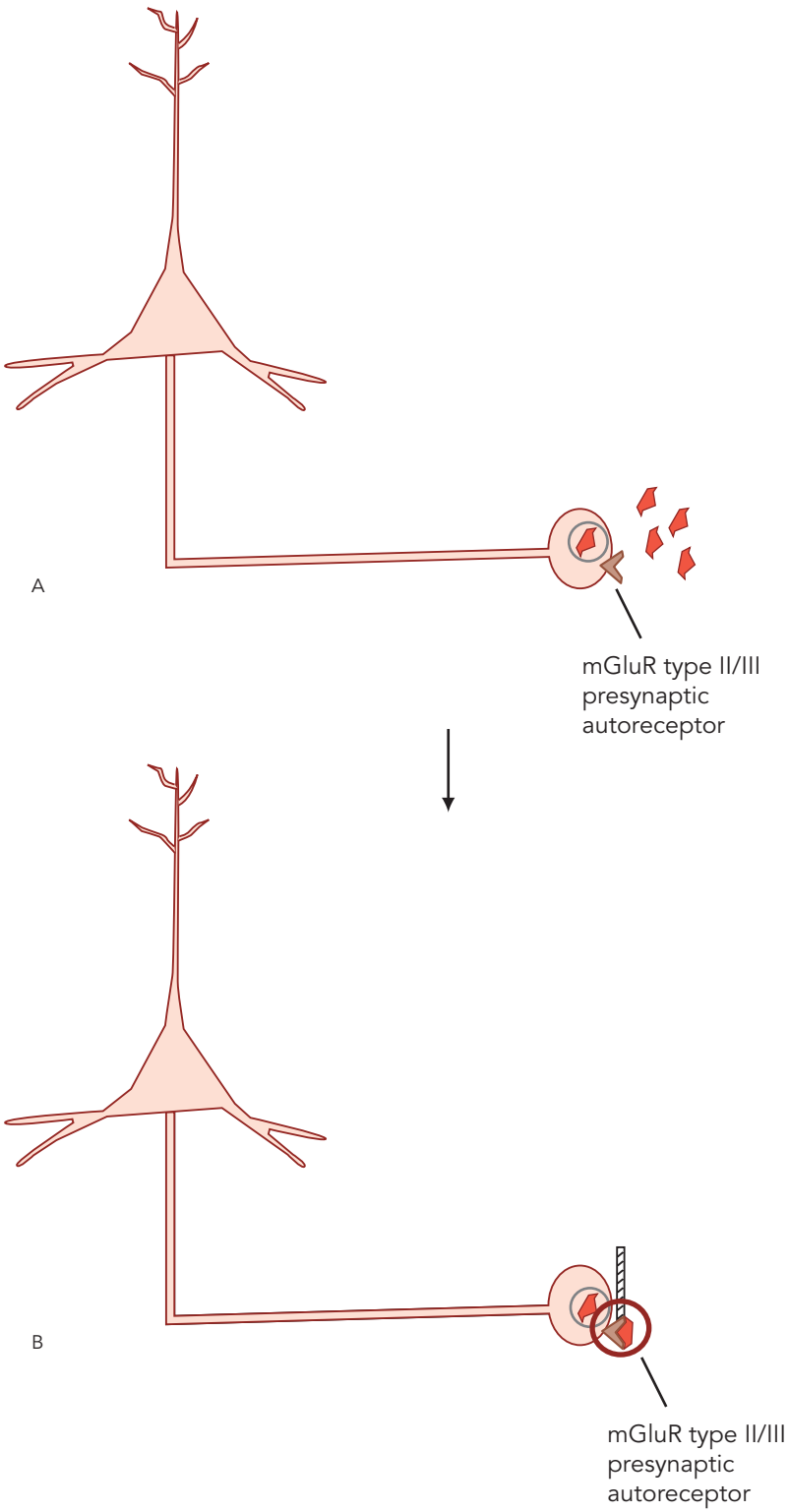


Figure 4-24 Metabotropic glutamate autoreceptors. Groups II and III metabotropic glutamate receptors can exist presynaptically as autoreceptors to regulate the release of glutamate. When glutamate builds up in the synapse (A), it is available to bind to the autoreceptor, which then inhibits glutamate release (B).

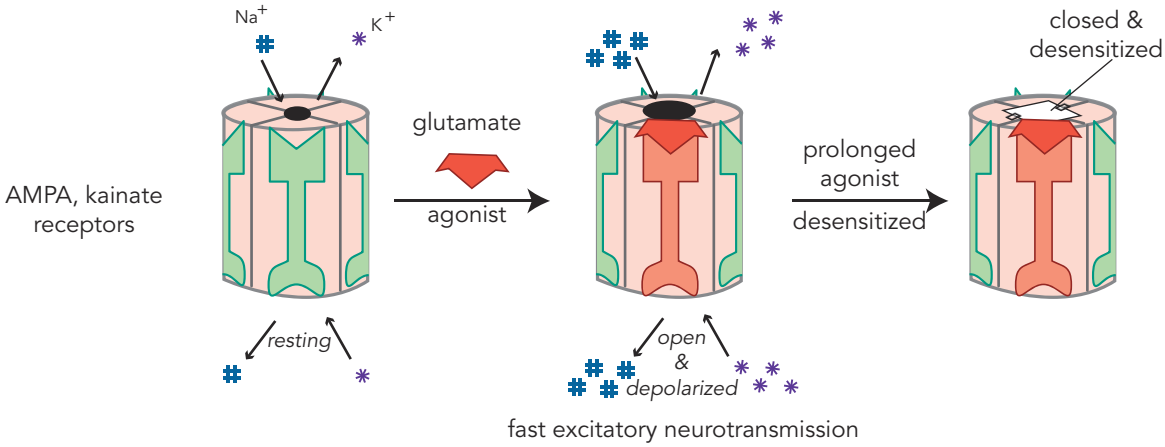


Figure 4-25 Glutamate at AMPA and kainate receptors. When glutamate binds to AMPA and kainate receptors, this leads to fast excitatory neurotransmission and membrane depolarization. Sustained binding of the agonist glutamate will lead to receptor desensitization, causing the channel to close and be transiently unresponsive to agonist.

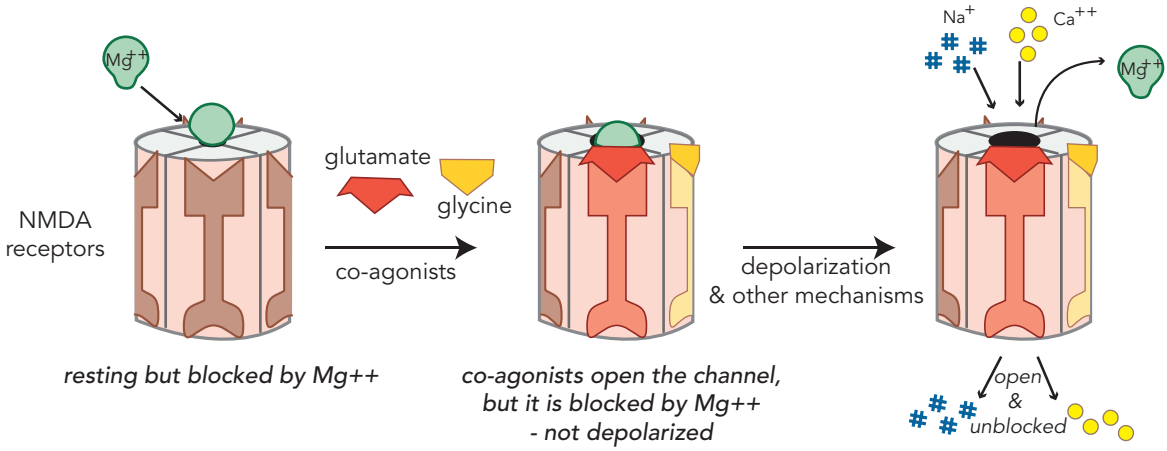


Figure 4-26 Magnesium as a negative allosteric modulator. Magnesium is a negative allosteric modulator at NMDA glutamate receptors. Opening of NMDA glutamate receptors requires the presence of both glutamate and glycine, each of which bind to a different site on the receptor. When magnesium is also bound and the membrane is not depolarized, it prevents the effects of glutamate and glycine and thus does not allow the ion channel to open. In order for the channel to open, depolarization must remove magnesium while both glutamate and glycine are bound to their sites on the ligand-gated ion-channel complex.

these excitatory cortico-glutamate neurons via γ-aminobutyric acid (GABA) interneurons in the brainstem *blocks* neurotransmitter release.

(b) **Cortico-striatal glutamate pathways.** A second descending glutamatergic output from cortical pyramidal neurons projects to the striatal complex (pathway b in Figure 4-28). This pathway is known as the cortico-striatal glutamate pathway. This descending glutamate pathway terminates on GABA neurons destined for a relay station in another part of the striatal complex called the globus pallidus.

(c) **Hippocampal-accumbens glutamate pathway.** Another key glutamate pathway projects from the hippocampus to the nucleus accumbens and is known as the hippocampal-accumbens glutamate pathway (c in Figure 4-28). Specific theories link this particular pathway to schizophrenia (see below). Like the cortico-striatal glutamate pathway (b in Figure 4-28), the hippocampal glutamate projection to the nucleus accumbens (c in Figure 4-28) also terminates on GABA neurons there that in turn project to a relay station in the globus pallidus.

(d) **Thalamo-cortical glutamate pathway.** The thalamo-cortical glutamate pathway (d in Figure 4-28) brings

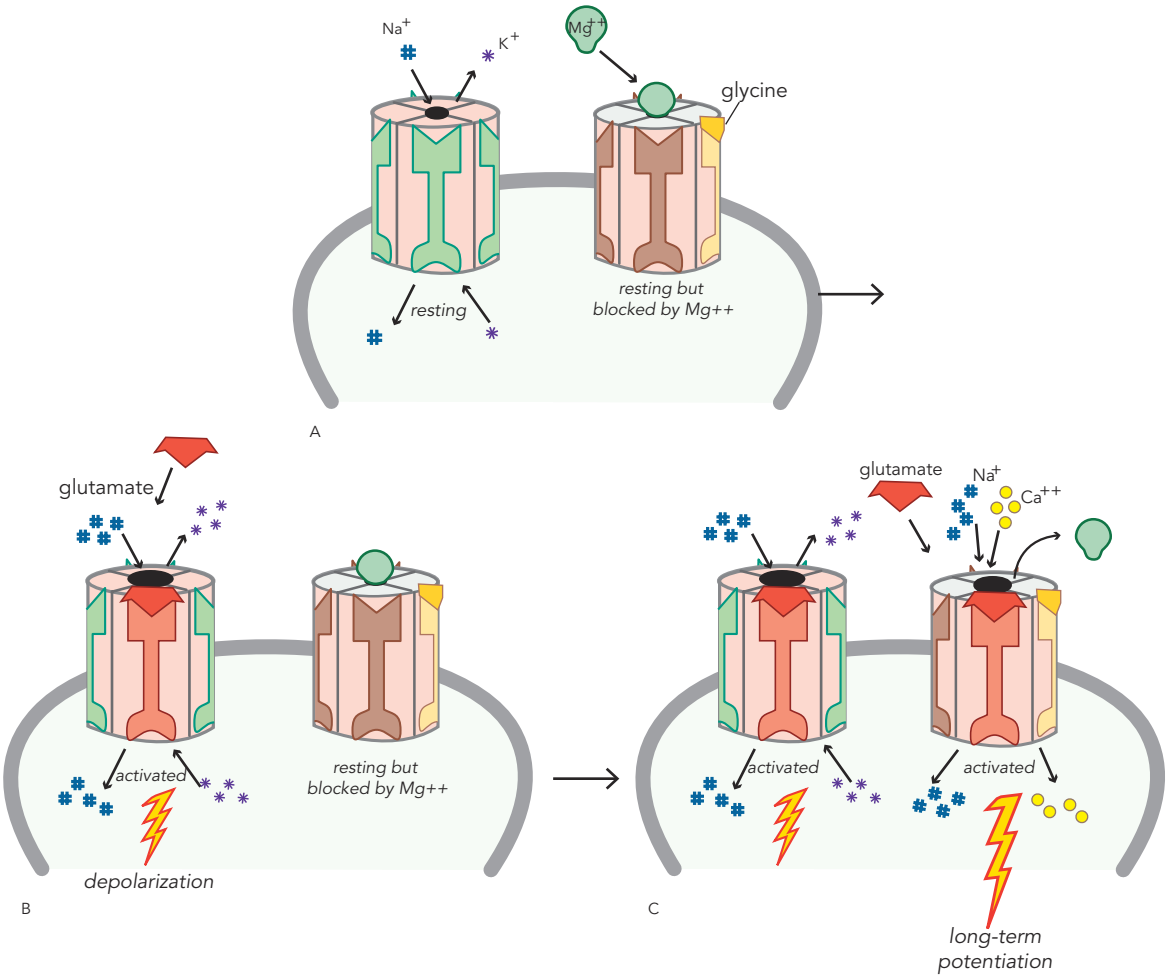


Figure 4-27 Signal propagation via glutamate receptors. (A) On the left is an AMPA receptor with its sodium channel in the resting state, allowing minimal sodium to enter the cell in exchange for potassium. On the right is an NMDA receptor in the resting state, with magnesium blocking the calcium channel and glycine bound to its site. (B) When glutamate arrives, it binds to the AMPA receptor, causing the sodium channel to open, thus increasing the flow of sodium into the dendrite and potassium out of the dendrite. This causes the membrane to depolarize and triggers a postsynaptic nerve impulse. (C) Depolarization of the membrane removes magnesium from the calcium channel. This, coupled with glutamate binding to the NMDA receptor in the presence of glycine, causes the NMDA receptor to open and allow calcium influx. Calcium influx through NMDA receptors contributes to long-term potentiation, a phenomenon that may be involved in long-term learning, synaptogenesis, and other neuronal functions.

information from the thalamus back into the cortex, often to process sensory information.

(e) **Cortico-thalamic glutamate pathway.** A fifth glutamate pathway, known as the cortico-thalamic glutamate pathway, projects directly back to the thalamus, where it may direct the manner in which neurons react to sensory information (pathway e in Figure 4-28).

(f) **Direct cortico-cortical glutamate pathways.** Finally, a complex of many cortico-cortical glutamate pathways is present within the cortex (Figure 4-28, pathways f and g). On the one hand, pyramidal neurons can excite each other within the cerebral cortex via direct synaptic input from their own neurotransmitter glutamate (f in Figure 4-28).

(g) **Indirect cortico-cortical glutamate pathways.** On the other hand, one pyramidal neuron can inhibit another via indirect input, namely via interneurons that release GABA (g in Figure 4-28).

The NMDA Glutamate Hypofunction Hypothesis of Psychosis: Faulty NMDA Neurotransmission at Glutamate Synapses on GABA Interneurons in Prefrontal Cortex

Although NMDA receptors and synapses are ubiquitous throughout the brain, the NMDA glutamate hypofunction

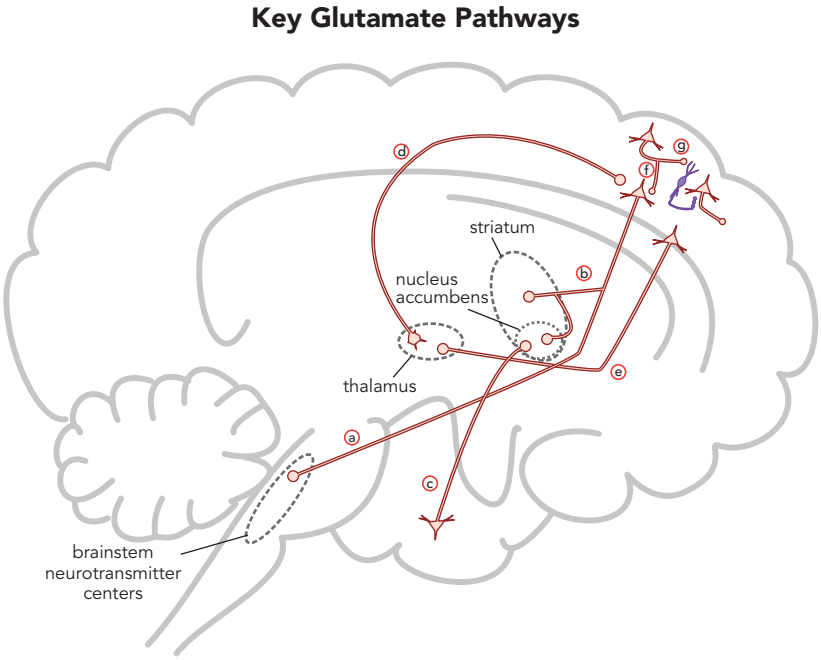


Figure 4-28 Glutamate pathways in the brain. Although glutamate can have actions at virtually all neurons in the brain, there are key glutamate pathways particularly relevant to schizophrenia. (a) The cortico-brainstem glutamate projection is a descending pathway that projects from cortical pyramidal neurons in the prefrontal cortex to brainstem neurotransmitter centers (raphe nucleus, locus coeruleus, ventral tegmental area, substantia nigra) and regulates neurotransmitter release. (b) Another descending glutamatergic pathway projects from the prefrontal cortex to the striatal complex (cortico-striatal glutamate pathway). (c) There is also a glutamatergic projection from the ventral hippocampus to the nucleus accumbens. (d) Thalamo-cortical glutamate pathways ascend from the thalamus and innervate pyramidal neurons in the cortex. (e) Cortico-thalamic glutamate pathways descend from the prefrontal cortex to the thalamus. (f) Intracortical pyramidal neurons can communicate directly with each other via the neurotransmitter glutamate; these pathways are known as direct cortico-cortical glutamatergic pathways and are excitatory. (g) Intracortical pyramidal neurons can also communicate via GABAergic interneurons; these indirect cortico-cortical glutamate pathways are therefore inhibitory.

theory of psychosis suggests that psychosis may be caused by dysfunction of glutamate synapses at a specific site: namely, at certain GABA interneurons in the prefrontal cortex (see g in Figure 4-28 and Figures 4-29A, 4-29B, and 4-29C). Dysfunction hypothetically can be caused by neurodevelopmental problems in schizophrenia (Figure 4-29B, box 1A), by drug toxicity in ketamine/phencyclidine abuse (Figure 4-29B, box 1B), or by neurodegenerative problems in dementia (Figure 4-29C).

First, interference with normal neurotransmission at these sites between glutamate and GABA neurons could hypothetically be due to neurodevelopmental abnormalities genetically and environmentally programmed in schizophrenia (compare Figure 4-29A, box 1 with Figure 4-29B, box 1A). The loss of function of these inhibitory GABA interneurons (Figure 4-29B, box 2) causes glutamate neurons that they innervate downstream to become "disinhibited" and thus hyperactive (see Figure 4-29B, box 3). Other problems with these GABA neurons in schizophrenia may be that they also have deficits in the enzyme that makes their own neurotransmitter GABA (namely, decreased activity of GAD67 [glutamic acid decarboxylase]), causing a compensatory increase in the postsynaptic amount of the α_2 subunit-containing $GABA_A$ receptors in the postsynaptic axon initial segment of the pyramidal neurons they innervate (Figure 4-29B, box 2; compare with Figure 4-29A, box 2).

Both ketamine and phencyclidine (PCP) can cause psychosis with some of the same clinical characteristics as the psychosis of schizophrenia (Table 4-1). Both agents also block NMDA receptors as antagonists at a site inside the ion channel (Figure 4-30). The mechanism of their psychotomimetic actions is hypothesized to be blocking NMDA receptors at the same sites on GABA interneurons as hypothesized for the neurodevelopmental abnormalities in schizophrenia (compare Figure 4-29B, boxes 1A and 1B). In the case of schizophrenia, the NMDA hypofunction is hypothesized to be caused neurodevelopmentally by genetic and environmental

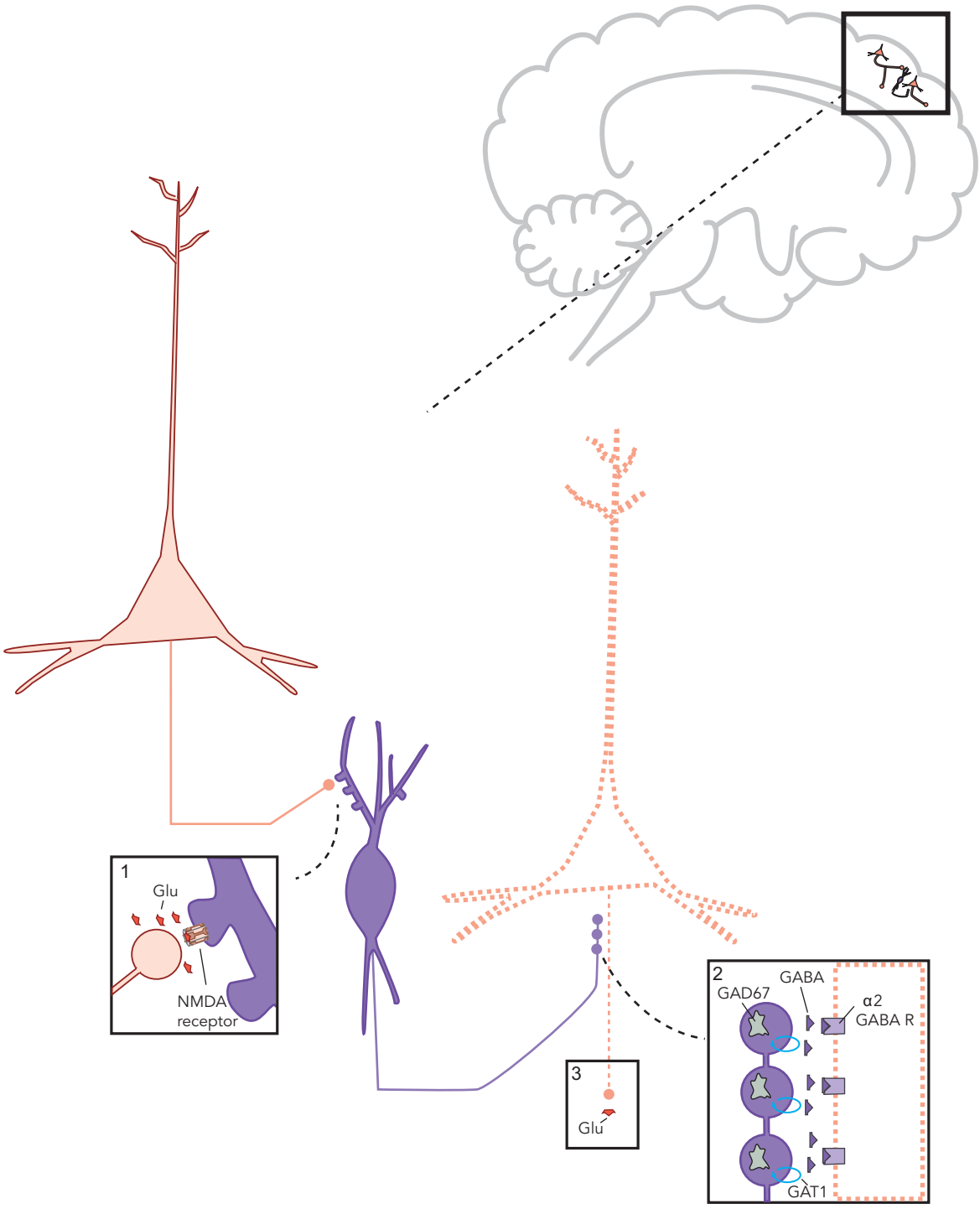


Figure 4-29A Hypothetical site of glutamate dysfunction in psychosis, part 1. Shown here is a close-up of intracortical pyramidal neurons communicating via GABAergic interneurons. (1) Glutamate is released from an intracortical pyramidal neuron and binds to an NMDA receptor on a GABAergic interneuron. (2) GABA is then released from the interneuron and binds to GABA receptors of the α_2 subtype that are located on the axon of another glutamate pyramidal neuron. (3) This inhibits the pyramidal neuron, thus reducing the release of cortical glutamate.

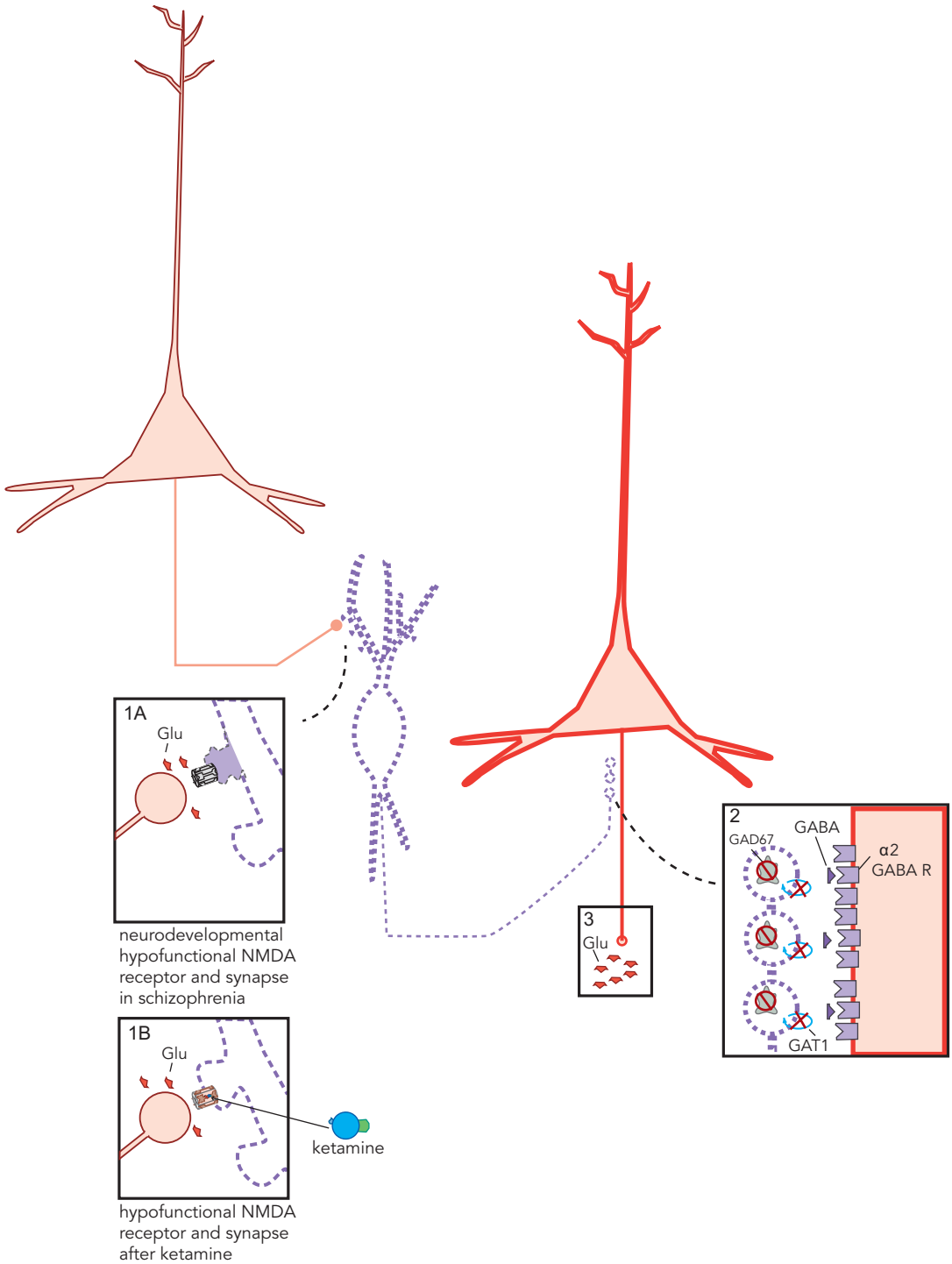


Figure 4-29B Hypothetical site of glutamate dysfunction in psychosis, part 2. Shown here is a close-up of intracortical pyramidal neurons communicating via GABAergic interneurons in the presence of hypofunctional NMDA receptors. (1) Glutamate is released from an intracortical pyramidal neuron. However, the NMDA receptor that it would normally bind to is hypofunctional, preventing glutamate from exerting its effects at the receptor. This could be due to neurodevelopmental abnormalities (1A) or to drug toxicity resulting from ketamine or phencyclidine abuse (1B). (2) This prevents GABA release from the interneuron; thus, stimulation of α_2 GABA receptors on the axon of another glutamate neuron does not occur. (3) When GABA does not bind to the α_2 GABA receptors on its axon, the pyramidal neuron is no longer inhibited. Instead, it is disinhibited and overactive, releasing excessive glutamate into the cortex.

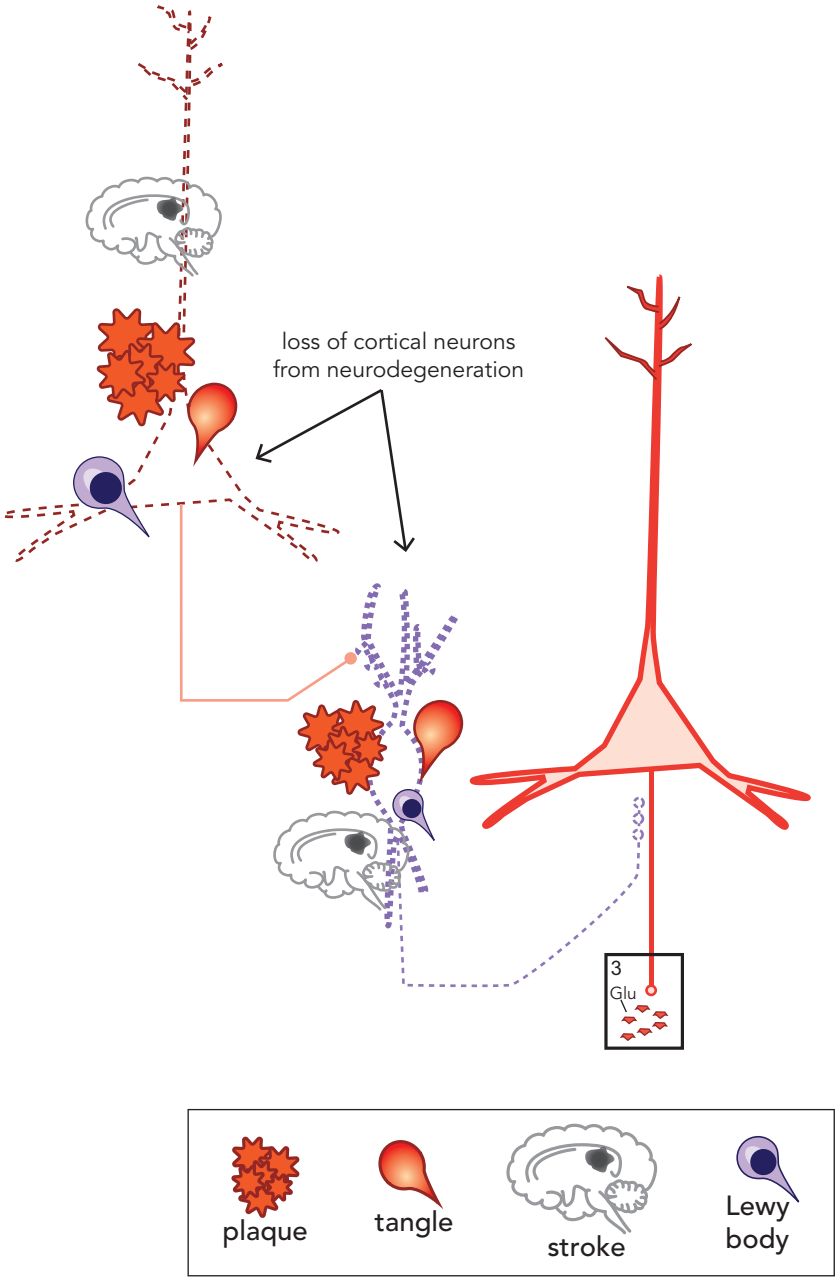


Figure 4-29C Hypothetical site of glutamate dysfunction in psychosis, part 3. Shown here is a close-up of intracortical pyramidal neurons communicating via GABAergic interneurons in the presence of neurodegeneration associated with dementia. Not all patients with dementia develop symptoms of psychosis. It may be that, in those that do, the neurodegeneration associated with the accumulation of amyloid plaques, tau tangles, and/or Lewy bodies, as well as the damage caused by strokes, may destroy some glutamatergic pyramidal neurons and GABAergic interneurons while leaving others intact, at least temporarily. The end result may be excessive glutamate activity in the cortex, as in schizophrenia (see Figure 4-29B, box 1A) or in ketamine abuse (see Figure 4-29B, box 1B).

input (Figure 4-29B, box 1A), whereas in ketamine/PCP psychosis, the NMDA hypofunction is hypothesized to be caused by acute and reversible pharmacological actions directly at NMDA receptors (Figure 4-29B, box 1B).

In neurodegenerative disorders that cause Alzheimer disease and other types of dementia, the accumulation of amyloid plaques, tau tangles, Lewy bodies, and/or strokes progressively knocks out neurons as the disease

progresses (Figure 4-29C). Up to half of patients with dementia may at some point in their clinical course experience psychosis (see Chapter 12 for a more extensive discussion on the behavioral symptoms of dementia). Why do some dementia patients experience psychosis and others not? One hypothesis is that in patients with dementia-related psychosis, the neurodegeneration has progressed in such a way as to knock out some glutamatergic pyramidal neurons and GABAergic interneurons in the prefrontal cortex while leaving other glutamatergic pyramidal neurons intact, at least temporarily (Figure 4-29C). This theoretically creates the same dysconnectivity (Figure 4-29C), but by a different mechanism, that occurs in both schizophrenia (Figure 4-29B, box 1A) and in ketamine/PCP psychosis (Figure 4-29B, box 1B). Hypothetically this occurs in only some patients with dementia and specifically only in those whose pattern of neuronal degeneration leaves glutamate neurons that drive dopamine neurons downstream intact. The significance of preserving these particular glutamate neurons is explained further below. Knocking out some neurons while preserving some others could explain why only certain patients develop psychosis as neurodegeneration in dementia progresses.

Linking the NMDA Glutamate Hypofunction Hypothesis of Psychosis to the Dopamine Hypothesis of Psychosis

What are the consequences to dopamine activity of the hypothetical dysconnectivity of glutamatergic pyramidal neurons with these particular GABAergic interneurons in schizophrenia, ketamine/PCP toxicity, and dementia (Figures 4-29A, 4-29B, and 4-29C)? The short answer is that it theoretically leads to the very same dopamine hyperactivity already discussed above for the dopamine hypothesis of psychosis.

Certain glutamate neurons directly innervate VTA/mesostriatal dopamine neurons, and when they lose their GABA inhibition from any cause they become

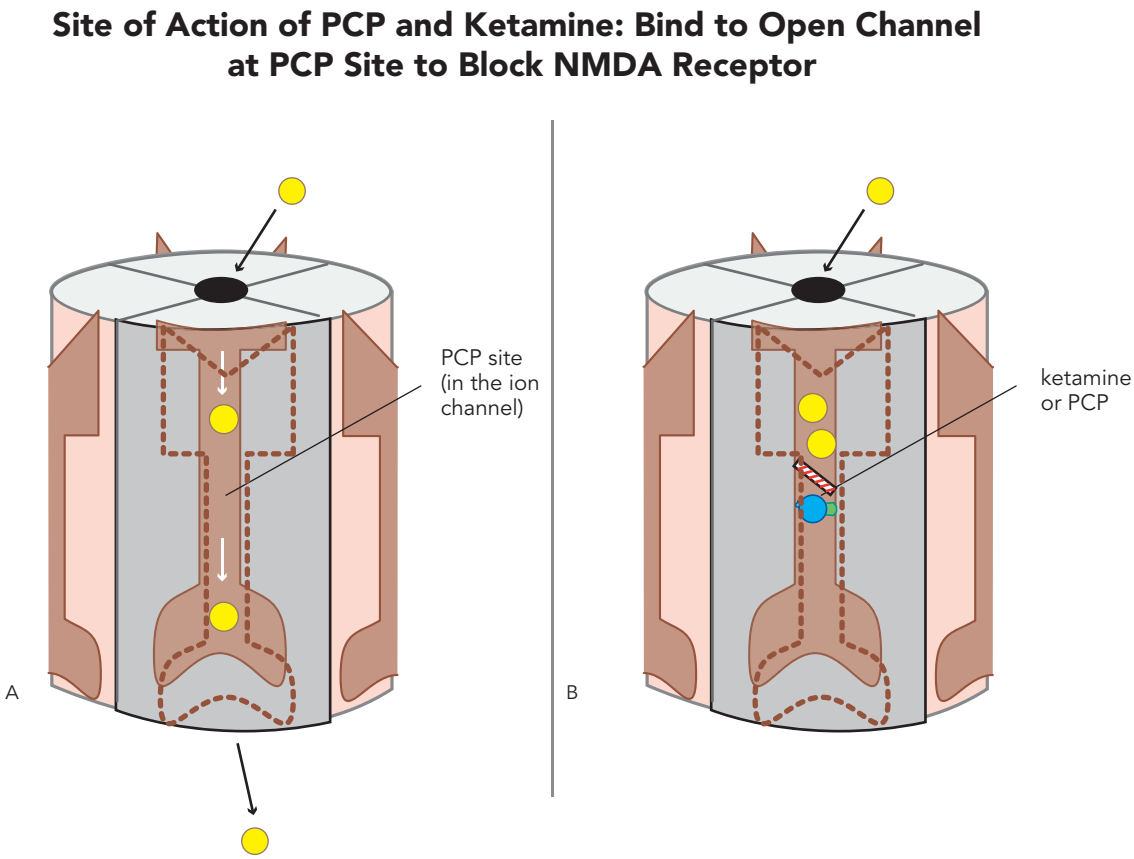


Figure 4-30 Site of action of PCP and ketamine. The anesthetic ketamine binds as an antagonist to the open channel conformation of the NMDA receptor. Specifically, it binds to a site within the calcium channel of this receptor, which is often termed the PCP site because it is also where phencyclidine (PCP) binds as an antagonist.

hyperactive and stimulate too much dopamine release from the mesostriatal projections of those dopamine neurons (Figures 4-31 through 4-34). As discussed in the previous section, neurodevelopmentally deficient NMDA synapses (Figure 4-29B, box 1A) hypothetically cause this downstream glutamate hyperactivity in schizophrenia (Figures 4-31 and 4-32). In PCP/ketamine abuse, the drug acting directly at these synapses (Figure 4-29B, box 1B) causes the downstream glutamate hyperactivity (Figure 4-33), and in dementia, neurodegeneration knocks out cortical neurons (Figure 4-29C) to cause this glutamate hyperactivity (Figure 4-34). In turn, glutamate hyperactivity from any cause (Figures 4-31 through 4-34) theoretically results in dopamine hyperactivity and the positive symptoms of psychosis.

Hyperactive glutamate output from the prefrontal cortex can hypothetically not only potentially explain positive symptoms, but also negative symptoms in the case of schizophrenia. When the cascade from NMDA hypofunction to glutamate hyperactivity *enhances* dopamine release (Figure 4-31), it hypothetically causes positive symptoms of psychosis; however, there is hypothetically a second population of glutamate neurons that project to a different set of VTA neurons, namely, those that are mesocortical rather than mesostriatal/mesolimbic (Figure 4-35). This circuit actually *inhibits* dopamine release, due to the presence of a key GABA interneuron in VTA for mesocortical dopamine projections to the prefrontal cortex that is hypothetically lacking for mesostriatal/mesolimbic projection to the striatum (compare Figures 4-31B and 4-35B). Hyperactivity of these specific glutamate neurons innervating mesocortical dopamine neurons in Figure 4-35B would lead to the opposite effects of those discussed for the population of glutamate neurons innervating mesostriatal dopamine neurons: namely, *reduced* dopamine release, and this hypothetically causes the negative, cognitive, and affective symptoms of psychosis (Figure 4-35B).

THE SEROTONIN HYPOTHESIS OF PSYCHOSIS AND SCHIZOPHRENIA

The serotonin theory of psychosis proposes that hyperactivity/imbalance of serotonin (5-hydroxytryptamine, 5HT) activity, particularly at serotonin $5HT_{2A}$ receptors, can result in psychosis (Table 4-1 and Figure 4-1). Disruption of 5HT functioning, leading to positive symptoms of psychosis, can be hypothetically due to the neurodevelopmental abnormalities in schizophrenia, to the neurodegeneration in Parkinson's disease as well as in Alzheimer disease and other dementias, and to drugs such as LSD, mescaline, and psilocybin (Figure 4-1 and Table 4-1). Interestingly, psychoses associated with serotonin imbalance tend to have more visual

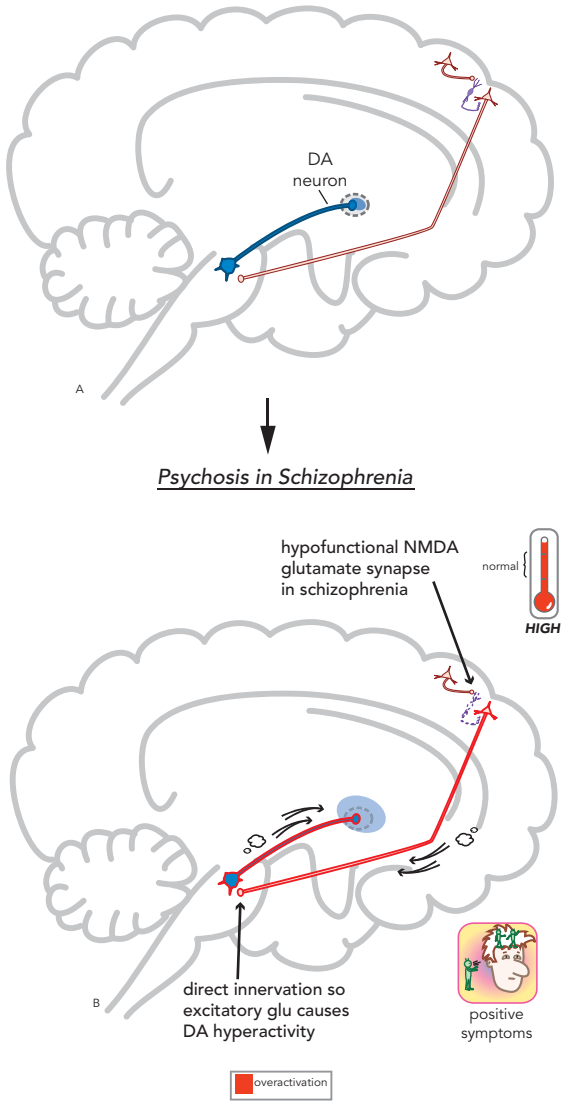


Figure 4-31 NMDA receptor hypofunction and psychosis in schizophrenia, part 1. (A) The cortical brainstem glutamate projection communicates with the mesolimbic dopamine pathway in the ventral tegmental area (VTA) to regulate dopamine release in the nucleus accumbens. (B) If NMDA receptors on cortical GABA interneurons are hypoactive, then GABA release is inhibited and the cortical brainstem pathway to the VTA will be overactivated, leading to excessive release of glutamate in the VTA. This will lead to excessive stimulation of the mesolimbic dopamine pathway and thus excessive dopamine release in the nucleus accumbens. This is the theoretical biological basis for the mesolimbic dopamine hyperactivity thought to be associated with the positive symptoms of psychosis.

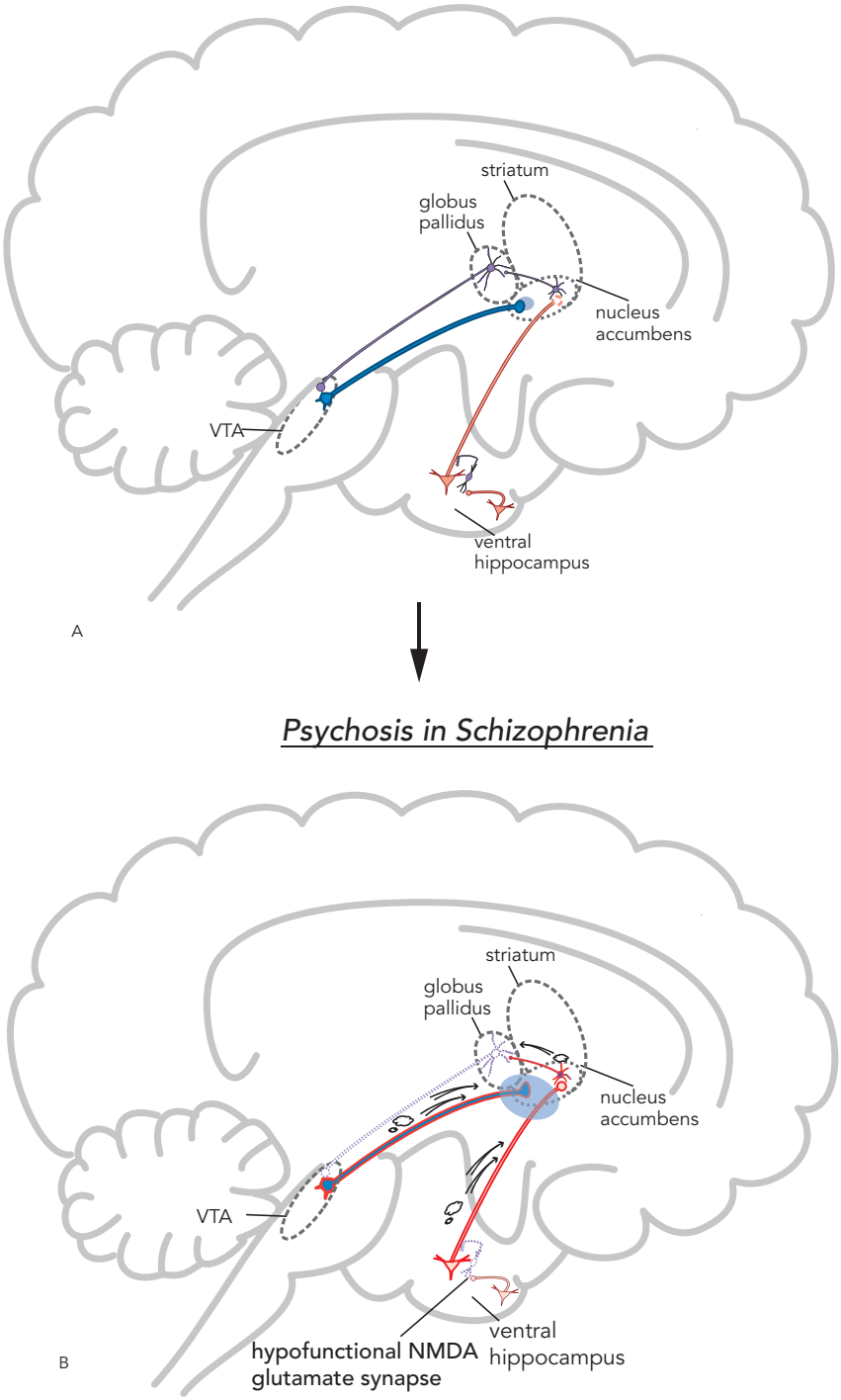


Figure 4-32 NMDA receptor hypofunction and psychosis in schizophrenia, part 2. Hypofunctional NMDA receptors at glutamatergic synapses in the ventral hippocampus can also contribute to mesolimbic dopamine hyperactivity. (A) Glutamate released in the ventral hippocampus binds to NMDA receptors on a GABAergic interneuron, stimulating the release of GABA. The GABA binds at receptors on a pyramidal glutamate neuron that projects to the nucleus accumbens; this prevents excessive glutamate release there. The normal release of glutamate in the nucleus accumbens allows for normal activation of a GABAergic neuron projecting to the globus pallidus, which in turn allows for normal activation of a GABAergic neuron projecting to the ventral tegmental area (VTA). This leads to normal activation of the mesolimbic dopamine pathway from the VTA to the nucleus accumbens. (B) If NMDA receptors on ventral hippocampal GABA interneurons are hypoactive, then the glutamatergic pathway to the nucleus accumbens will be overactivated, leading to excessive release of glutamate in the nucleus accumbens. This will lead to excessive stimulation of GABAergic neurons projecting to the globus pallidus, which in turn will inhibit release of GABA from the globus pallidus into the VTA. This will lead to disinhibition of the mesolimbic dopamine pathway and thus excessive dopamine release in the nucleus accumbens.

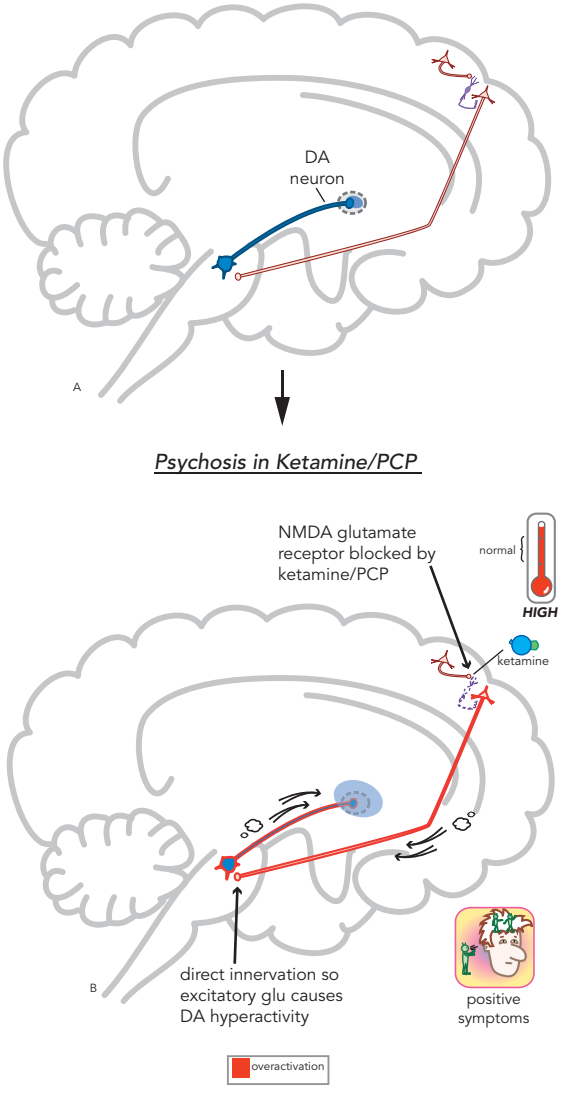


Figure 4-33 NMDA receptor blockade and psychosis in ketamine abuse. (A) The cortical brainstem glutamate projection communicates with the mesolimbic dopamine pathway in the ventral tegmental area (VTA) to regulate dopamine release in the nucleus accumbens. (B) If ketamine blocks NMDA receptors on cortical GABA interneurons, then GABA release is inhibited and the cortical brainstem pathway to the VTA will be overactivated, leading to excessive release of glutamate in the VTA. This will lead to excessive stimulation of the mesolimbic dopamine pathway and thus excessive dopamine release in the nucleus accumbens.

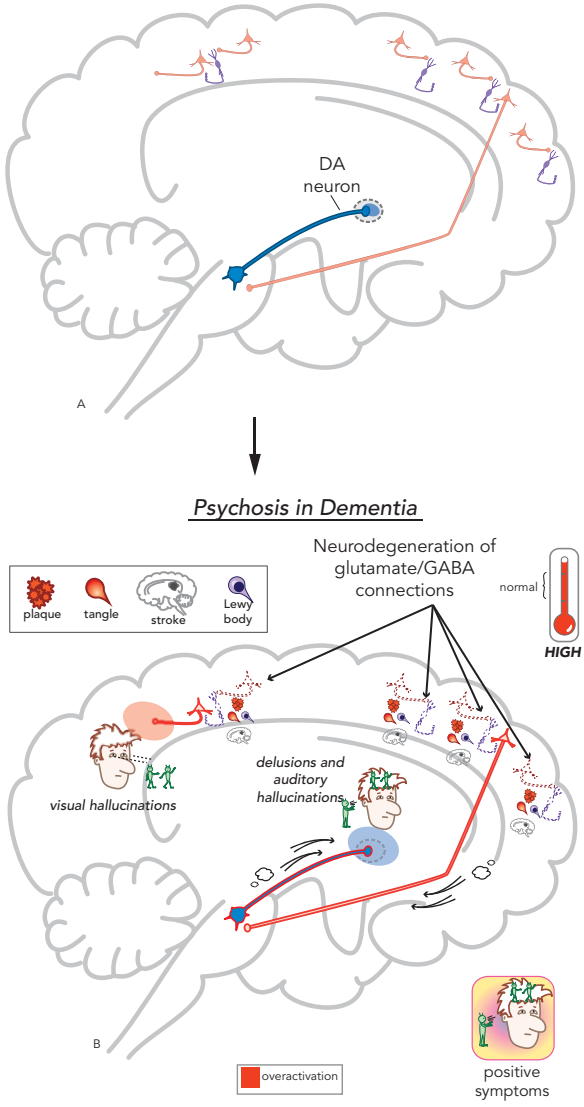


Figure 4-34 Neurodegeneration and psychosis in dementia. (A) The cortical brainstem glutamate projection communicates with the mesolimbic dopamine pathway in the ventral tegmental area (VTA) to regulate dopamine release in the nucleus accumbens. (B) If neurodegeneration leads to the destruction of some glutamatergic neurons and some GABAergic interneurons, but not others, then this could lead to excessive release of glutamate in various brain regions. In the VTA, this could lead to excessive stimulation of the mesolimbic dopamine pathway and thus excessive dopamine release in the nucleus accumbens, resulting in delusions and auditory hallucinations. In the visual cortex, excessive glutamatergic activity could result in visual hallucinations.

hallucinations, whereas those associated principally with dopamine have more auditory hallucinations. In order to understand how hyperactivity of serotonin at $5HT_{2A}$ receptors could lead to the positive symptoms of psychosis in various disorders, we will first review serotonin and its extensive set of receptors and pathways.

The Serotonin Neurotransmitter Network

Serotonin, better known as 5HT (5-hydroxytryptamine), is a monoamine neurotransmitter which regulates a brain network that is one of the most targeted by psychotropic

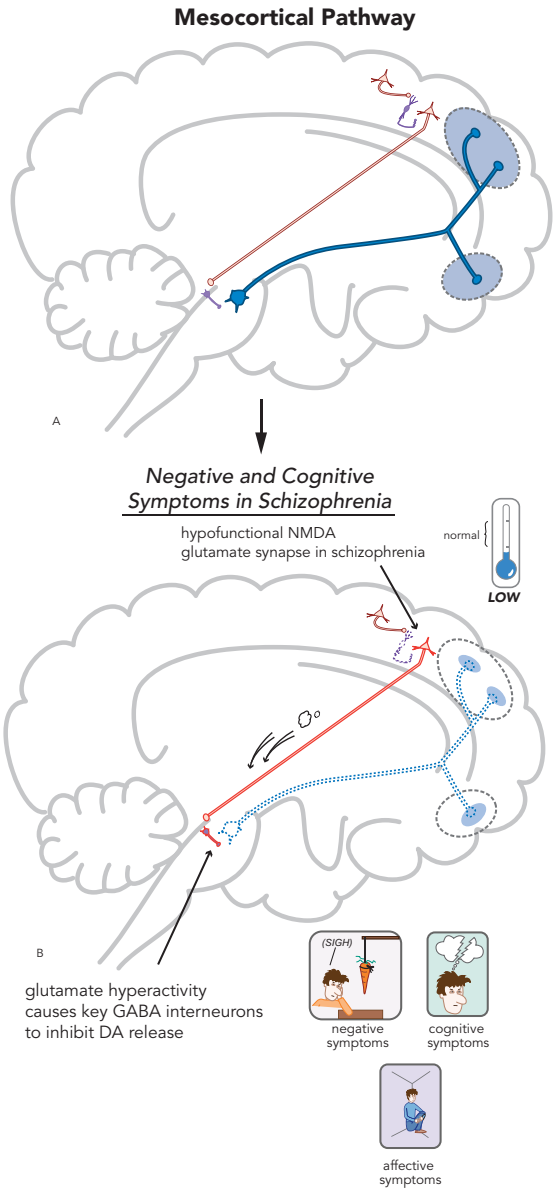


Figure 4-35 NMDA receptor hypofunction and negative symptoms of schizophrenia. (A) The cortical brainstem glutamate projection communicates with the mesocortical dopamine pathway in the ventral tegmental area (VTA) via GABAergic interneurons, thus regulating dopamine release in the prefrontal cortex. (B) If NMDA receptors on cortical GABA interneurons are hypoactive, then the cortical brainstem pathway to the VTA will be overactivated, leading to excessive release of glutamate in the VTA. This will lead to excessive stimulation of the brainstem GABA interneurons, which in turn leads to inhibition of mesocortical dopamine neurons. This reduces dopamine release in the prefrontal cortex and is the theoretical biological basis for the negative symptoms of psychosis.

drugs. For example, many if not most drugs that treat psychosis and mood target, in one way or another, the serotonin network. Thus, a thorough understanding of serotonin neurotransmission is critical in order to grasp some of the most important principles across the breadth of psychopharmacology, from psychosis to mood and beyond.

Serotonin Synthesis and Termination of Action

Synthesis of 5HT begins with the amino acid tryptophan, which is transported into the brain from the plasma to serve as the 5HT precursor (Figure 4-36). Two synthetic enzymes then convert tryptophan into serotonin: firstly, tryptophan hydroxylase (TRY-OH) converts tryptophan into 5-hydroxytryptophan (5HTP), and then aromatic amino acid decarboxylase (AAADC) converts 5HTP into 5HT (Figure 4-36). After synthesis, 5HT is taken up into synaptic vesicles by a vesicular monoamine transporter (VMAT2) and stored there until it is used during neurotransmission.

5HT action is terminated when it is enzymatically destroyed by monoamine oxidase (MAO) and converted into an inactive metabolite (Figure 4-37). Serotonergic neurons themselves contain monoamine oxidase B (MAO-B), but it has low affinity for 5HT, so 5HT is only enzymatically degraded when its intracellular concentrations are high. The 5HT neuron also has a presynaptic transport pump for serotonin called the serotonin transporter (SERT) that is unique for 5HT and that terminates serotonin's actions by pumping it out of the synapse and back into the presynaptic nerve terminal where it can be re-stored in synaptic vesicles for subsequent use in another neurotransmission (Figure 4-37). Unlike dopamine neurons, some of which do not contain their dopamine transporter (DAT), all 5HT neurons are thought to contain SERTs. Also, there are functional polymorphisms in the gene that codes for SERT, which have become of intense interest since they alter the amount of synaptic serotonin and may help predict which patients are less likely to respond as well as more likely to have side effects when given drugs for depression that block SERT. This will be discussed in more detail in Chapter 7 on treatments for mood disorders.

5HT Receptors: Overview

Serotonin has more than a dozen receptors, and at least half of them have known clinical relevance (Figure 4-38). Only a few 5HT receptors are located on the serotonin neuron itself ($5HT_{1A}$, $5HT_{1B/D}$, $5HT_{2B}$) (Figures 4-38 through 4-41), and their purpose is to regulate the presynaptic serotonin neuron directly, especially its firing and how it releases and stores its own serotonin. Just to be confusing, these same receptors can also be located postsynaptically, as can all known 5HT receptors. First, we describe how those 5HT receptors that are presynaptic

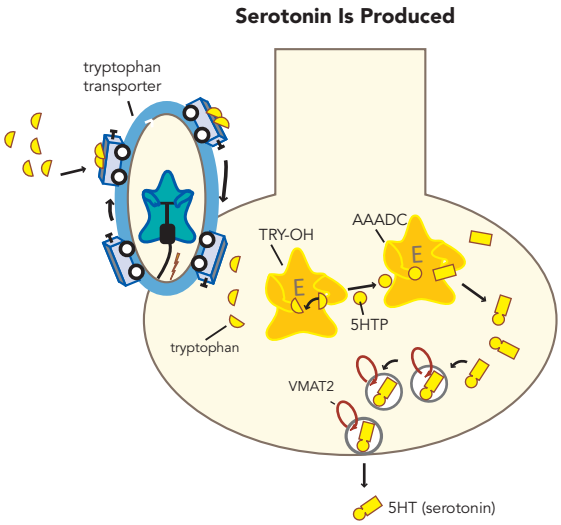


Figure 4-36 Serotonin is produced. Serotonin (5-hydroxytryptamine [5HT]) is produced from enzymes after the amino acid precursor tryptophan is transported into the serotonin neuron. Once transported into the serotonin neuron, tryptophan is converted by the enzyme tryptophan hydroxylase (TRY-OH) into 5-hydroxytryptophan (5HTP), which is then converted into 5HT by the enzyme aromatic amino acid decarboxylase (AAADC). Serotonin is then taken up into synaptic vesicles via the vesicular monoamine transporter (VMAT2), where it stays until released by a neuronal impulse.

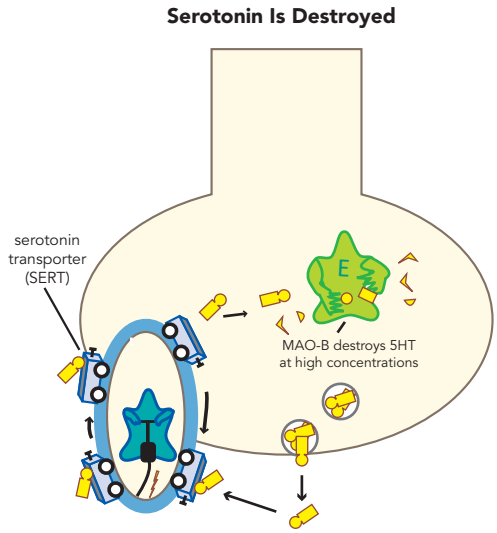


Figure 4-37 Serotonin's action is terminated. Serotonin's (5HT) action is terminated enzymatically by monoamine oxidase B (MAO-B) within the neuron when it is present in high concentrations. These enzymes convert serotonin into an inactive metabolite. There is also a presynaptic transport pump selective for serotonin, called the serotonin transporter (SERT), which clears serotonin out of the synapse and back into the presynaptic neuron.

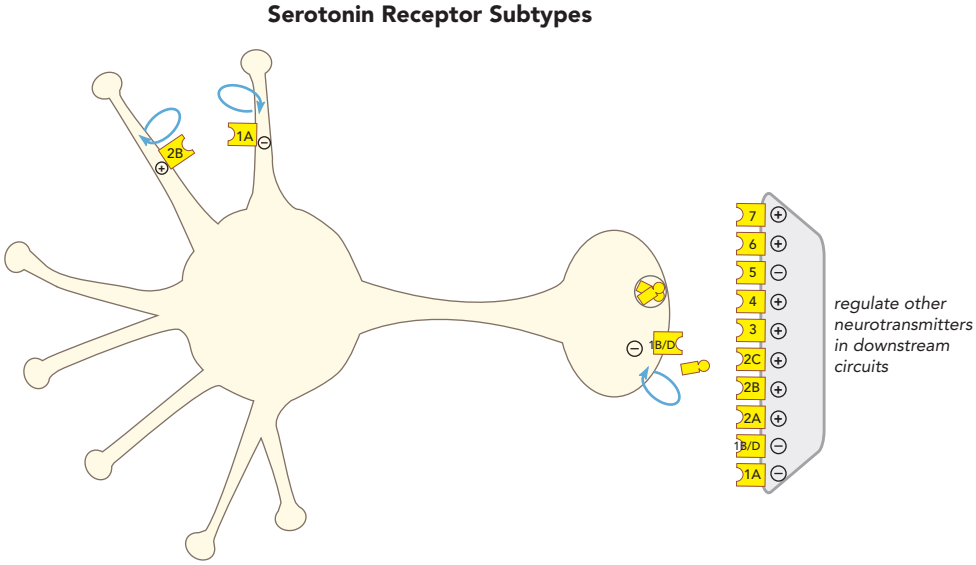


Figure 4-38 Serotonin receptors. Presynaptic serotonin (5HT) receptors include $5HT_{1A}$, $5HT_{1B/D}$, and $5HT_{2B}$, all of which act as autoreceptors. There are also numerous postsynaptic serotonin receptors, which regulate other neurotransmitters in downstream circuits.

(located on the serotonin neuron itself) regulate serotonin, and then we discuss how postsynaptic 5HT receptors regulate essentially every other neurotransmitter in a network of downstream brain circuits.

Presynaptic Receptors: Serotonin Regulating Serotonin

As for all monoamine neurons, the serotonin neuron has receptors both on its axon terminals (axon-

terminal autoreceptors) and on its dendrites and soma (somatodendritic autoreceptors), both to help regulate serotonin release (Figures 4-38 through 4-41). Both are considered to be presynaptic. Whereas the dopamine (earlier in this chapter and Figures 4-5 through 4-8) and norepinephrine (Chapter 6 and Figures 6-14

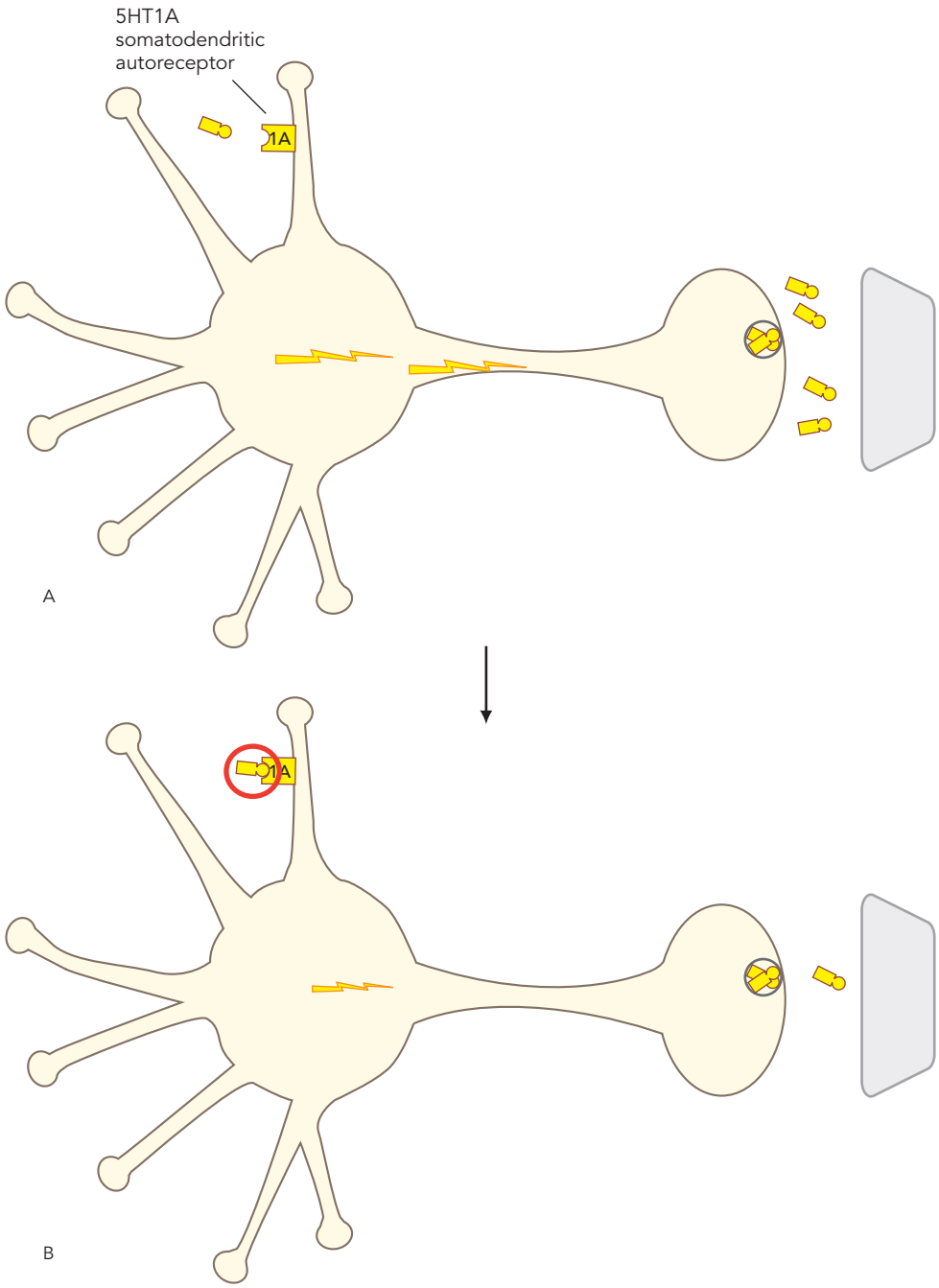


Figure 4-39 Serotonin (5HT) 1A autoreceptors. (A) Presynaptic $5HT_{1A}$ receptors are autoreceptors located on the cell body and dendrites, and are therefore called somatodendritic autoreceptors. (B) When serotonin is released somatodendritically, it binds to these $5HT_{1A}$ receptors and causes a shutdown of 5HT neuronal impulse flow, depicted here as decreased electrical activity and a reduction in the release of 5HT from the synapse on the right.

through 6-16) neurons have the same receptors at both ends, for the serotonin neuron, the axon-terminal receptors (with $5HT_{1B/D}$ pharmacology) (Figures 4-38 and 4-41) are different from the somatodendritic receptors (with $5HT_{1A}$ and $5HT_{2B}$ pharmacology) (Figures 4-38 through 4-40).

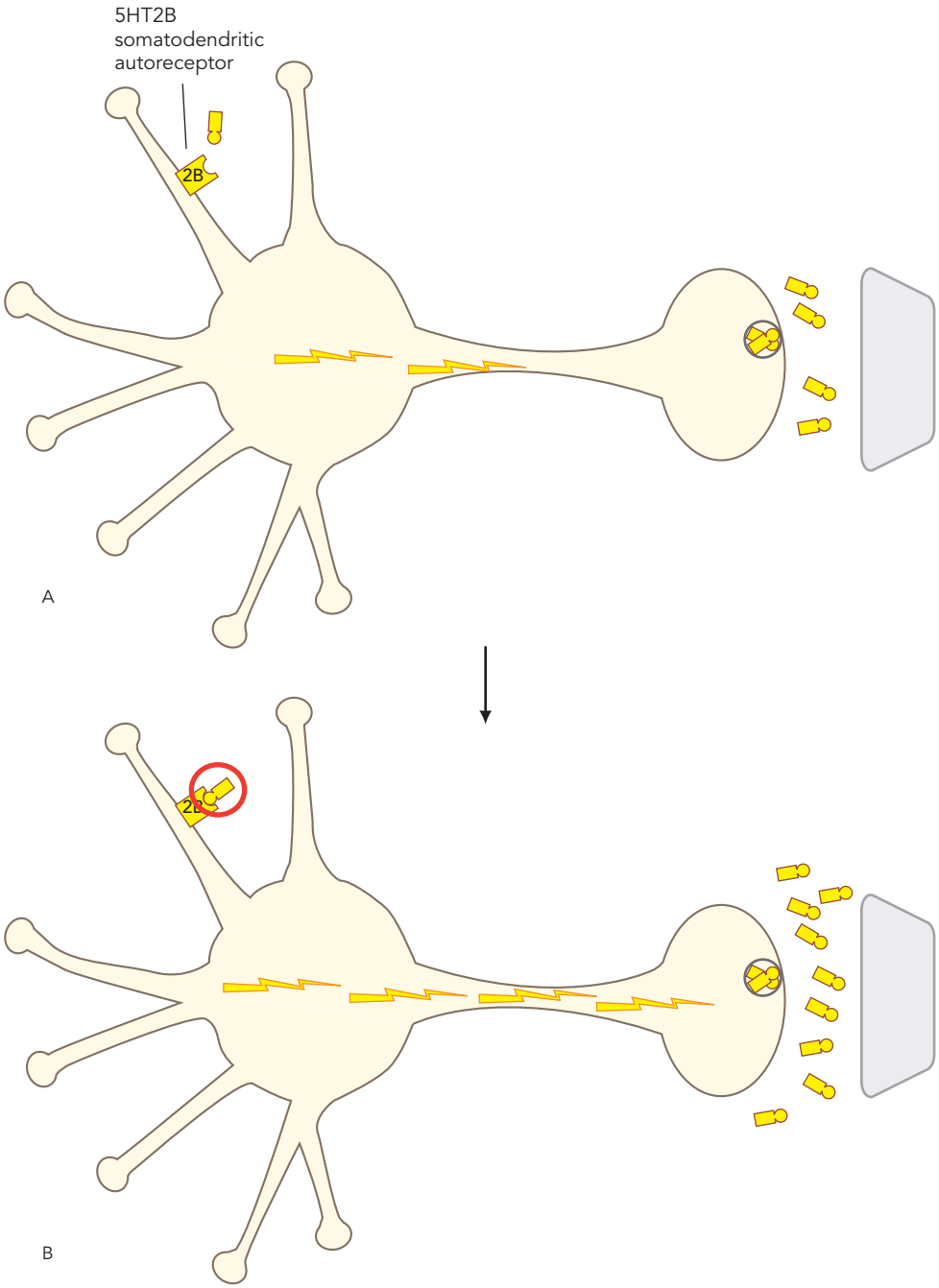


Figure 4-40 Serotonin (5HT) 2B autoreceptors. (A) Presynaptic $5HT_{2B}$ receptors are autoreceptors located on the cell body and dendrites, and are therefore called somatodendritic autoreceptors. (B) When 5HT is released somatodendritically, it binds to these $5HT_{2B}$ receptors and causes increased 5HT neuronal impulse flow, depicted here as increased electrical activity and increased release of 5HT from the synapse on the right.

Presynaptic $5HT_{1A}$ Receptors

Located on the dendrites and cell bodies of serotonin neurons in the midbrain raphe (Figure 4-39A), these presynaptic somatodendritic $5HT_{1A}$ receptors detect serotonin released from dendrites. How serotonin is released at the opposite end of the neuron from where its classic presynaptic nerve terminals are located is still not yet fully understood, but this appears to be an important process for how the serotonin neuron regulates release at the presynaptic end. When 5HT is released somatodendritically, it activates these $5HT_{1A}$ autoreceptors and this causes a slowing of neuronal impulse flow through the serotonin neuron and a reduction of serotonin release from its axon terminal

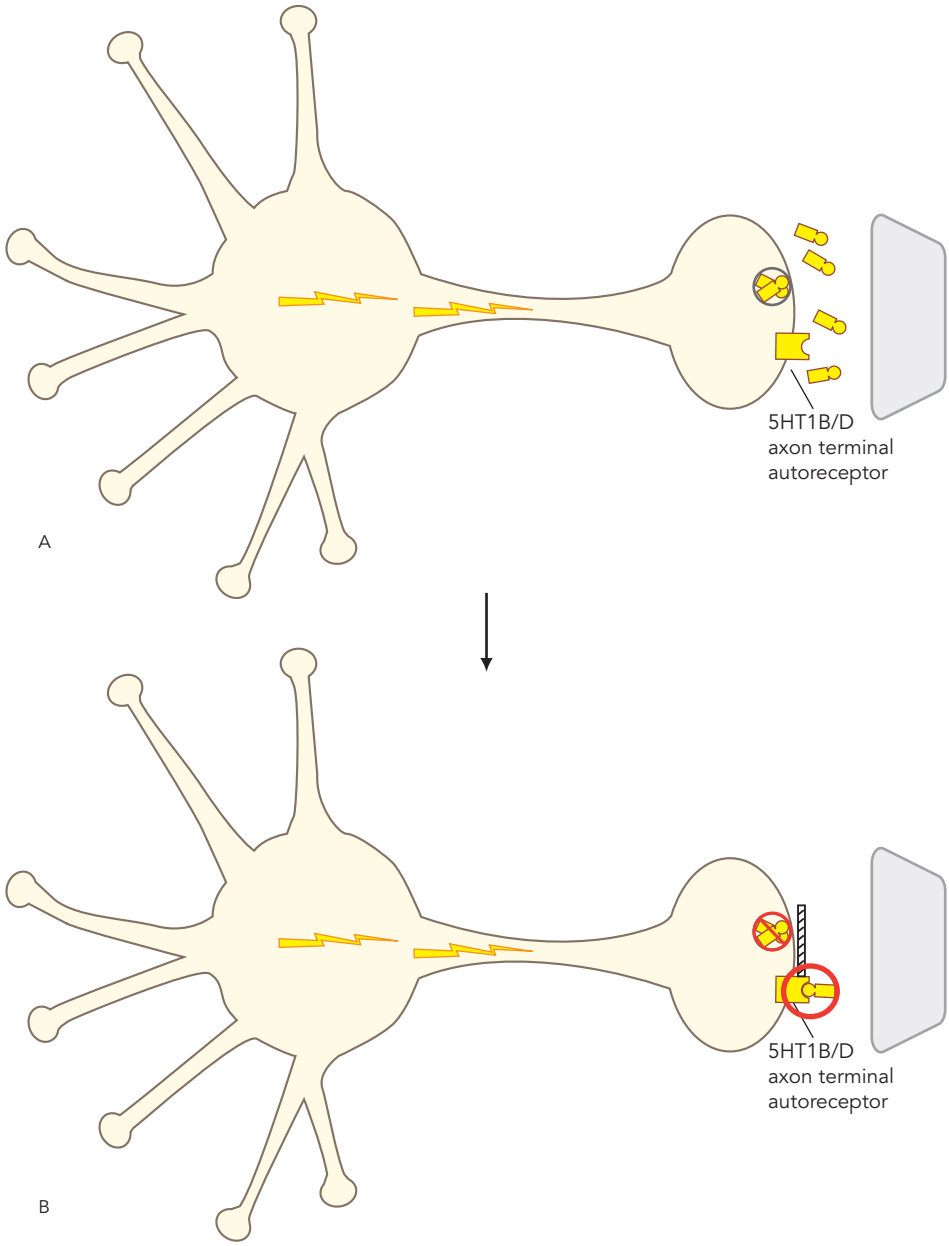


Figure 4-41 Serotonin (5HT) 1B/D autoreceptors. Presynaptic $5HT_{1B/D}$ receptors are autoreceptors located on the presynaptic axon terminal. They act by detecting the presence of 5HT in the synapse and causing a shutdown of further 5HT release. When 5HT builds up in the synapse (A), it is available to bind to the autoreceptor, which then inhibits serotonin release (B).

(Figure 4-39B). Downregulation and desensitization of these presynaptic $5HT_{1A}$ somatodendritic autoreceptors are thought to be critical to the antidepressant actions of drugs that block serotonin reuptake (discussed in Chapter 7 on treatments for mood disorders).

Presynaptic $5HT_{2B}$ receptors

Recently, it has been discovered that the somatodendritic area of 5HT neurons is regulated by a second receptor, the $5HT_{2B}$ receptor (Figure 4-40), which acts in *opposition* to the $5HT_{1A}$ receptor. That is, $5HT_{2B}$ receptors *activate* the serotonin neuron to cause *more* impulse flow and *increased* serotonin release from presynaptic nerve terminals. Thus, it appears at this point in time that the $5HT_{2B}$ receptors are "feed forward" receptors whereas $5HT_{1A}$ receptors are "negative feedback" receptors. It is not yet clear which 5HT neurons in the midbrain raphe contain $5HT_{1A}$ receptors, which contain $5HT_{2B}$ receptors, and which contain both. Clearly, much more is yet to be learned about $5HT_{2B}$ receptors and the drugs that act upon them. However, it already appears likely that the balance between actions at presynaptic somatodendritic $5HT_{1A}$ versus $5HT_{2B}$ receptors is important in regulating how much serotonin activity and serotonin release is occurring at serotonin presynaptic nerve terminals throughout the brain.

Presynaptic $5HT_{1B/D}$ Receptors

Presynaptic 5HT receptors on the axon terminal have the $5HT_{1B/D}$ subtype and act as negative-feedback autoreceptors to detect the presence of 5HT, causing a shutdown of further 5HT release and 5HT neuronal impulse flow (Figure 4-41). When 5HT is detected in the synapse by presynaptic 5HT receptors on axon terminals, it occurs via a $5HT_{1B/D}$ receptor, which is also called a *terminal autoreceptor* (Figure 4-41). In the case of the $5HT_{1B/D}$ terminal autoreceptor, 5HT occupancy of this receptor causes a blockade of 5HT release (Figure 4-41B).

Postsynaptic Serotonin Regulates Other Neurotransmitters in Downstream Brain Circuits

It turns out that each neurotransmitter not only controls its own synthesis and release from presynaptic sites; each neurotransmitter also controls the actions of the other neurotransmitters via postsynaptic actions and networks of brain circuits. So, if every neurotransmitter regulates every other neurotransmitter, it's complicated! No longer can we think of a neurotransmitter acting only synaptically; neurotransmitters also act trans-synaptically in brain circuits that both control other neurotransmitters and are controlled by other neurotransmitters. So, how are we supposed to figure out what is the net effect of a drug acting at a receptor if these receptors are all over the place and if they do different things at different sites? Furthermore, how can we possibly understand psychiatric illnesses involving serotonin if this same neurotransmitter does quite different things in different circuits and in different synapses?

The answer in part is to step back and appreciate the wonderful complexity of the brain's neurotransmitter systems, and that we are only beginning to scratch the surface of how these neurotransmitter systems theoretically work as the substrates of normal feelings and emotions as well as the symptoms of mental illnesses. Here we will hazard a mere glimpse of how neurotransmitters regulate each other's neurotransmission by acting through networks of neurons communicating with each other, not only with different neurotransmitters at different nodes in the various neuronal networks, but with different receptor subtypes for the same neurotransmitters at nodes or connecting points within these neuronal networks. Hypothetically, when neural networks are experiencing inefficient information processing (i.e., one could say they are "out of tune"), this in part mediates the symptoms of mental illnesses. A corollary to this notion is that when our drugs "tune" these neuronal networks by their actions at specific receptor subtypes, they have the potential for improving the efficiency of information processing in these neuronal networks, thereby reducing the symptoms of mental illnesses. Although oversimplified and perhaps a bit naïvely reductionistic in presentation, this discussion is the next step past the now dated notion that mental illnesses and drugs that treat them are simply "chemical imbalances" at synapses. In considering the modern neurobiology of mental illnesses and their treatments, one would be well advised to remain humble about what we know and perhaps recall how *The Devil's Dictionary* (by Ambrose Bierce) defined the mind in the nineteenth century:

> MIND, n. A mysterious form of matter secreted by the brain. Its chief activity consists in the endeavor to ascertain its own nature, the futility of the attempt being due to the fact that it has nothing but itself to know itself with.

Constructing the 5HT Network

Serotonin, as do all neurotransmitters, interacts downstream with other neurons and the neurotransmitters these neurons release (Figures 4-42 and 4-43). Thus, what happens after serotonin is released

depends not only upon what receptor it interacts with (see nine different serotonin receptors in Figure 4-42), but also very much upon what neuron it is communicating with and the neurotransmitter that neuron releases (see interactions with glutamate and GABA neurons in Figure 4-42 and with glutamate, GABA, norepinephrine (NE), dopamine (DA), histamine (HA), and acetylcholine (ACh) in Figure 4-43). Note all the options that serotonin has for control: it can excite or inhibit depending upon the serotonin receptor subtype where it is interacting, and upon whether the postsynaptic neuron itself releases the excitatory neurotransmitter glutamate or the inhibitory neurotransmitter GABA. When serotonin has neurotransmission simultaneously in both excitatory and inhibitory situations, which predominates? The short answer is that it seems to depend upon whether a specific receptor is expressed in a specific location; the density of that receptor, with response more likely with densely

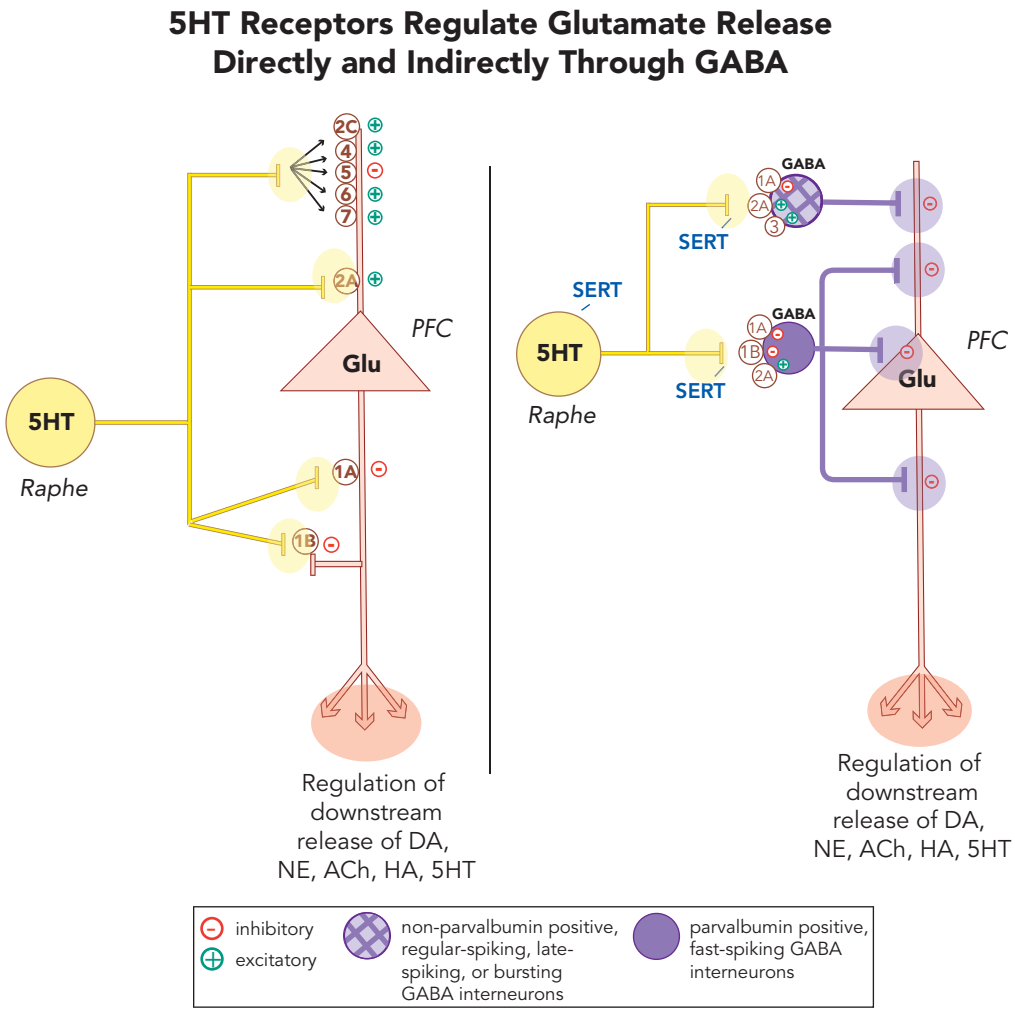


Figure 4-42 Serotonin (5HT) regulates glutamate release directly and indirectly. Most 5HT receptor subtypes are postsynaptic heteroreceptors and reside on the neurons that release any of a number of neurotransmitters; thus, serotonin (like all neurotransmitters) can regulate downstream release of numerous neurotransmitters. Left: 5HT's direct influence on glutamate pyramidal neurons can be both excitatory (e.g., at $5HT_{2A}$, $5HT_{2C}$, $5HT_4$, $5HT_6$, and $5HT_7$ receptors) and inhibitory (at $5HT_{1A}$, $5HT_5$, and possibly postsynaptic $5HT_{1B}$ heteroreceptors). Glutamate neurons, in turn, synapse with the neurons of most other neurotransmitters to regulate their downstream release. Right: Glutamate output can also be controlled indirectly by 5HT receptors on inhibitory GABAergic interneurons. With so many ways to stimulate and to inhibit the glutamate neurons, and with some 5HT receptors having opposing actions on glutamate release due to their presence on both glutamate neurons and GABA interneurons (e.g., $5HT_{2A}$), it seems that the coordinated actions of 5HT at its various receptors may serve to "tune" glutamate output and keep it in balance. The net effects of 5HT upon glutamate release depend on the regional and cellular expression patterns of 5HT receptor subtypes, the density of 5HT receptors, and the local concentration of 5HT.

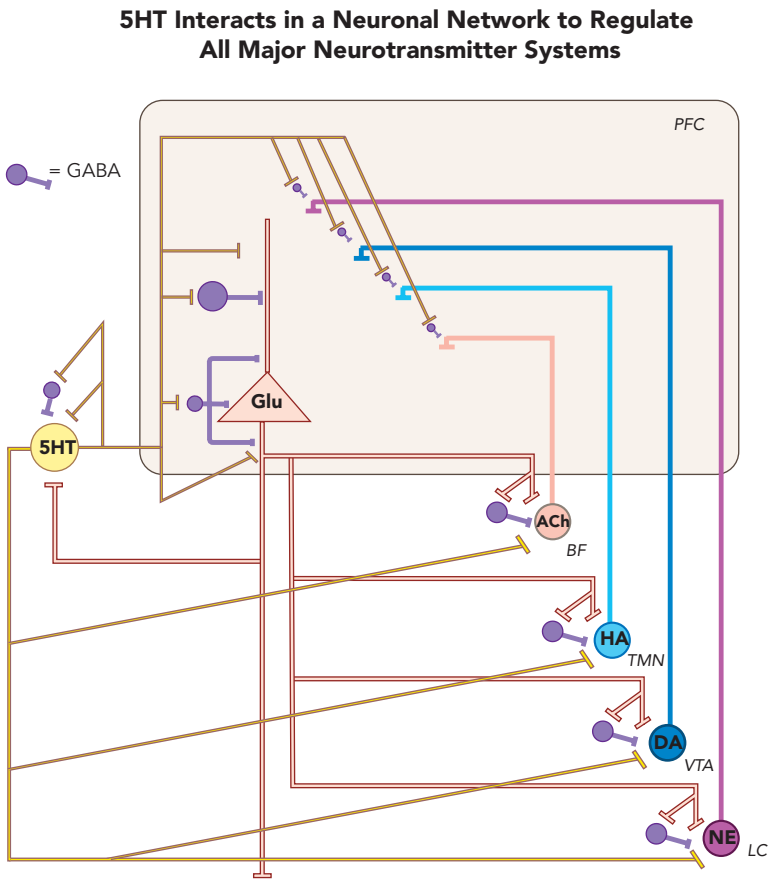
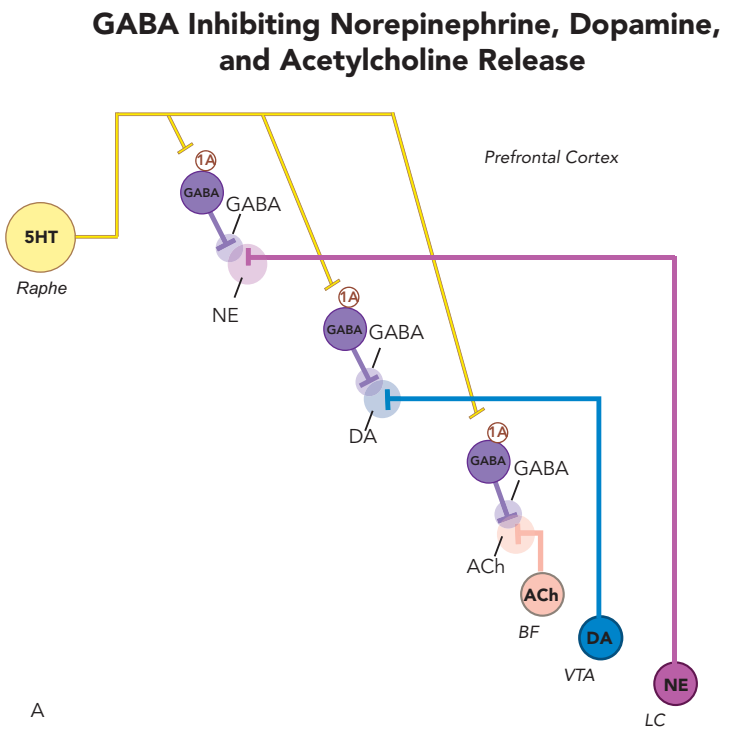


Figure 4-43 Serotonin (5HT) interacts in a neuronal network to regulate all major neurotransmitter systems. 5HT circuits arise from discrete brainstem nuclei, including the dorsal and median raphe nuclei. These circuits project to a wide range of cortical and subcortical brain areas, including the prefrontal cortex (PFC) and the loci for the cell bodies of neurons of other neurotransmitters, such as the locus coeruleus (LC) for norepinephrine, the ventral tegmental area (VTA) for dopamine, the tuberomammillary nucleus of the hypothalamus (TMN) for histamine, and the basal forebrain (BF) for acetylcholine. Through these connections, the 5HT network may both modulate itself and directly and indirectly influence virtually all other neurotransmitter networks. Thus, it is not surprising that the 5HT network is thought to regulate a variety of behaviors, including mood, sleep, and appetite, or that dysregulation of the 5HT network has been implicated in many psychiatric disorders.

versus sparsely populated receptors; the sensitivity of a receptor to serotonin; and the amount of release and the firing rate of the serotonin neuron, with some receptors more sensitive to low levels of serotonin than others. Finally, it depends upon whether the interaction is direct (e.g., serotonin directly acting at a glutamate neuron – Figure 4-42, left – or a GABA neuron – Figure 4-42, right) or indirect (e.g., serotonin indirectly acting at glutamate neurons via a GABA neuron that itself innervates a glutamate neuron – Figure 4-42, right). Norepinephrine, dopamine, histamine, and acetylcholine can also receive input directly from serotonin neurons, especially at their cell bodies, or indirectly via glutamate and/or GABA neurons as intermediaries (Figure 4-43). Thus, it can readily be seen that a drug acting directly on serotonin neurons and their receptors not only can affect serotonin itself, but can have profound downstream effects on all the other neurotransmitters. Which ones are affected, in what priority, and at which sites are currently the subject of intense investigation. However, these networks and how they are organized can explain why a drug that acts first and directly at a particular receptor of a particular neurotransmitter can have profound net effects on all sorts of neurotransmitters. Understanding a bit about neural networks can also be the foundation for beginning to grasp why the frequent practice of giving drugs with two or more mechanisms of action (or two different agents with two or more different actions) can have either additive/synergistic effects or canceling/antagonistic effects. This is reflected in the corresponding effects on drug efficacy and side effects.

$5HT_{1A}$ Receptors

$5HT_{1A}$ receptors can promote the release of other neurotransmitters (Figure 4-44). $5HT_{1A}$ receptors are always inhibitory, but they are very frequently localized upon postsynaptic GABA neurons, which means that the net downstream effect in this case is actually excitatory (Figure 4-44). For example, $5HT_{1A}$ receptors are located on GABA interneurons in the prefrontal cortex and these GABA interneurons in turn act to inhibit neurotransmitter release from glutamate neurons (see Figure 4-42B). $5HT_{1A}$



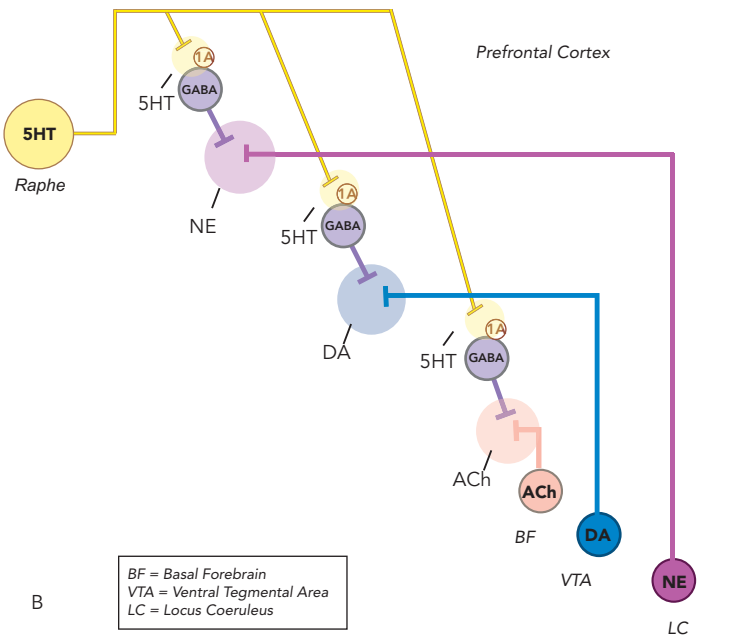


Figure 4-44 **Serotonin (5HT) 1A stimulation indirectly increases release of other neurotransmitters.** (A) $5HT_{1A}$ heteroreceptors on GABA interneurons in the prefrontal cortex can indirectly regulate the release of norepinephrine (NE), dopamine (DA), and acetylcholine (ACh). (B) Stimulation of $5HT_{1A}$ receptors is inhibitory; thus, serotonin binding at these receptors could reduce GABA output and in turn disinhibit norepinephrine, dopamine, and acetylcholine release.

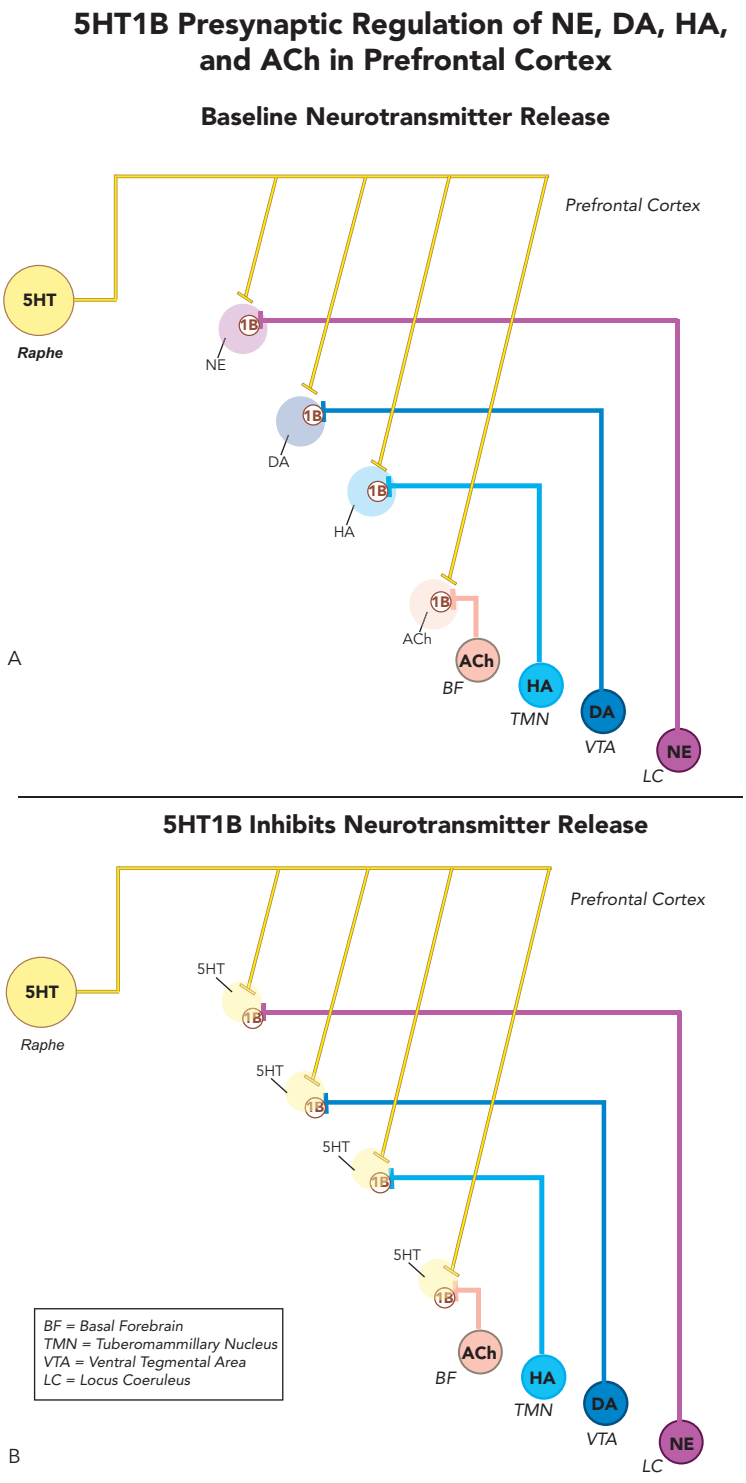


Figure 4-45 **Serotonin (5HT) 1B stimulation decreases release of other neurotransmitters.** (A) $5HT_{1B}$ receptors on the presynaptic nerve terminals of norepinephrine (NE), dopamine (DA), acetylcholine (ACh), and histamine (HA) neurons can theoretically regulate the release of these neurotransmitters. (B) Stimulation of $5HT_{1B}$ heteroreceptors on ACh, HA, DA, and NE neurons is inhibitory; thus, serotonin binding at these receptors could potentially decrease the release of these neurotransmitters.

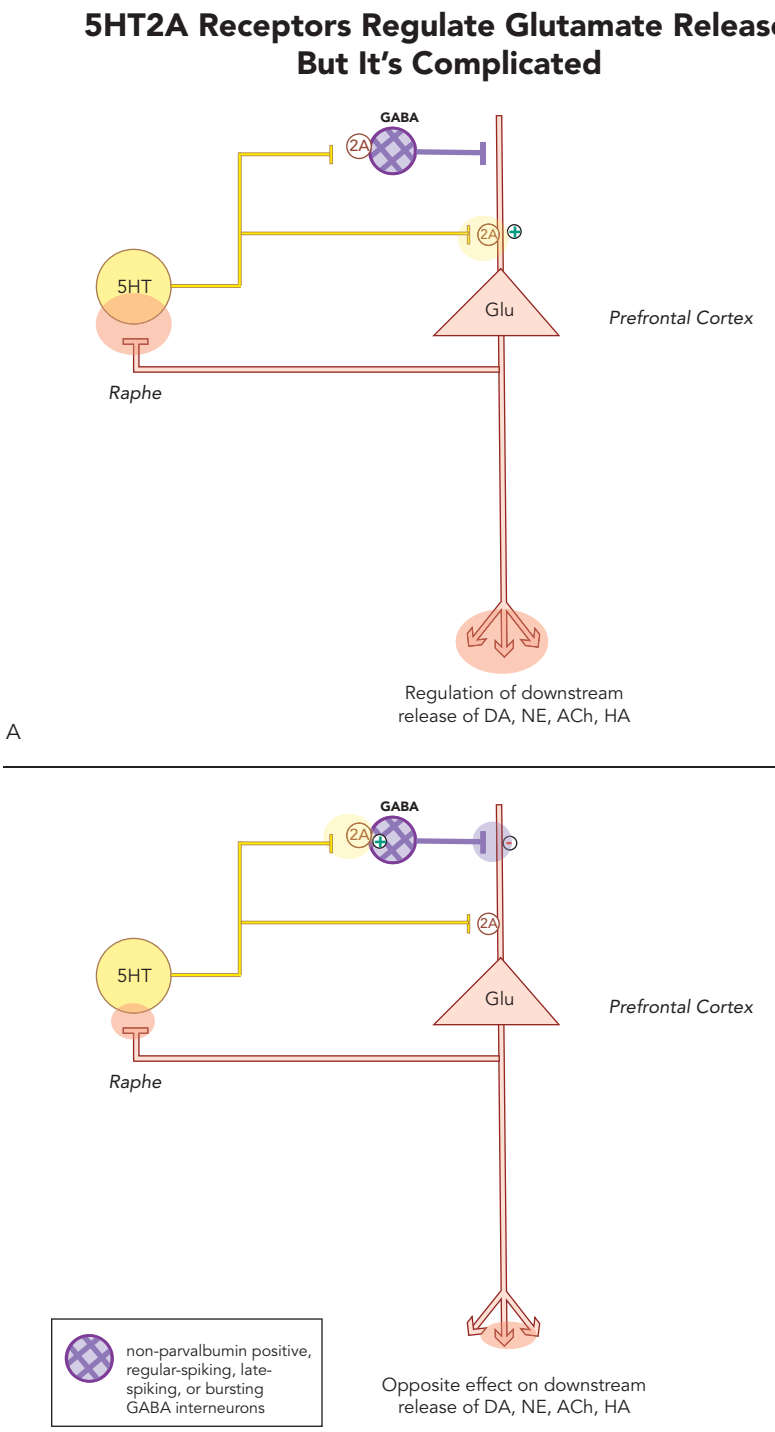


Figure 4-46 Serotonin (5HT) 2A stimulation both promotes and inhibits glutamate release. $5HT_{2A}$ receptors are always excitatory, but depending on their localization can either stimulate or inhibit glutamate release. (A) $5HT_{2A}$ receptors are located on glutamate pyramidal neurons, and through the stimulation of these receptors can increase glutamate release. (B) However, $5HT_{2A}$ receptors are also present on GABA interneurons and when stimulated cause GABAergic inhibition of glutamate. Thus, the net effects of $5HT_{2A}$ stimulation – or of $5HT_{2A}$ antagonism – on glutamate neurotransmission will depend on multiple factors, including the density of the receptors and the local concentration of 5HT.

receptors located on other GABA interneurons also inhibit neurotransmitter release from presynaptic terminals of norepinephrine, dopamine, and acetylcholine neurons.

Shown in Figure 4-44A is the baseline condition where a low tonic GABA release allows only a correspondingly low baseline of norepinephrine, dopamine, and

acetylcholine release. However, when serotonin is released at $5HT_{1A}$ receptors localized on GABA interneurons (Figure 4-44B), this receptor action inhibits the GABA interneurons, reducing their inhibitory GABA release and allowing an increase in the release of downstream norepinephrine, dopamine, and acetylcholine. Thus, serotonin action at these $5HT_{1A}$ receptors facilitates downstream norepinephrine, dopamine, and acetylcholine release. As will be explained in subsequent chapters, many psychotropic drugs that treat psychosis, mood, and anxiety are $5HT_{1A}$ agonists or partial agonists.

$5HT_{1B}$ Receptors

$5HT_{1B}$ receptors are inhibitory and can specifically inhibit neurotransmitter release from norepinephrine, dopamine, histamine, and acetylcholine neurons when these receptors are localized upon presynaptic nerve terminals of these neurons (Figure 4-45). When a receptor for a neurotransmitter other than the one the neuron uses as its own neurotransmitter is present, it is called a "heteroreceptor" (literally, other receptor). In the case of $5HT_{1B}$ receptors present on non-serotonin presynaptic nerve terminals, they are inhibitory and act to prevent release of those other neurotransmitters (Figure 4-45A). At baseline, some amount of neurotransmitter is shown being released from four different neurons in the prefrontal cortex: norepinephrine, dopamine, histamine, and acetylcholine (Figure 4-45A). However, when serotonin is released upon their presynaptic inhibitory $5HT_{1B}$ heteroreceptors, this reduces the release of these four neurotransmitters (Figure 4-45B). Thus, serotonin inhibits norepinephrine, dopamine, histamine, and acetylcholine release at $5HT_{1B}$ receptors. A few agents known to be $5HT_{1B}$ antagonists that may thus enhance the release of these four neurotransmitters are used to treat depression and are discussed in Chapter 7 on drug treatments for mood disorders.

$5HT_{2A}$ Receptors

$5HT_{2A}$ receptors can both promote and inhibit the release of other neurotransmitters. That is, although $5HT_{2A}$ receptors are always excitatory, the variability of their location in the brain means that these receptors can both facilitate and inhibit the release of various downstream neurotransmitters. For example, when $5HT_{2A}$ receptors are localized on glutamate neurons, generally upon the apical dendrites of glutamate neurons, they are excitatory, leading to excitatory glutamate release on downstream targets (Figure 4-46A). On the other hand, when $5HT_{2A}$ receptors are localized on GABA interneurons that innervate glutamate neurons, excitatory $5HT_{2A}$ input to the GABA interneuron leads to GABA release, and this GABA is inhibitory to the glutamate neuron it innervates, with opposite effects on neurons downstream to glutamate neurons (Figure 4-46B). Many drugs that treat psychosis and mood have $5HT_{2A}$ antagonist properties and will be discussed extensively in Chapter 5 on drugs for psychosis and in Chapter 7 on drugs for mood disorders. Additionally, most hallucinogens have $5HT_{2A}$ agonist properties and this will be discussed in Chapter 13 on drug abuse.

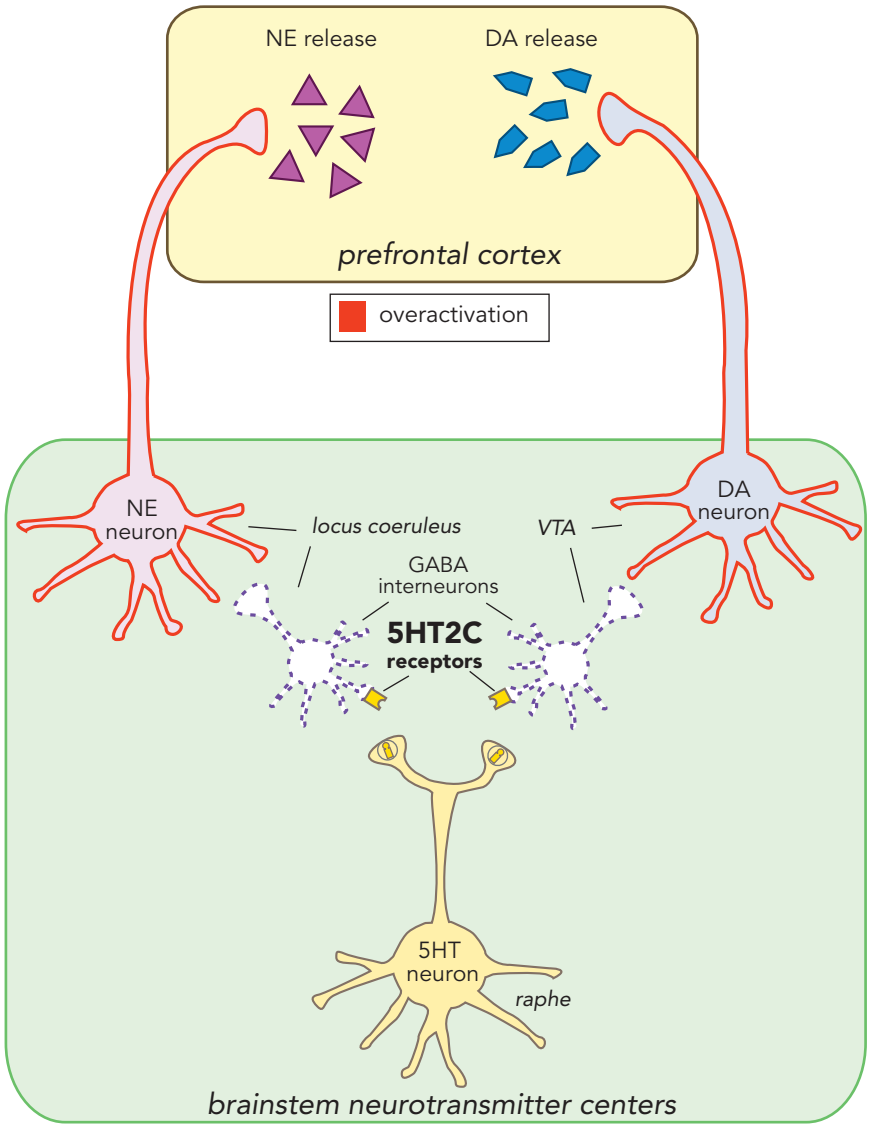
$5HT_{2C}$ Receptors

$5HT_{2C}$ receptors generally inhibit the release of downstream neurotransmitters. $5HT_{2C}$ receptors are excitatory, postsynaptic, and are mostly present upon GABA interneurons (Figures 4-47A and 4-47B). This means that $5HT_{2C}$ receptors have net inhibitory effects wherever their GABA interneurons go. For example, when those GABA interneurons with $5HT_{2C}$ receptors on them innervate downstream norepinephrine or dopamine neurons, the net effect of 5HT is to inhibit norepinephrine and dopamine release (compare baseline levels of norepinephrine and dopamine in the prefrontal cortex in Figure 4-47A with the levels of norepinephrine and dopamine after serotonin release at $5HT_{2C}$ receptors in Figure 4-47B). Agonists of $5HT_{2C}$ receptors can treat obesity and antagonists of $5HT_{2C}$ receptors treat psychosis and mood disorders.

$5HT_3$ Receptors

$5HT_3$ receptors located in the brainstem chemoreceptor trigger zone outside of the blood–brain barrier are well known for their role in centrally mediated nausea and vomiting. However, elsewhere in the central nervous system, especially in the prefrontal cortex, $5HT_3$ receptors are localized on a particular type of GABA interneuron (specifically that with the properties of not binding to a calcium dye called parvalbumin, and also having a characteristic GABA interneuron firing pattern that is regular-spiking, late-spiking, or bursting, see Figure 4-42, right). Just like $5HT_{2C}$ receptors, $5HT_3$ receptors are excitatory upon the GABA neurons they innervate, meaning $5HT_3$ receptors also exert net inhibitory effects wherever their GABA interneurons go.

$5HT_3$ receptors specifically inhibit the release of acetylcholine and norepinephrine at the cortical level (Figure 4-48). That is, interneurons containing $5HT_3$ receptors terminate upon the nerve endings of presynaptic acetylcholine and norepinephrine neurons to inhibit them (see baseline state with a low level of GABA release allowing a low level of acetylcholine and norepinephrine release in Figure 4-48A). Acetylcholine and norepinephrine release are reduced

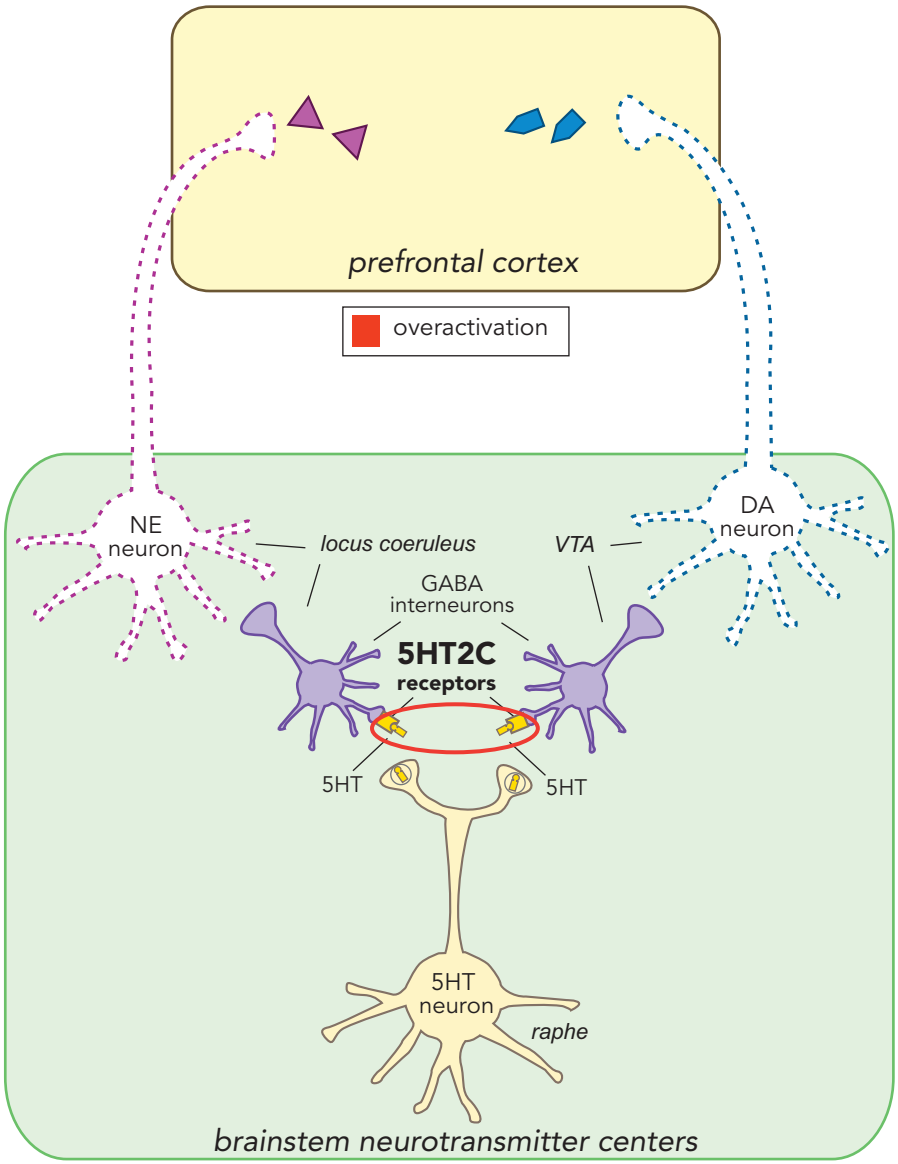


A

Figure 4-47A Serotonin (5HT) 2C stimulation, part 1. Excitatory $5HT_{2C}$ receptors are mostly present on GABA interneurons. When serotonin is absent, the GABA receptors are not stimulated, and thus downstream neurons, in this case norepinephrine (NE) and dopamine (DA) neurons projecting to the prefrontal cortex, are active.

when GABA release is increased by serotonin exciting the interneuron at excitatory $5HT_3$ receptors (Figure 4-48B). Thus, serotonin acting at $5HT_3$ receptors inhibits both acetylcholine and norepinephrine release. $5HT_3$ antagonists, including some drugs that treat depression, would be expected to have the opposite effect, namely enhancing the release of acetylcholine and norepinephrine (discussed further in Chapter 7).

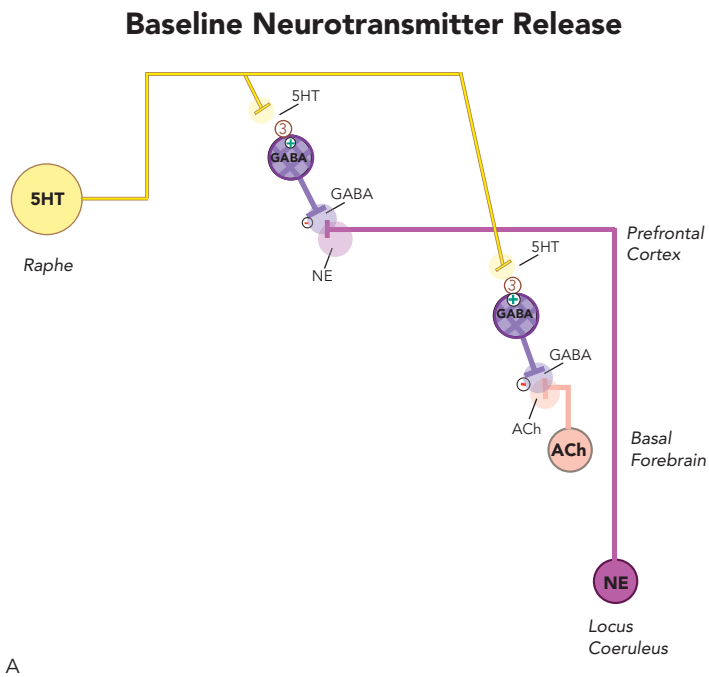
One of the more important regulatory controls upon excitatory glutamate output from the prefrontal cortex is tonic inhibition by GABA interneurons receiving 5HT input upon their $5HT_3$ receptors (Figure 4-49A). When 5HT input onto these $5HT_3$ receptors is increased, the firing rate of the glutamatergic pyramidal neuron is diminished (Figure 4-49B). Not only does this reduce the excitatory effects of glutamate on a plethora of



B

Figure 4-47B Serotonin (5HT) 2C stimulation, part 2. Serotonin binding at $5HT_{2C}$ receptors on GABA interneurons inhibits norepinephrine (NE) and dopamine (DA) release in the prefrontal cortex.

downstream sites it innervates, it also specifically reduces the excitatory feedback loop of glutamate upon serotonin neurons at the level of the midbrain raphe (Figure 4-49B). So, not only does this circuit show serotonin regulating glutamate (i.e., reducing glutamate release by $5HT_3$ receptor actions at GABA interneurons), it demonstrates one way in which glutamate reciprocally regulates serotonin (i.e., in a feedback loop that normally excites serotonin release from glutamate actions on serotonin cell bodies in the raphe, but now is diminished due to the inhibition of glutamate release by serotonin). This is but one simple example of reciprocal regulations of neurotransmitters by each other.



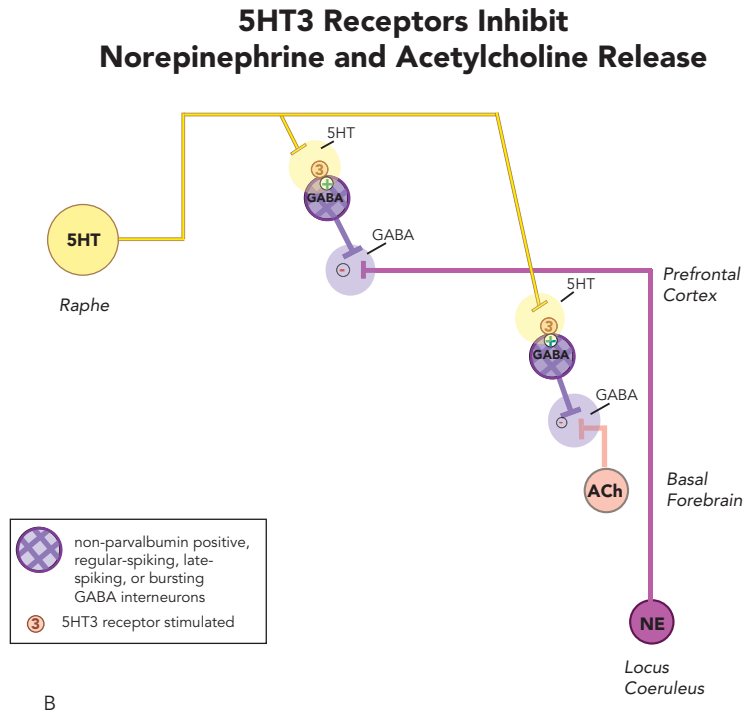
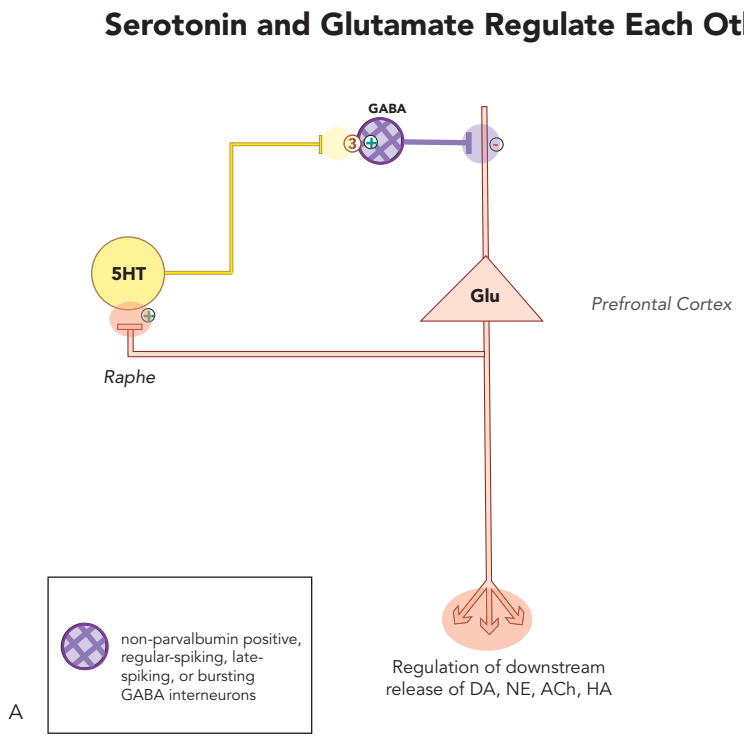


Figure 4-48 Serotonin (5HT) 3 stimulation inhibits norepinephrine and acetylcholine release. Excitatory $5HT_3$ receptors located on the terminals of GABA interneurons in the prefrontal cortex can regulate the release of norepinephrine (NE) and acetylcholine (ACh). (A) At baseline, tonic GABA release allows for a low level of NE and ACh release. (B) When 5HT is released, it binds to $5HT_3$ receptors on GABAergic neurons, causing phasic release of GABA onto noradrenergic and cholinergic neurons, thus reducing the release of NE and ACh, respectively.



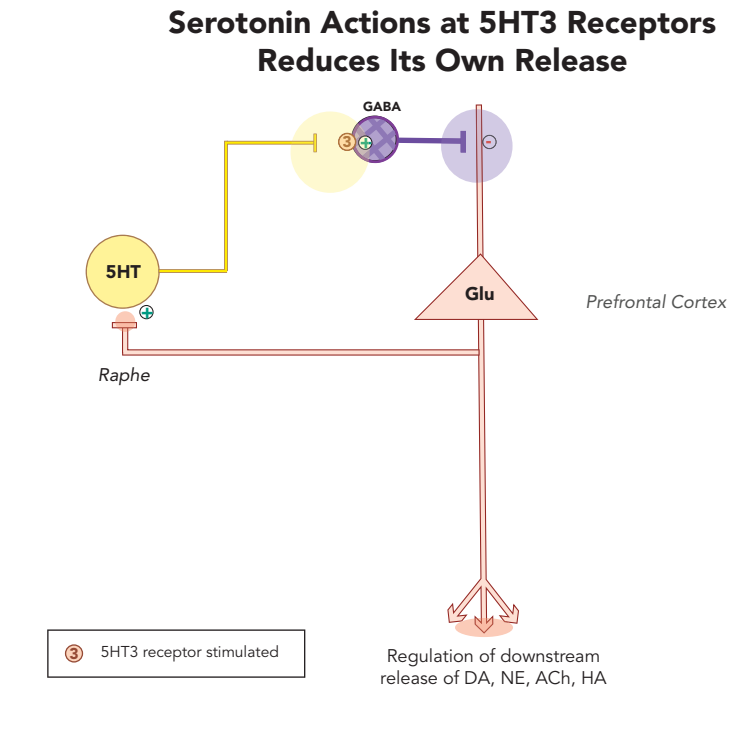


Figure 4-49 Serotonin (5HT) 3 stimulation inhibits serotonin release. Excitatory $5HT_3$ receptors located on the terminals of GABA interneurons in the prefrontal cortex can regulate the release of glutamate, and glutamate in turn can regulate release of serotonin. (A) At baseline, low-level serotonin release stimulates $5HT_3$ receptors on GABA interneurons, which synapse with pyramidal glutamate neurons. Glutamate release downstream regulates release of downstream dopamine (DA), norepinephrine (NE), acetylcholine (ACh), and histamine (HA). Glutamate also regulates 5HT release in the raphe. (B) When concentrations of 5HT are higher, the stimulation at $5HT_3$ receptors on GABA interneurons increases GABA release. GABA, in turn, inhibits glutamate pyramidal neurons, reducing glutamate output. Decreased release of excitatory glutamate means that there may be a resultant decrease in downstream release of neurotransmitters, including 5HT.

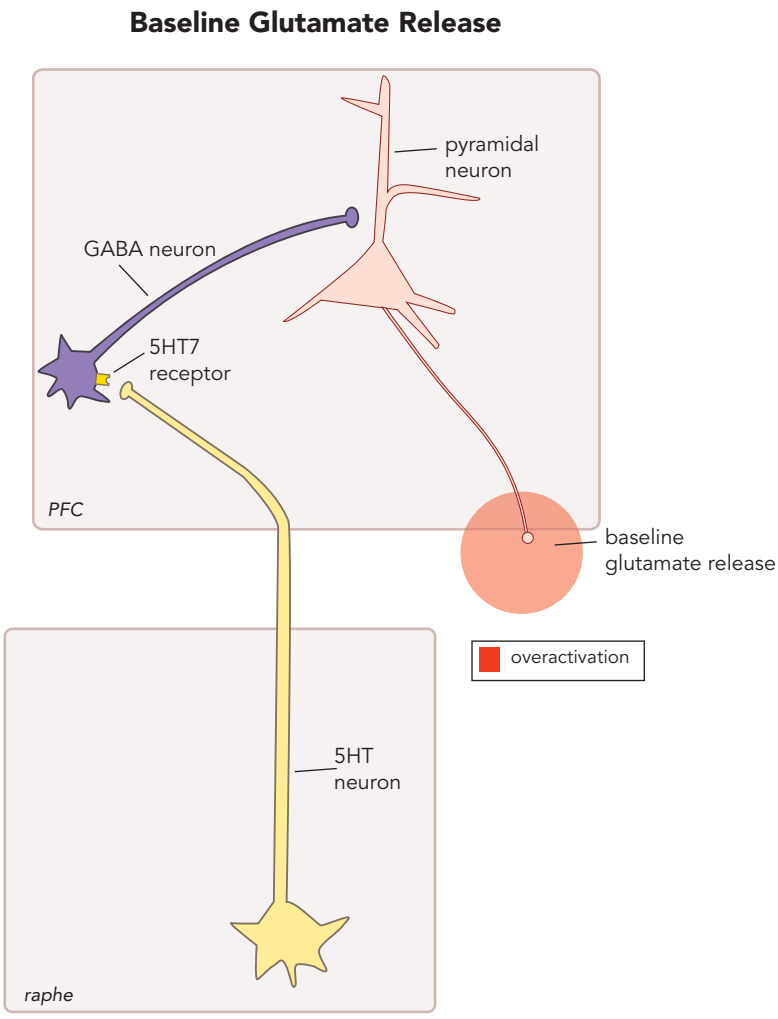
$5HT_6$ Receptors

$5HT_6$ receptors are postsynaptic and may be key regulators of the release of acetylcholine release and of control of cognitive processes. Blocking this receptor improves learning and memory in experimental animals, so $5HT_6$ antagonists have been proposed as novel pro-cognitive agents for the cognitive symptoms of schizophrenia, Alzheimer disease, and other disorders.

$5HT_7$ Receptors

$5HT_7$ receptors are postsynaptic, excitatory, and frequently localized on inhibitory GABA interneurons, same as discussed above for the $5HT_{1A}$, $5HT_{2C}$, and $5HT_3$ receptors. Just like these other receptors localized on GABA interneurons, $5HT_7$ receptors generally inhibit the release of downstream neurotransmitters. $5HT_7$ receptors specifically inhibit the release of glutamate at the cortical level (Figure 4-50B). That is, cortical interneurons containing $5HT_7$ receptors terminate on apical dendrites of glutamatergic pyramidal neurons (see baseline state with a normal level of glutamate release in the absence of $5HT_7$ receptor activation in Figure 4-50A). When serotonin binds to $5HT_7$ receptors on these cortical GABA interneurons, this inhibits glutamate output (Figure 4-50B).

$5HT_7$ receptors also regulate serotonin release at the level of the brainstem raphe (Figures 4-51A and 4-51B). That is, a recurrent collateral from the serotonin neuron loops backwards to innervate a GABA neuron that



A

Figure 4-50A Serotonin (5HT) 7 stimulation inhibits glutamate release, part 1. $5HT_7$ receptors are located on GABA interneurons that synapse with glutamate pyramidal neurons. In the absence of serotonin, tonic GABA release results in normal glutamate release downstream.

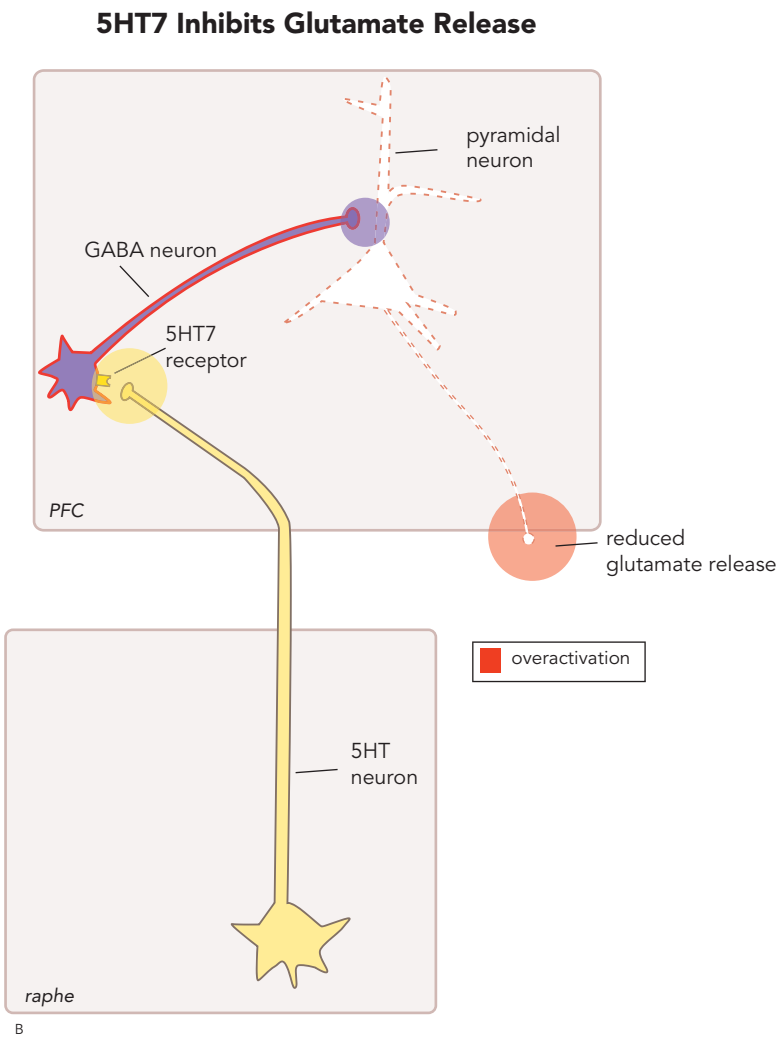


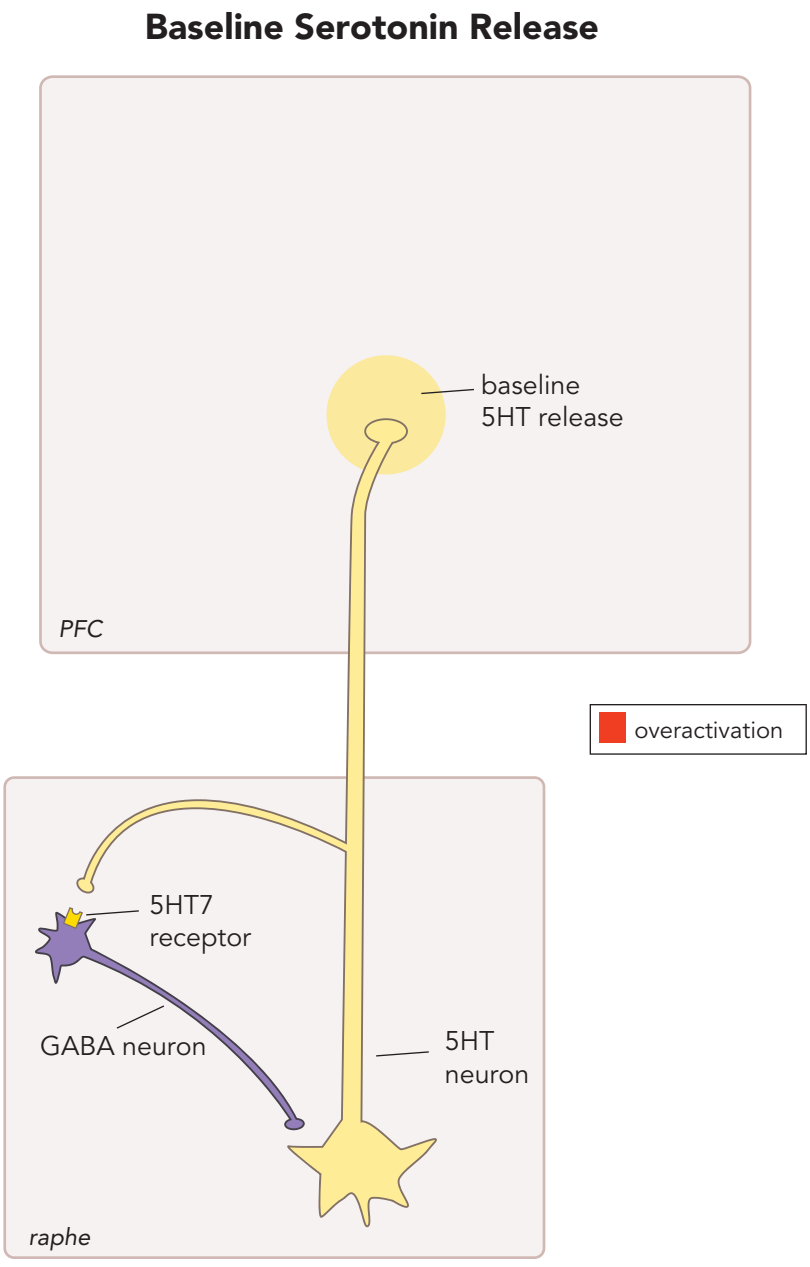
Figure 4-50B Serotonin (5HT) 7 stimulation inhibits glutamate release, part 2. When serotonin binds to $5HT_7$ receptors on GABA interneurons, the phasic GABA release leads to inhibition of glutamate release.

innervates the serotonin cell body. At baseline, serotonin release is not affected by this inhibitory feedback system (Figure 4-51A). However, when serotonin release gets high, this activates serotonin release from the recurrent collateral, stimulating the $5HT_7$ receptor there (Figure 4-51B). This activates GABA release, which in turn inhibits further serotonin release by its inhibitory actions at the cell body of the serotonin neuron (Figure 4-51B). $5HT_7$ antagonists are used for the treatment of psychosis and mood and are discussed in more detail in Chapter 7.

The Serotonin Hyperfunction Hypothesis of Psychosis

If the glare of the dopamine hypothesis blinded some of us to the possibility of alternate explanations for psychosis, it created a dilemma for patients with psychosis secondary to Parkinson's disease or Alzheimer disease, since treatment with D_2 blockers causes harm to these patients, worsening movements in Parkinson's disease and increasing the risk of stroke and death in Alzheimer disease. Until recently, dogma dictated that all psychoses were due to excessive mesolimbic dopamine and all treatments needed to block D_2 receptors there. While this characterization worked well for patients with schizophrenia, it obviously was not ideal for patients with psychosis in Parkinson's disease or in dementia, since it meant that the only available drugs for psychosis were relatively contraindicated for them.

Although serotonin receptors and synapses are ubiquitous throughout the brain, the serotonin hyperfunction hypothesis of psychosis suggests that



A

Figure 4-51A Serotonin (5HT) 7 stimulation inhibits serotonin release, part 1. Excitatory $5HT_7$ receptors located on the terminals of GABA interneurons in the raphe can regulate serotonin release. When $5HT_7$ receptors are not occupied, serotonin is released into the prefrontal cortex (PFC).

psychosis may be caused by an imbalance in excitatory $5HT_{2A}$ receptor stimulation of those glutamate pyramidal neurons discussed above, which directly innervate VTA/mesostriatal integrated hub dopamine neurons and visual cortex neurons (Figures 4-52A–D and Figures 4-53 through 4-55). The hallucinogens LSD, mescaline, and psilocybin, which are all powerful $5HT_{2A}$ agonists, have long been known to induce psychosis, dissociative experiences, and especially visual hallucinations by overstimulating prefrontal and visual cortex $5HT_{2A}$ receptors (compare Figure 4-52A and 4-52B; see also Figure 4-53). These symptoms can be blocked by $5HT_{2A}$ antagonists, demonstrating that hallucinogens cause psychosis by $5HT_{2A}$ stimulation.

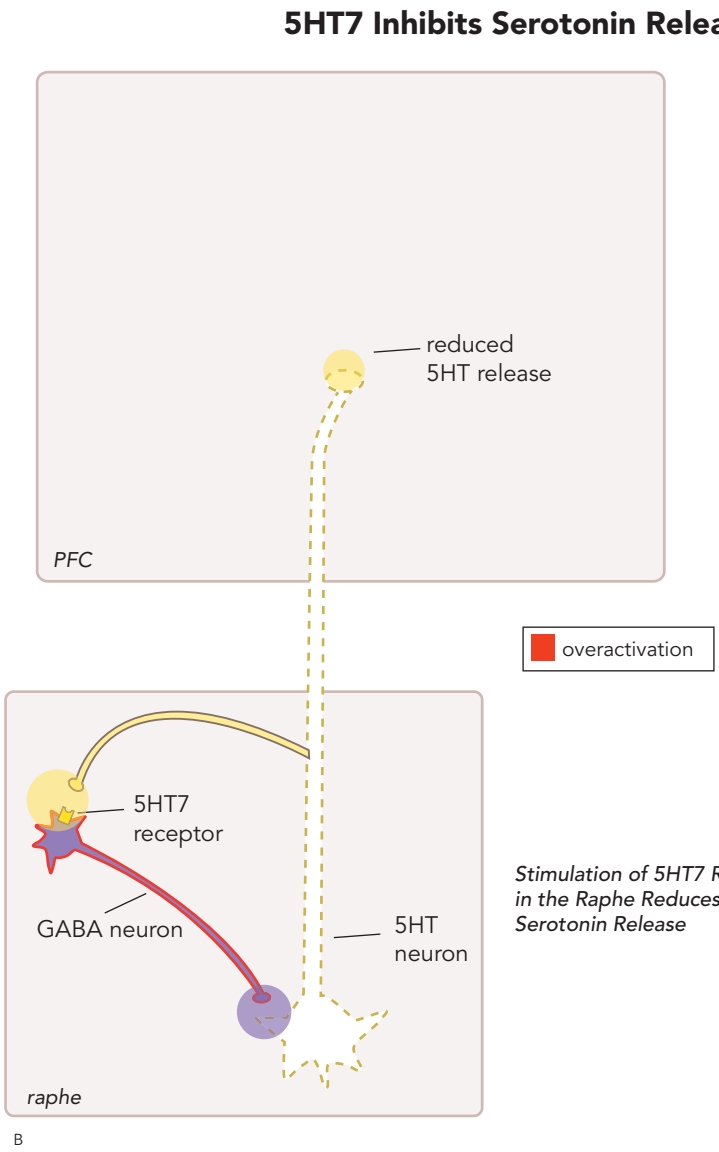


Figure 4-51B **Serotonin (5HT) 7 stimulation inhibits serotonin release, part 2.** When serotonin binds to $5HT_7$ receptors that innervate GABA neurons in the raphe nucleus, this causes the release of inhibitory GABA, which then turns off further serotonin release.

Stimulation of 5HT7 Receptors in the Raphe Reduces Serotonin Release

The next link in the serotonin hyperfunction hypothesis of $5HT_{2A}$ overstimulation causing psychosis comes from work in Parkinson's disease psychosis (PDP), affecting up to half of Parkinson's patients, especially later in the disease. Postmortem examinations as well as neuroimaging in living patients with PDP have demonstrated not only loss of dopamine nerve terminals in the motor striatum of the nigrostriatal pathway that causes the classic motor symptoms of Parkinson's disease, but also loss of serotonin nerve terminals in the prefrontal and visual cortex (Figure 4-52C). This loss of serotonin and serotonin nerve terminals leads to upregulation and too many $5HT_{2A}$ receptors in the cortex, perhaps a futile attempt to overcome serotonin loss (Figure 4-52C). The overabundance of $5HT_{2A}$ receptors leads to an imbalance in their excitatory actions on glutamate dendrites from the remaining serotonin in the cortex, and consequently, the symptoms of psychosis (Figures 4-52C and 4-54). Drugs with $5HT_{2A}$ antagonist actions can block these symptoms of PDP, as will be explained in further detail in Chapter 5 on drugs for psychosis. These observations support the serotonin

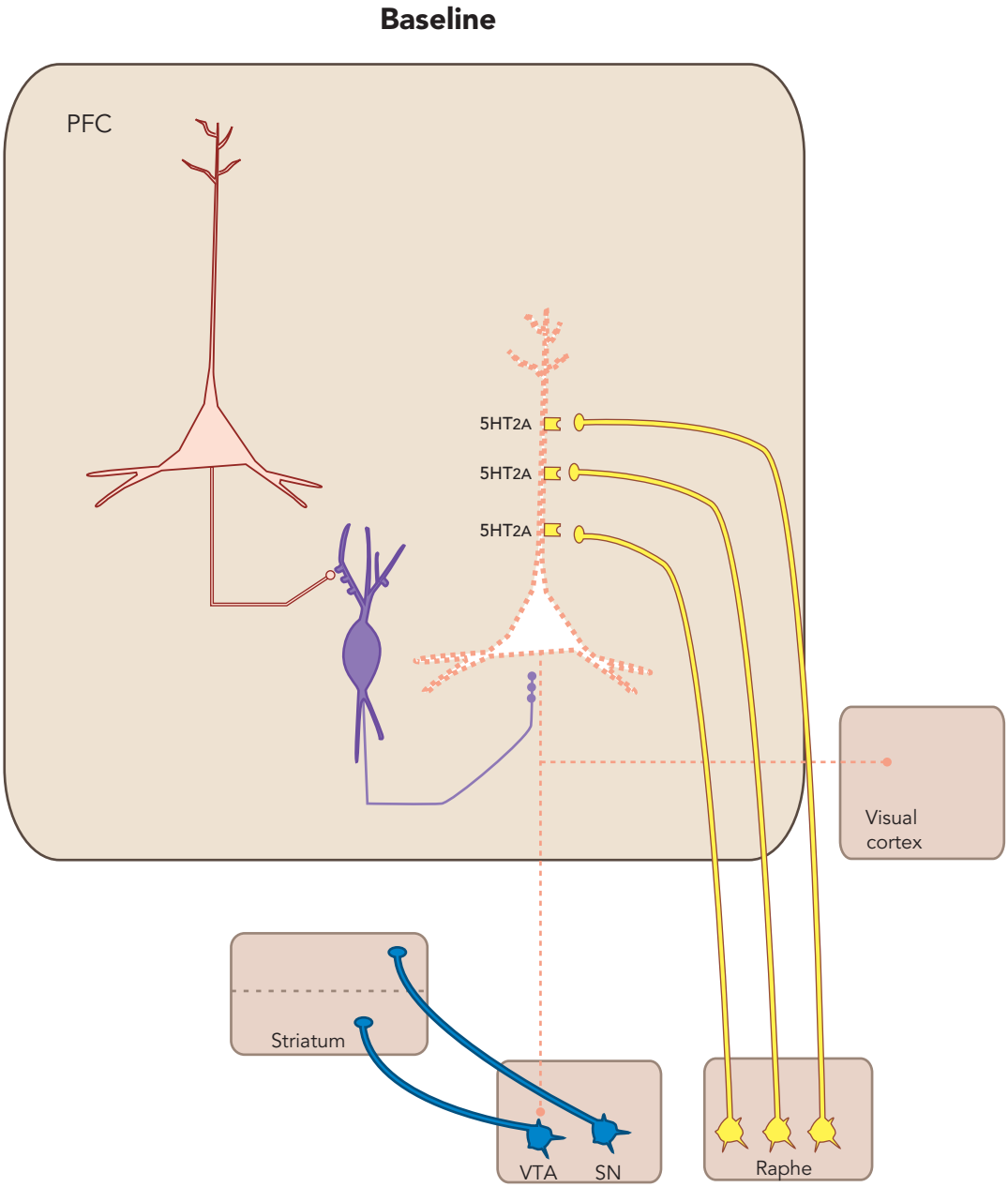


Figure 4-52A Serotonin (5HT) 2A receptors and psychosis, baseline. Glutamatergic pyramidal neurons in the prefrontal cortex (PFC) project to the ventral tegmental area (VTA) and to the visual cortex. Activity of the glutamatergic pyramidal neurons is regulated by serotonergic neurons that project from the raphe nucleus as well as by GABA interneurons in the PFC. At baseline, when excitatory $5HT_{2A}$ receptors are not stimulated and GABA neurotransmission is tonic, the glutamatergic neurons are not active.

hyperfunction hypothesis of psychosis by demonstrating that PDP is related to serotonin hyperfunction at $5HT_{2A}$ receptors that results from the malfunctioning and upregulation of $5HT_{2A}$ receptors by the disease process of Parkinson's disease.

Psychosis in dementia and its link to serotonin hyperfunction at $5HT_{2A}$ receptors appears to be different from what is happening with hallucinogen psychosis or PDP, where there is postulated overstimulation of $5HT_{2A}$ receptors. In dementia-

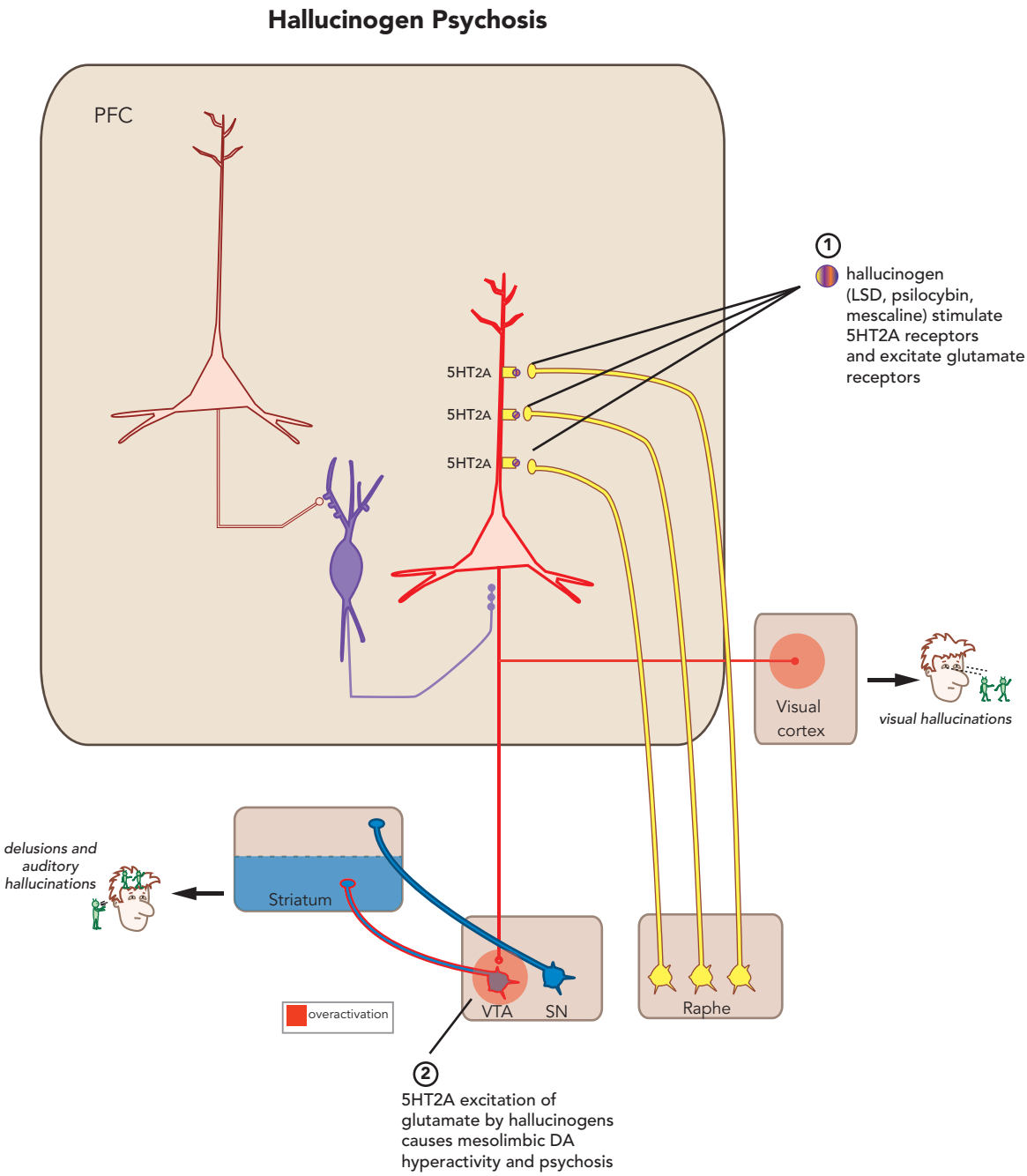


Figure 4-52B **Serotonin (5HT) 2A receptors and psychosis, hallucinogens.** Hallucinogens such as LSD, psilocybin, and mescaline are $5HT_{2A}$ agonists. (1) When these agents stimulate $5HT_{2A}$ receptors on glutamatergic pyramidal neurons in the prefrontal cortex (PFC), this causes overactivation of the glutamate neuron. (2) The resultant release of glutamate into the ventral tegmental area (VTA) causes hyperactivity of the mesolimbic dopamine (DA) pathway, resulting in delusions and auditory hallucinations. Excessive glutamate release in the visual cortex can cause visual hallucinations.

related psychosis there is no consistent evidence for upregulation of $5HT_{2A}$ receptors like there is in PDP. Instead, in dementia, the accumulation of plaques, tangles, and Lewy bodies, as well as the damage from strokes, hypothetically knocks out cortical neurons and leads to a lack of inhibition of

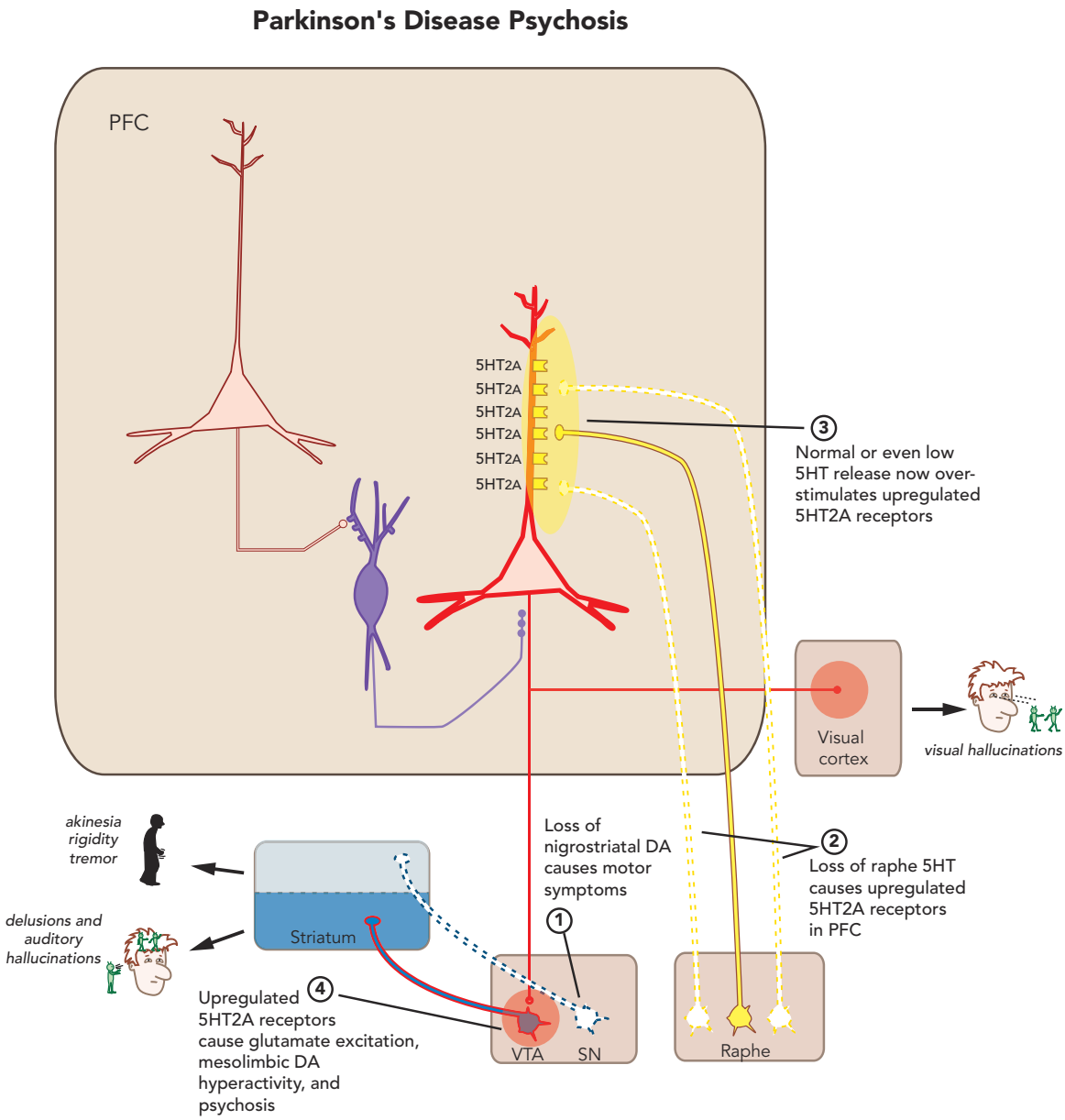


Figure 4-52C Serotonin (5HT) 2A receptors and psychosis, Parkinson's disease psychosis. (1) Loss of nigrostriatal dopamine neurons causes the motor symptoms of Parkinson's disease, such as akinesia, rigidity, and tremor. (2) Parkinson's disease also causes loss of serotonergic neurons that project from the raphe to the prefrontal cortex (PFC). (3) This leads to upregulation of 5HT2A receptors, in which case normal or even low serotonin release can overstimulate these receptors, causing overactivation of the glutamatergic pyramidal neuron. (4) Excessive glutamate release into the ventral tegmental area (VTA) causes hyperactivity of the mesolimbic dopamine pathway, resulting in delusions and auditory hallucinations. Excessive glutamate release in the visual cortex can cause visual hallucinations.

the surviving glutamate neurons (Figure 4-29C and Figure 4-52D). If there is not enough GABA inhibition to counter the normal $5HT_{2A}$ stimulation coming to surviving glutamate neurons projecting to the VTA/mesostriatum integrated hub and to the visual cortex, this enhanced output theoretically causes psychosis in these dementia patients (Figure 4-52D and 4-55). It is now known that selective $5HT_{2A}$ antagonism reduces

Psychosis in Dementia

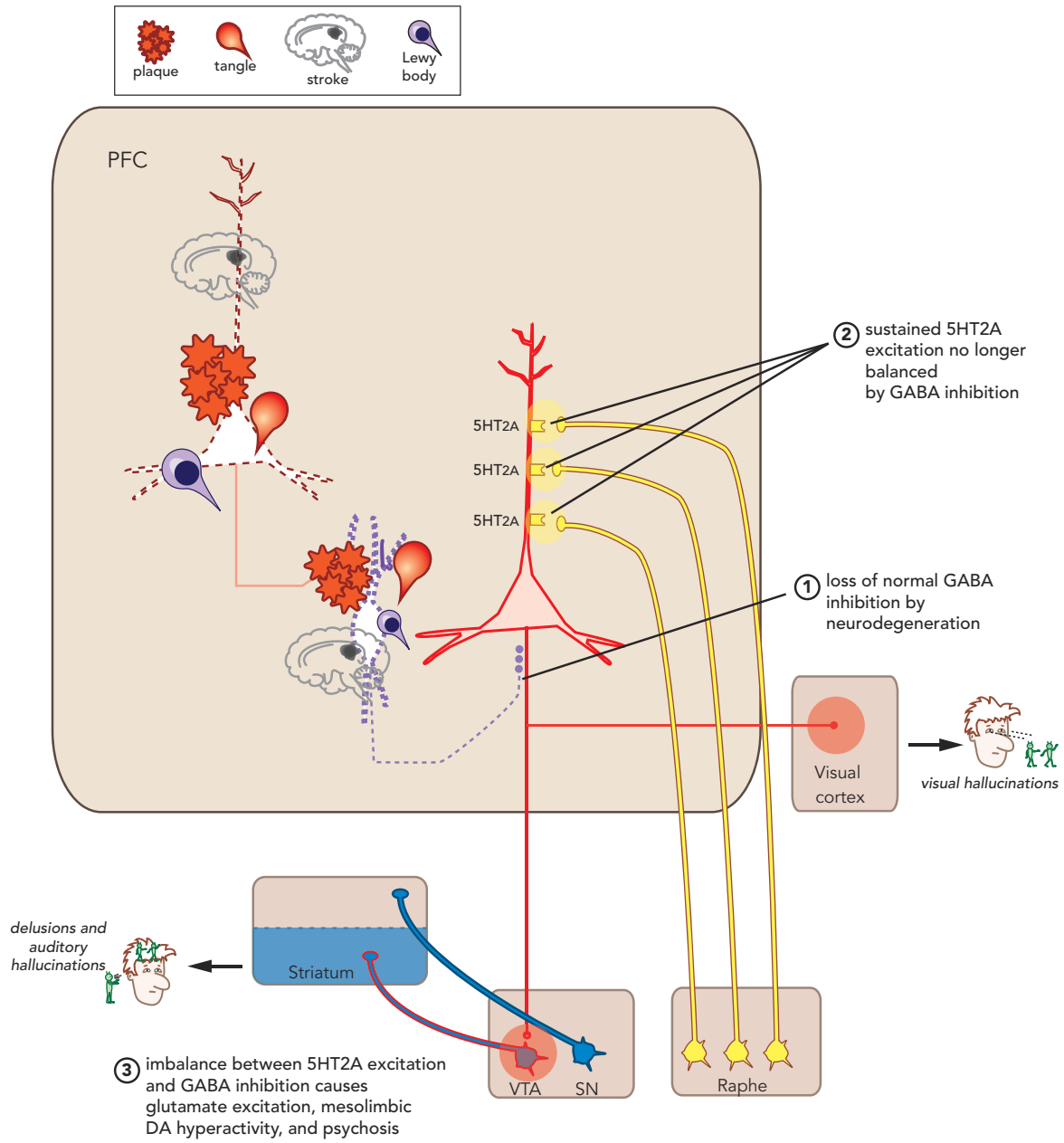


Figure 4-52D **Serotonin (5HT) 2A receptors and psychosis, dementia.** (1) Accumulation of amyloid plaques, tau tangles, and/or Lewy bodies, as well as the damage caused by strokes, may destroy some glutamatergic pyramidal neurons and GABAergic interneurons while leaving others intact. The loss of GABA inhibition upsets the balance of control over glutamatergic pyramidal neurons. (2) When the effects of stimulation of excitatory $5HT_{2A}$ receptors are not countered by GABA inhibition, there is a net increase in glutamatergic neurotransmission. (3) Excessive glutamate release into the ventral tegmental area (VTA) causes hyperactivity of the mesolimbic dopamine pathway, resulting in delusions and auditory hallucinations. Excessive glutamate release in the visual cortex can cause visual hallucinations.

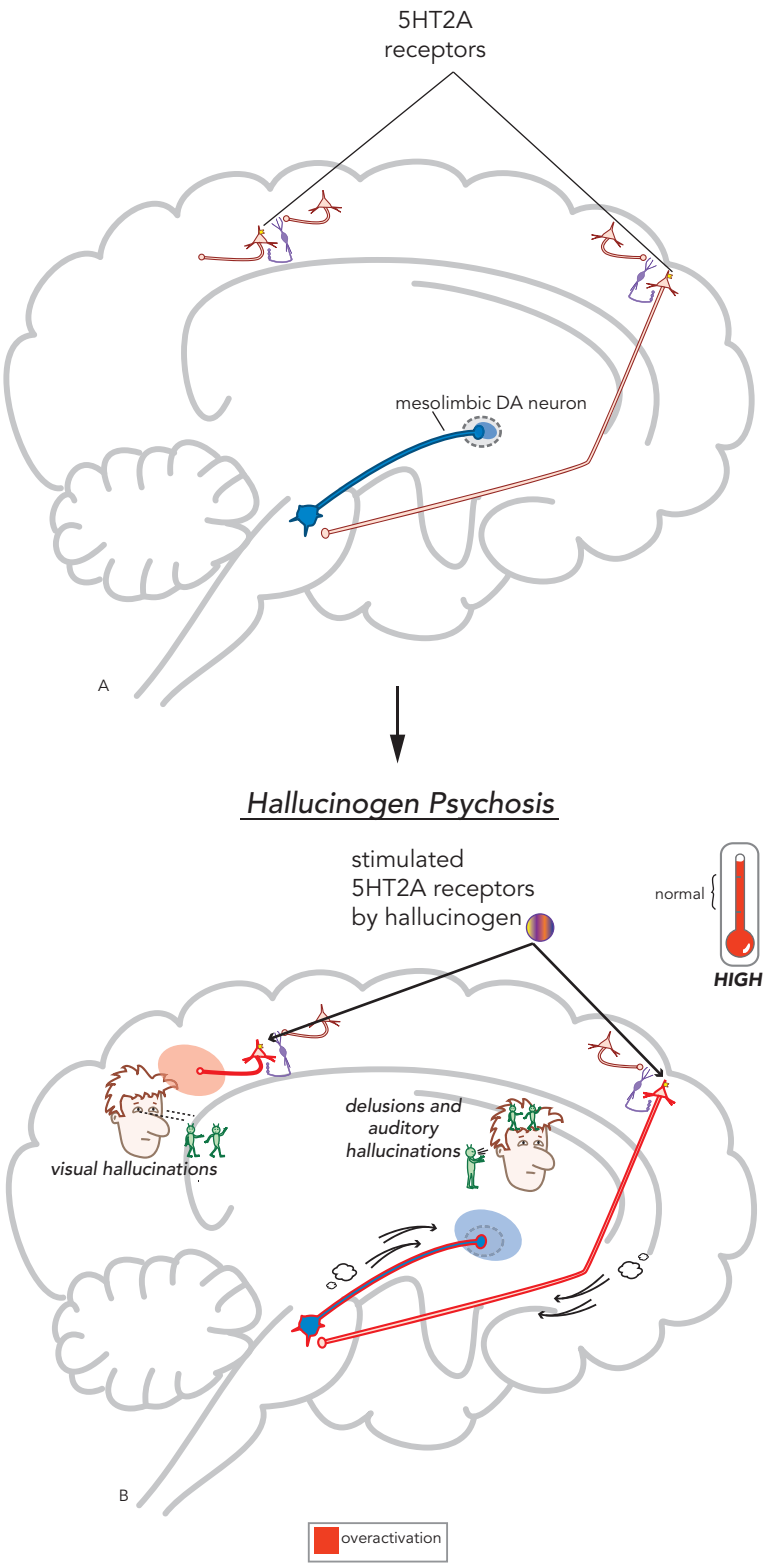


Figure 4-53 Serotonin (5HT) 2A receptors and psychosis, hallucinogens. (A) Shown here is a cortico-brainstem glutamatergic pathway projecting from the prefrontal cortex to the ventral tegmental area (VTA), and an indirect cortico-cortical glutamatergic pathway in the visual cortex. Activity of both pathways is regulated by serotonergic neurons that project from the raphe nucleus as well as by GABA interneurons in the prefrontal cortex. At baseline, normal stimulation of excitatory $5HT_{2A}$ receptors on the glutamate neurons is balanced by tonic stimulation of GABA receptors on the same neurons; the net effect is thus normal activation of the glutamatergic neurons. (B) Hallucinogens such as LSD, psilocybin, and mescaline are $5HT_{2A}$ agonists. When these agents stimulate $5HT_{2A}$ receptors on glutamatergic pyramidal neurons in the prefrontal cortex, this causes overactivation of the glutamate neurons. Excessive glutamate release into the VTA causes hyperactivity of the mesolimbic dopamine (DA) pathway, resulting in delusions and auditory hallucinations. Excessive glutamate release in the visual cortex can cause visual hallucinations.

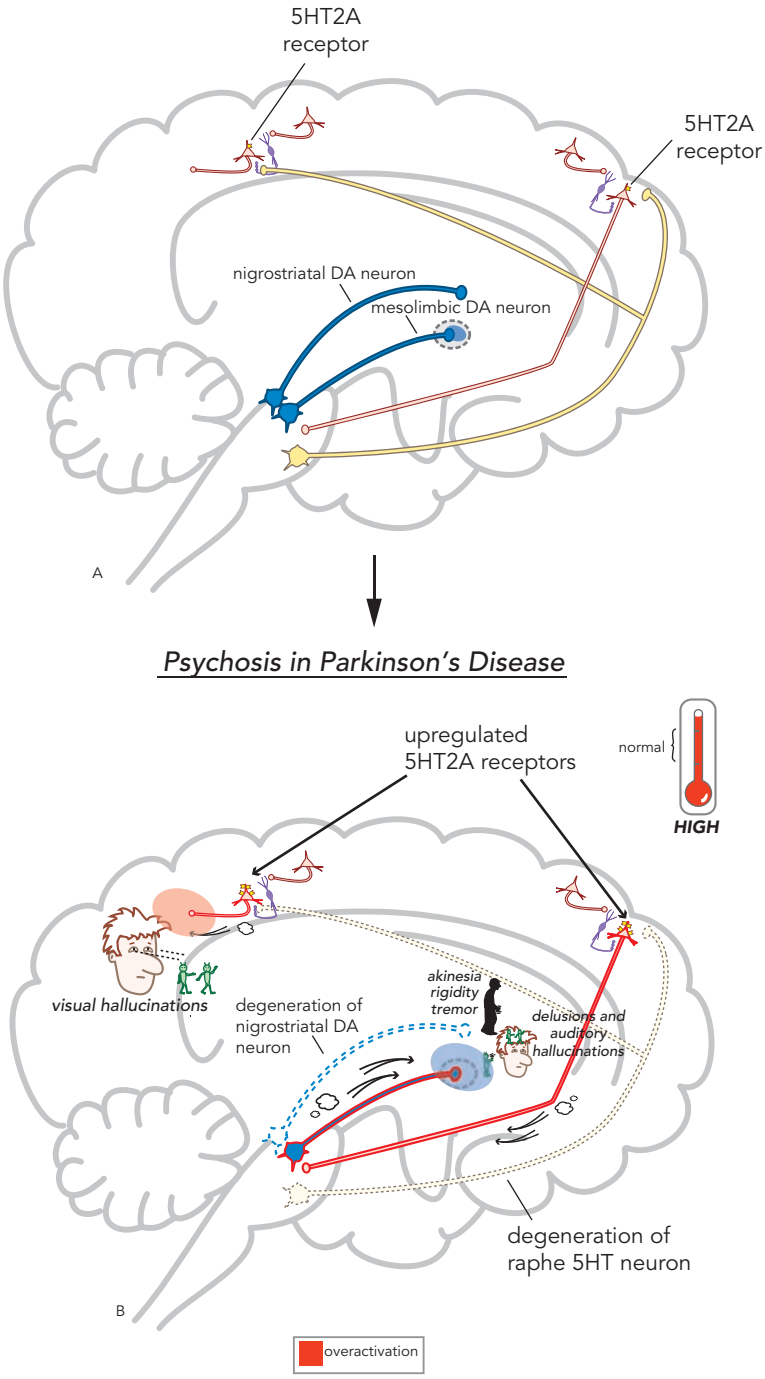


Figure 4-54 **Serotonin (5HT) 2A receptors and psychosis, Parkinson's disease psychosis.** (A) Shown here is a cortico-brainstem glutamatergic pathway projecting from the prefrontal cortex to the ventral tegmental area (VTA), and an indirect cortico-cortical glutamatergic pathway in the visual cortex. Activity of both pathways is regulated by serotonergic neurons that project from the raphe nucleus as well as by GABA interneurons in the prefrontal cortex. At baseline, normal stimulation of excitatory $5HT_{2A}$ receptors on the glutamate neurons is balanced by tonic stimulation of GABA receptors on the same neurons; the net effect is thus normal activation of the glutamatergic neurons. (B) Loss of nigrostriatal dopamine neurons causes the motor symptoms of Parkinson's disease, such as akinesia, rigidity, and tremor. Parkinson's disease also causes loss of serotonergic neurons that project from the raphe to the prefrontal cortex and to the visual cortex. This leads to upregulation of $5HT_{2A}$ receptors on glutamatergic pyramidal neurons in the prefrontal cortex, in which case normal or even low serotonin release can overstimulate these receptors. Excessive glutamate release into the VTA causes hyperactivity of the mesolimbic dopamine (DA) pathway, resulting in delusions and auditory hallucinations. Excessive glutamate release in the visual cortex can cause visual hallucinations.

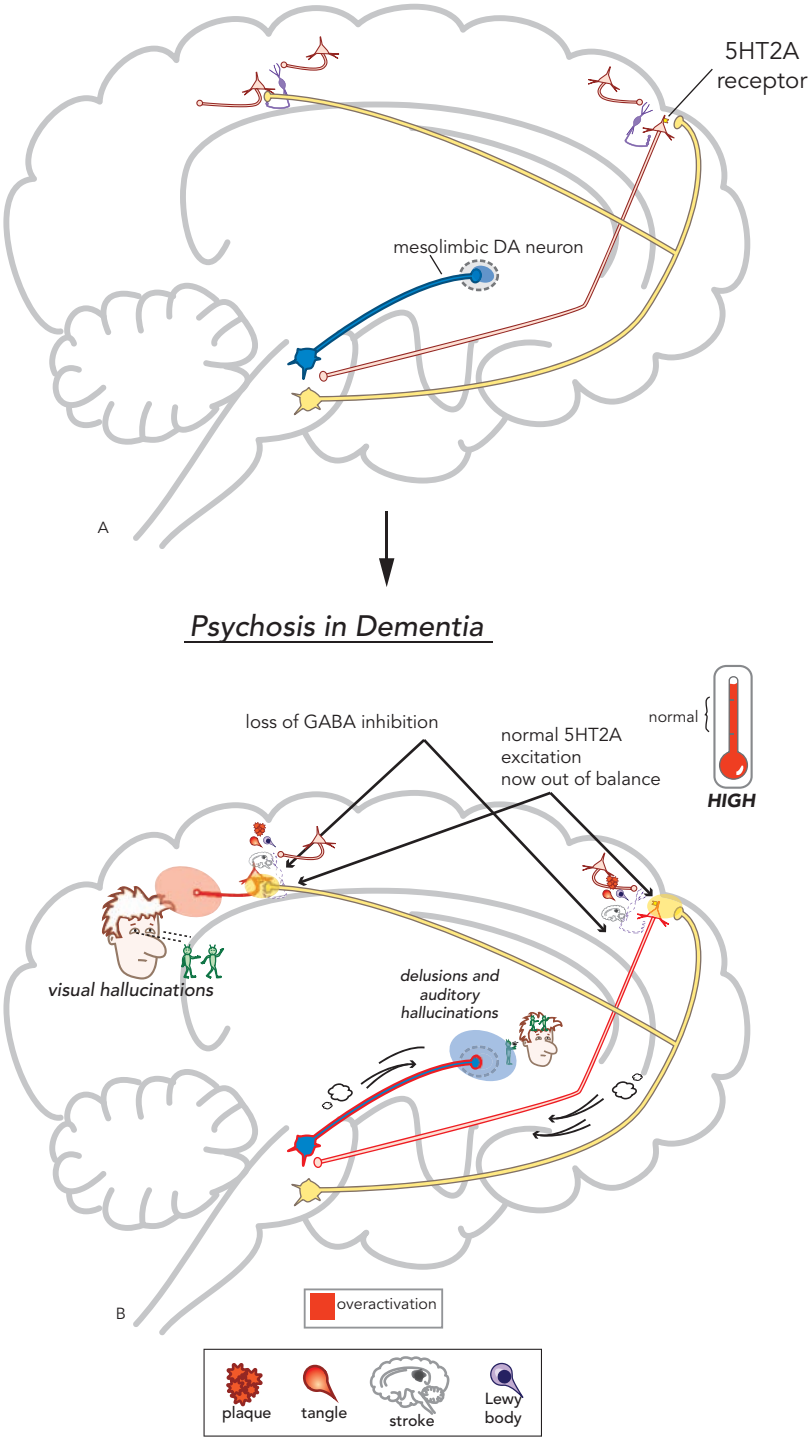


Figure 4-55 Serotonin (5HT) 2A receptors and psychosis, dementia. (A) Shown here is a cortico-brainstem glutamatergic pathway projecting from the prefrontal cortex to the ventral tegmental area (VTA), and an indirect cortico-cortical glutamatergic pathway in the visual cortex. Activity of both pathways is regulated by serotonergic neurons that project from the raphe nucleus as well as by GABA interneurons in the prefrontal cortex. At baseline, normal stimulation of excitatory $5HT_{2A}$ receptors on the glutamate neurons is balanced by tonic stimulation of GABA receptors on the same neurons; the net effect is thus normal activation of the glutamatergic neurons. (B) Accumulation of amyloid plaques, tau tangles, and/or Lewy bodies, as well as the damage caused by strokes, may destroy some glutamatergic pyramidal neurons and GABA interneurons while leaving others intact. When the effects of stimulation of excitatory $5HT_{2A}$ receptors are not countered by GABA inhibition, there is a net increase in glutamatergic neurotransmission. Excessive glutamate release into the VTA causes hyperactivity of the mesolimbic dopamine pathway, resulting in delusions and auditory hallucinations. Excessive glutamate release in the visual cortex can cause visual hallucinations.

the psychosis associated with dementia. Presumably this is due to lowering the normal $5HT_{2A}$ stimulation to surviving glutamate neurons that have lost their GABA inhibition by neurodegeneration. This hypothetically could rebalance the output of the surviving glutamate neurons so that $5HT_{2A}$ antagonism and its reduction of neuronal stimulation compensates for the loss of GABA inhibition. $5HT_{2A}$ antagonist treatment of dementia-related psychosis will be discussed in further detail in Chapter 5 and in Chapter 12 on the treatment of the behavioral symptoms of dementia.

Linking the Psychosis Hypothesis of Serotonin Hyperfunction at $5HT_{2A}$ Receptors to the Dopamine Hypothesis of Psychosis

What are the consequences to dopamine activity of the hypothetical excessive or imbalanced $5HT_{2A}$ stimulation at glutamatergic pyramidal neurons? The short answer is that it theoretically leads to the very same dopamine hyperactivity already discussed above for the dopamine hypothesis of psychosis and for the NMDA hypofunction hypothesis of psychosis (Figures 4-52 through 4-55).

That is, when those glutamate neurons that directly innervate VTA dopamine neurons lose either their serotonin input due to neurodegeneration of serotonin neurons in Parkinson's disease or their GABA inhibition from neurodegeneration of any cause, they become hyperactive and stimulate too much dopamine release from the mesostriatal projections of those dopamine neurons (Figure 4-52 through 4-55), just as happens in schizophrenia.

Summary and Conclusions Regarding Dopamine, NMDA, and Serotonin Neurotransmission in Psychosis

In summary, there are three interconnected pathways theoretically linked to hallucinations and delusions:

(1) Dopamine hyperactivity at D_2 receptors in the mesolimbic/mesostriatal pathway, which extends from the VTA/mesostriatum integrated hub to the ventral striatum
(2) NMDA receptor hypoactivity at GABAergic interneurons with loss of GABAergic inhibition in the prefrontal cortex
(3) Serotonin hyperactivity/imbalance at $5HT_{2A}$ receptors on glutamate neurons in the cerebral cortex

All three neuronal networks and neurotransmitters are linked together, and both $5HT_{2A}$ and NMDA receptor actions can hypothetically result in hyperactivity of the downstream mesolimbic dopamine pathway. Targeting at any node in this dysfunctional psychosis circuit could theoretically be therapeutic for psychosis of many causes.

SCHIZOPHRENIA AS THE PROTOTYPICAL PSYCHOTIC DISORDER

Schizophrenia is the prototypical psychotic disorder since it is the most common and best known and expresses prototypical psychotic symptoms. Schizophrenia affects about 1% of the population anywhere in the world and is one of the most devastating illnesses in medicine. Its onset during adolescence and early adulthood coincides with the years of life that should be the most dynamic and formative. Instead, this illness has a chronic course, with marked and lifelong functional disability, decreased lifespan of 25 to 30 years, and an alarming mortality rate that is three to four times that of the general population. On top of all of this misfortune is the fact that 5% of patients with schizophrenia complete suicide. Although the treatments described in this book do improve symptoms, they do not return most patients to normal functioning, nor do they necessarily adequately reduce the anguish that patients and their families feel from the ravages of this illness.

Schizophrenia by definition is a disturbance that must last for 6 months or longer, including at least one month of positive symptoms (i.e., delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior) or negative symptoms.

Positive symptoms are listed in Table 4-3 and shown in Figure 4-56. These symptoms of schizophrenia are often emphasized since they can be dramatic, can erupt suddenly when a patient decompensates into a psychotic episode (often called a psychotic "break," as in break from reality), and are the symptoms most effectively treated by medications. *Delusions* are one type of positive symptom, and these usually involve a misinterpretation of perceptions or experiences. The most common content of a delusion in schizophrenia is persecutory, but may include a variety of other themes including referential (i.e., erroneously thinking that something refers to oneself), somatic, religious, or grandiose. *Hallucinations* are also a type of positive symptom (Table 4-3) and may occur in any sensory modality (e.g., auditory, visual, olfactory, gustatory, and tactile) but auditory hallucinations are by far the most common and characteristic hallucinations in schizophrenia. Positive symptoms generally reflect an *excess* of normal functions, and in addition to delusions and hallucinations may

also include distortions or exaggerations in language and communication (disorganized speech) as well as in behavioral monitoring (grossly disorganized or catatonic or agitated behavior). Positive symptoms are well known because they are dramatic, are often the cause of bringing a patient to the attention of medical professionals and law enforcement, and are the major target of drug treatments for schizophrenia.

Negative symptoms of schizophrenia are listed in Tables 4-4 and 4-5 and shown in Figure 4-56. Classically, there are at least five types of negative symptoms all starting with the letter A (Table 4-5):

- *alogia* – dysfunction of communication; restrictions in the fluency and productivity of thought and speech
- *affective blunting or flattening* – restrictions in the range and intensity of emotional expression
- *asociality* – reduced social drive and interaction
- *anhedonia* – reduced ability to experience pleasure
- *avolition* – reduced desire, motivation, or persistence; restrictions in the initiation of goal-directed behavior

Negative symptoms in schizophrenia commonly are considered a reduction in normal functions, such as blunted affect, emotional withdrawal, poor rapport, passivity and apathetic social withdrawal, difficulty in abstract thinking, stereotyped thinking, and lack of spontaneity. Negative symptoms in schizophrenia are associated with long periods of hospitalization and poor social functioning. As will be discussed below, it can be

Table 4-3 Positive symptoms of psychosis and schizophrenia

Delusions
Hallucinations
Distortions or exaggerations in language and communication
Disorganized speech
Disorganized behavior
Catatonic behavior
Agitation

Table 4-4 Negative symptoms of schizophrenia

Blunted affect
Emotional withdrawal
Poor rapport
Passivity
Apathetic social withdrawal
Difficulty in abstract thinking
Lack of spontaneity
Stereotyped thinking
Alogia: restrictions in fluency and productivity of thought and speech
Avolition: restrictions in initiation of goal-directed behavior
Anhedonia: lack of pleasure
Attentional impairment

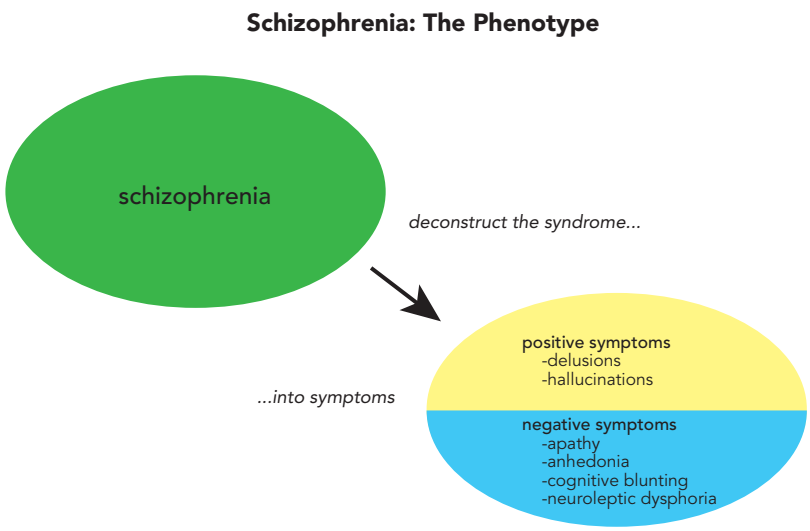


Figure 4-56 Positive and negative symptoms. The syndrome of schizophrenia consists of a mixture of symptoms that are commonly divided into two major categories, positive and negative. Positive symptoms, such as delusions and hallucinations, reflect the development of the symptoms of psychosis; they can be dramatic and may reflect loss of touch with reality. Negative symptoms reflect the loss of normal functions and feelings, such as losing interest in things and not being able to experience pleasure.

Table 4-5 What are negative symptoms?

Domain	Descriptive term	Translation
Dysfunction of communication	Alogia	Poverty of speech; e.g., talks little, uses few words
Dysfunction of affect	Blunted affect	Reduced range of emotions (perception, experience, and expression); e.g., feels numb or empty inside, recalls few emotional experiences, good or bad
Dysfunction of socialization	Asociality	Reduced social drive and interaction; e.g., little sexual interest, few friends, little interest in spending time with (or little time spent with) friends
Dysfunction of capacity for pleasure	Anhedonia	Reduced ability to experience pleasure; e.g., finds previous hobbies or interests unpleasurable
Dysfunction of motivation	Avolition	Reduced desire, motivation, persistence; e.g., reduced ability to undertake and complete everyday tasks; may have poor personal hygiene

quite difficult to tell the difference between the negative symptoms of schizophrenia, the cognitive symptoms of schizophrenia, the affective/mood symptoms of schizophrenia, particularly depression, and the side effects of drugs that treat psychosis (discussed in Chapter 5). Although formal rating scales can be used to measure negative symptoms versus cognitive symptoms versus affective symptoms for research studies, in clinical practice it may be more practical to identify and monitor mostly negative symptoms and to do this quickly by observation alone (Figure 4-57) or by some simple questioning (Figure 4-58). Negative symptoms are not just part of the syndrome of schizophrenia; they can also be part of a "prodrome" that begins with subsyndromal symptoms that do not meet the full diagnostic criteria of schizophrenia and occur before the onset of the full syndrome of schizophrenia. Prodromal negative symptoms are important to detect and monitor over time in high-risk patients so that treatment can be initiated at the first signs of psychosis. Negative symptoms can also persist between psychotic episodes once schizophrenia has begun and reduce social and occupational functioning in the absence of positive symptoms.

Beyond the Positive and Negative Symptoms of Schizophrenia

Although not recognized formally as part of the diagnostic criteria for schizophrenia, numerous studies subcategorize the symptoms of this illness into five

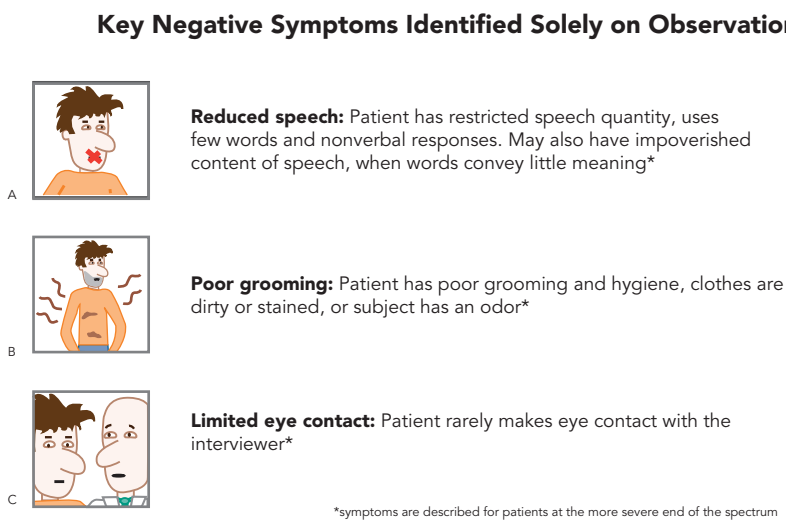


Figure 4-57 Negative symptoms identified by observation. Some negative symptoms of schizophrenia – such as reduced speech, poor grooming, and limited eye contact – can be identified solely by observing the patient.

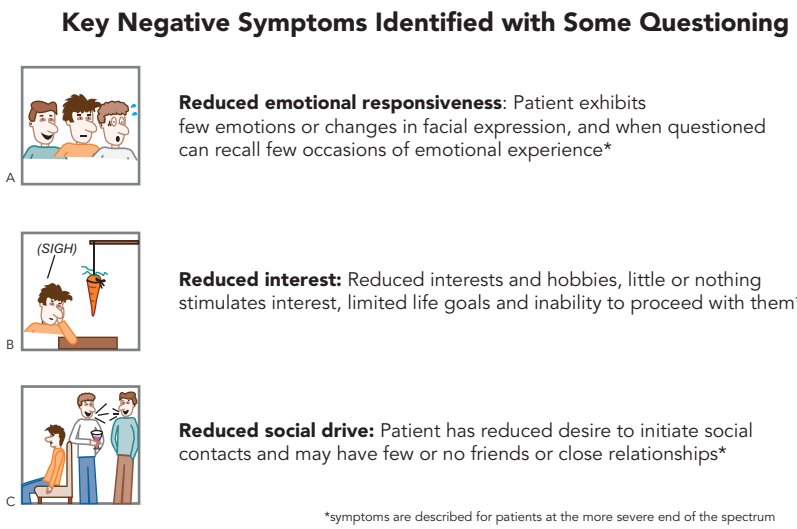


Figure 4-58 Negative symptoms identified by questioning. Other negative symptoms of schizophrenia can be identified by simple questioning. For example, brief questioning can reveal the degree of emotional responsiveness, interest level in hobbies or pursuing life goals, and desire to initiate and maintain social contacts.

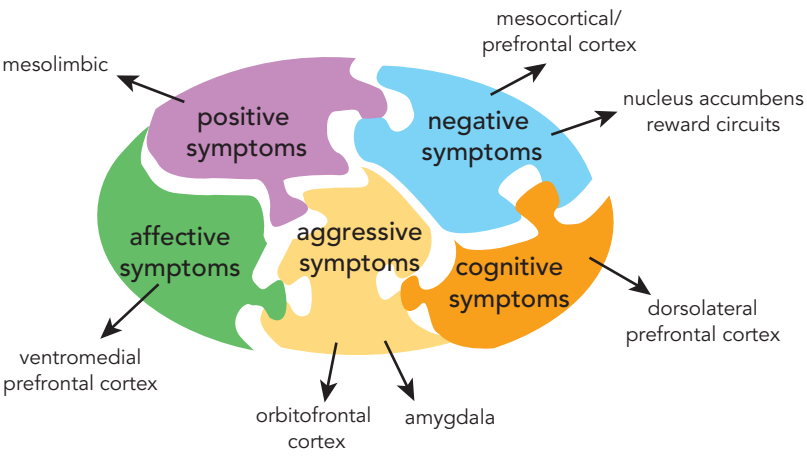


Figure 4-59 Localization of symptom domains. The different symptom domains of schizophrenia may best be subcategorized into five dimensions: positive, negative, cognitive, affective, and aggressive. Each of these symptom domains may hypothetically be mediated by unique brain regions.

dimensions: not just positive and negative symptoms, but also cognitive symptoms, affective symptoms, and aggressive symptoms (Figure 4-59). This is perhaps a more sophisticated if complicated manner of describing the symptoms of schizophrenia.

Cognitive symptoms of schizophrenia include impaired attention and information processing, manifesting as difficulties with verbal fluency (i.e., the ability to produce spontaneous speech), problems with serial learning (of a list of items or a sequence of events), and impairment in vigilance for executive functioning (i.e., problems with sustaining and focusing attention, concentrating, prioritizing, and modulating behavior based upon social cues). Important cognitive symptoms of schizophrenia are listed in Table 4-6. Cognitive symptoms begin before the onset of the first psychotic illness and manifest as lower than expected IQ scores. IQ and cognition then worsen during the prodrome before the onset of full-blown psychosis, and then progressively worsen throughout the course of schizophrenia. Cognitive symptoms in schizophrenia do not include the same symptoms commonly seen in dementia, such as short-term memory disturbance; instead, cognitive symptoms of schizophrenia emphasize "executive dysfunction,"

Table 4-6 Cognitive symptoms of schizophrenia

Problems representing and maintaining goals
Problems allocating attentional resources
Problems focusing attention
Problems sustaining attention
Problems evaluating functions
Problems monitoring performance
Problems prioritizing
Problems modulating behavior based upon social cues
Problems with serial learning
Impaired verbal fluency
Difficulty with problem solving

which includes problems representing and maintaining goals, allocating attentional resources, evaluating and monitoring performance, and utilizing these skills to solve problems.

Affective symptoms are frequently associated with schizophrenia, but this does not necessarily mean that they fulfill the full diagnostic criteria for a comorbid anxiety or affective disorder. Nevertheless, depressed mood, anxious mood, guilt, tension, irritability, and worry frequently accompany schizophrenia. These various symptoms are also prominent features of major depressive disorder, numerous anxiety disorders, psychotic depression, bipolar disorder, schizoaffective disorder, organic dementias, childhood psychotic disorders, and treatment-resistant cases of depression, bipolar disorder, and schizophrenia, among many others. Affective symptoms of schizophrenia, particularly symptoms of depressed mood, anhedonia, lack of motivation, and lack of pleasure, can also be quite difficult to distinguish from the negative symptoms of schizophrenia and from a comorbid mood or anxiety disorder.

Wherever encountered, affective symptoms need to be treated. In the case of schizophrenia, when affective symptoms are not sufficiently improved by traditional drugs for the positive symptoms of psychosis, consideration can be given to adding drugs used to treat anxiety and/or depression (e.g., selective serotonin reuptake inhibitors, SSRIs), not only to relieve the current affective symptoms, but also to prevent suicide, which is unfortunately very common in patients with schizophrenia. There is no drug treatment for the disorder of schizophrenia itself, only for the symptoms of schizophrenia. Thus, whenever possible, consideration should be given to treat the affective symptoms of schizophrenia even if they do not reach full criteria for a comorbid mood or anxiety disorder. Even though affective symptoms in a patient with schizophrenia may very well respond to drug treatments for depression or anxiety, these same treatments are not very effective if at all for true negative symptoms.

Aggressive symptoms, such as overt hostility, assaultiveness and physical abuse, frank violence, verbally abusive behaviors, sexually acting-out behaviors, self-injurious behaviors including suicide, and arson and other property damage can all occur in schizophrenia. Aggression is different from agitation in that aggression tends to refer to intentional harm, while agitation is a more nonspecific and often nondirected state of heightened psychomotor or verbal activity, accompanied by an unpleasant state of tension and irritability. In schizophrenia, both can occur alongside positive symptoms, particularly when positive symptoms are out of control, and both agitation and aggression often improve when positive symptoms are reduced by drugs that treat psychosis.

Both agitation and aggression can also occur in patients with dementia but must be distinguished from positive psychotic symptoms, since new treatments are evolving for agitation in dementia that differ from treatments for psychosis in dementia and these also differ from treatments for psychosis in schizophrenia. Treatments of agitation and aggression are discussed in more detail in Chapter 5 on treatments for psychosis and in Chapter 12 on treatments for the behavioral symptoms of dementia. Aggressive symptoms can also occur in numerous other disorders that exhibit problems with impulse control such as bipolar disorder, childhood psychosis, borderline personality disorder, antisocial personality disorder, drug abuse, attention deficit hyperactivity disorder, conduct disorders in children, and many others.

For schizophrenia, the topic of violence – a type of aggression – is controversial. The stereotype of schizophrenia patients as frequent violent perpetrators of mass shootings is an unfortunate exaggeration contributing to the stigma of this illness. Most patients with schizophrenia in fact are not violent, and patients are more likely to be a victim of violence than a perpetrator. However, some studies do suggest that schizophrenia patients commit violence more often than the general population, although the increased rate is

not large, and the violence is often linked to a lack of adequate medication treatment as well as to concomitant substance abuse.

Not surprisingly, schizophrenia patients who commit violence often become involved in the criminal justice system. This may be a sorry reflection of the lack of adequate outpatient treatment as well as the lack of short-term crisis and inpatient beds in the community for treating patients with schizophrenia. It is a shocking fact that in the United States we have "criminalized" serious mental illnesses such as schizophrenia, since our largest "mental health institutions" are now jails and prisons. For example, the twin towers of the Los Angeles County Jail, the New York City jail at Rikers Island, and the Cook County Chicago jail are the largest mental health facilities in the country. Up to a quarter of the 2 million inmates in jails and prisons throughout the country have serious mental illnesses. Although patients with schizophrenia do get treatment in jail and prison, this treatment is widely acknowledged to be substandard in correctional environments and the correctional environment itself is inherently counter-therapeutic. Furthermore, when released, patients often do not take medication, are homeless, and eventually are re-arrested for another violent offense. In California, the numbers of patients with serious mental illnesses who are arrested for a felony and found incompetent to stand trial because of their illness and who have had 15 or more prior arrests have been increasing; half of them have not accessed reimbursable mental health services including medication for the six months prior to their arrest and half are in an unsheltered homeless condition. Fortunately, innovative treatment programs modeled on a successful program in Miami, Florida seek to decriminalize the treatment of schizophrenia by diversion programs sending patients to treatment with housing rather than to jail and prison.

Nevertheless, once sent to jail, prison, or state forensic hospitals, patients with schizophrenia can frequently experience and cause violence. Some of this is due to the fact that institutions have violent environments and some of this is due to the fact that those with serious mental illnesses who find themselves in institutions are a small subset of all patients, specifically those most likely to commit violence. If schizophrenia is roughly 1% of the population, there are an estimated 400,000 patients with this illness in the State of California, whose population is about 40 million. If up to 200,000 individuals are incarcerated in California and perhaps 25% of them (or approximately 40,000 of them) have a serious mental illness requiring treatment with drugs for psychosis, this would mean that perhaps 10% of all patients with schizophrenia in California are in prison or jail – again probably those who are the most likely to engage in violence when unmedicated and/or abusing drugs.

An even smaller subpopulation of patients with schizophrenia are those who commit a violent felony and are judged either incompetent to stand trial or insane, and sent to one of the five state forensic hospitals in California. This population is only a few thousand patients, or perhaps only 1% of all patients with schizophrenia in California. Unfortunately, they are the most violent subset of schizophrenia patients: not surprising, as a violent felony put them in the state forensic hospital in the first place. Studies show that violence in this setting is actually associated with criminogenic risk, suggesting that it is the process of criminalization from living in an institutional setting, and not the positive symptoms of psychosis, that are driving a lot of this violence. Once in the state forensic hospitals they often continue to commit violent acts, even when treated and medicated. But not all patients with schizophrenia even in state forensic hospitals are violent; only about a third of them commit a violent act during hospitalization, usually a single event within the first 120 days. Actually, about 3% of state forensic patients (a few hundred at most or fewer than 1 per 100,000 patients with schizophrenia in California) commit about 40% of the violence within the state forensic hospital, about half against staff and about half against other patients. Thus, only a tiny fraction of patients with schizophrenia commit a lot of violence, and the number of patients with violence is frequently exaggerated by media. Nevertheless, working in a state forensic hospital can be very dangerous, as can living as a patient in these settings. Treating violence in patients with schizophrenia can be very important in state forensic hospitals, jails, and prisons, as can preventing violence in these patients when they leave these settings.

Rather than lumping all forms of violence together, experts parse violence in institutionalized patients with schizophrenia into three types: impulsive, predatory, and psychotic (Figure 4-60). *Psychotic violence*, associated with positive symptoms of psychosis, which typically command hallucinations and/or delusions, is actually the least common type of violence in institutional settings, despite the fact that these patients have a psychotic illness (Figure 4-60). This is presumably

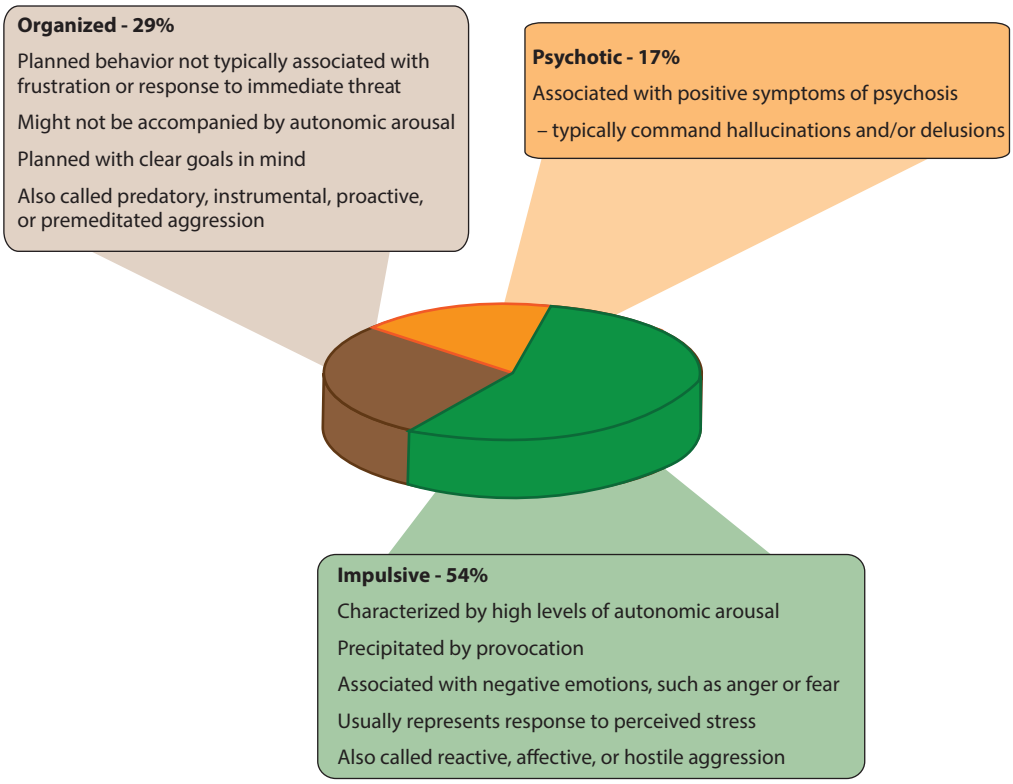


Figure 4-60 Three types of violence. There are at least three different types of violence: psychotic, impulsive, and organized/psychopathic. Psychotic violence is associated with positive symptoms of psychosis. The most common form of violence is impulsive; it is associated with autonomic arousal and often precipitated by stress, anger, or fear. Organized or psychopathic violence is planned and is not accompanied by autonomic arousal.

because treatment in institutional settings is often effective for positive symptoms. However, treating positive symptoms does not quell all violence, since the most common form of violence in institutional settings is actually *impulsive violence* – often precipitated by provocation as a response to stress and associated with negative emotions such as anger or fear (Figure 4-60). For these reasons, impulsive violence is also called reactive, affective, or hostile aggression. The third form of violence, also more common than psychotic violence, is *psychopathic* or *organized* and is planned behavior not typically associated with frustration or response to immediate threat (Figure 4-60). If psychotic violence and impulsive violence are "hot-blooded" with emotional arousal, organized violence is "cold-blooded" and not accompanied by autonomic arousal as it is planned with clear goals in mind (Figure 4-60). Organized violence is what is commonly seen in patients with psychopathic or antisocial personalities and is associated with criminogenic behaviors more than with psychotic symptoms. Nevertheless, psychotic patients in institutional settings can also have psychopathic tendencies and commit organized violence, which may require forms of confinement rather than drugs in order to manage. Certain treatments, such as clozapine or high doses of standard drugs for schizophrenia, may also be useful for psychotic or impulsive violence in patients with underlying psychotic disorders, but behavioral interventions may be particularly helpful to prevent violence linked to poor impulsivity associated with violence (i.e., by reducing provocations from the environment). Impulsive and organized violence in schizophrenia are not as clearly related to dopamine D_2 overactivity as psychotic violence when positive symptoms of schizophrenia are out of control, especially in the small population of frequent aggressors. In California state forensic hospitals, these frequent aggressors that can be so difficult to manage have an underlying psychotic illness, exhibit psychotic or impulsive violence rather than organized violence, and

have a cognitive deficiency beyond that usually associated with schizophrenia. Aggression and violence are discussed in further detail in Chapter 13 on impulsivity and compulsivity and are also differentiated from agitation and from positive symptoms or psychosis in dementia in Chapter 12.

What is the Cause of Schizophrenia?

What causes schizophrenia: nature (i.e., genetics) or nurture (i.e., the environment or epigenetics)? Is schizophrenia neurodevelopmental or neurodegenerative? The modern answer indeed may be "yes" in part to all of these.

Genetics and Schizophrenia

Modern theories of mental illness have long abandoned the notion that single genes cause any of the major mental illnesses (Figure 4-61). Genes do not code directly for mental illnesses or for psychiatric symptoms, behaviors, personalities, or temperaments. Instead, genes code directly for proteins and epigenetic regulators (see Figures 1-31 and 1-32). It is thought that the actions of genes must "conspire" amongst themselves (Figure 4-62, upper left) and amongst environmental stressors (Figure 4-62, upper right) in order to produce a mental illness (Figure 4-62, bottom). Thus, current theories state that inheriting many risk genes for a mental illness sets the stage for a mental illness, but does not cause a mental illness per se. More properly, individuals inherit *risk* for mental illness, but they do not inherit mental illness. Whether this risk evolves into a manifest mental disorder is hypothesized to be dependent upon what happens in the environment to an individual who has risk genes.

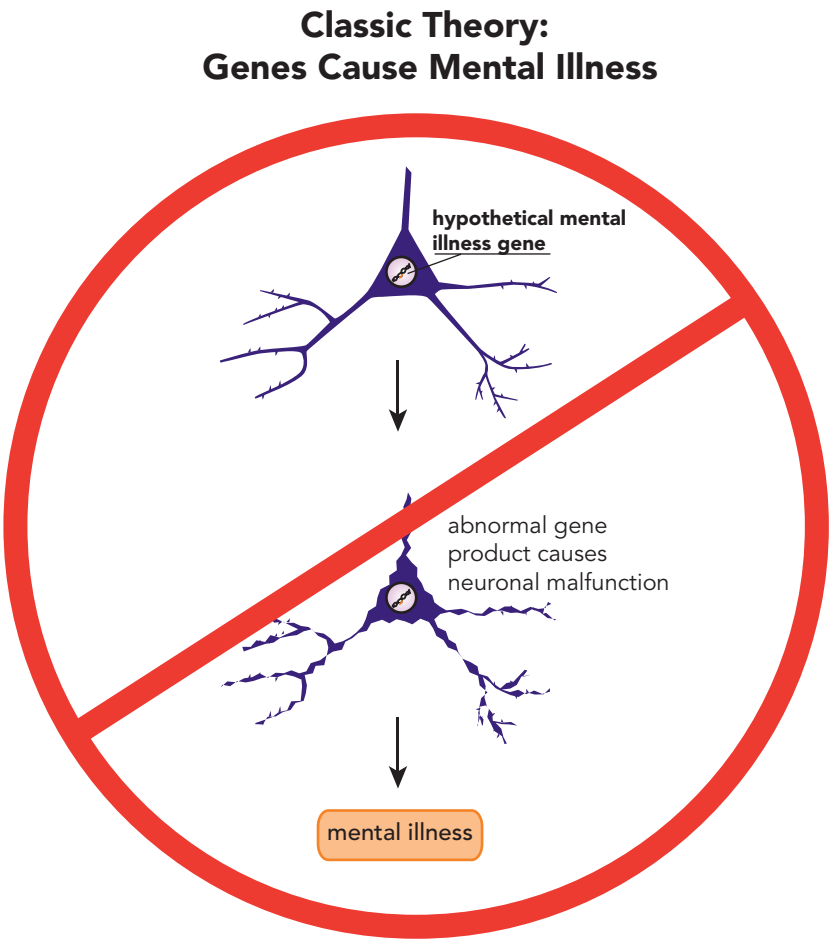


Figure 4-61 Classic theory of inherited disease. According to the classic theory of inherited disease, a single abnormal gene can also cause a mental illness. That is, an abnormal gene would produce an abnormal gene product, which, in turn, would lead to neuronal malfunction that directly causes a mental illness. However, no such gene has been identified, and there is no longer any expectation that such a discovery might be made. This is indicated by the red cross-out sign over this theory.

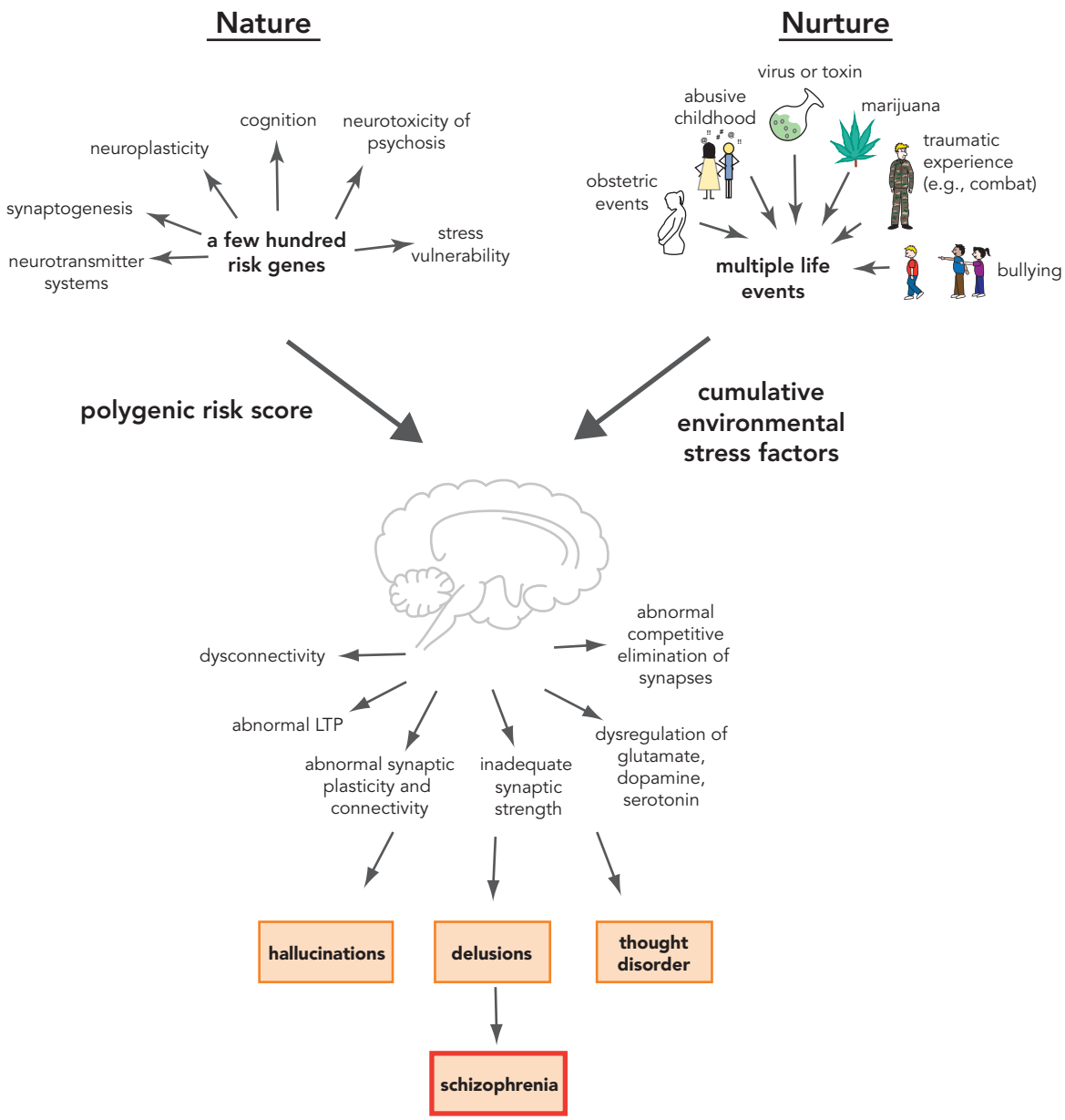


Figure 4-62 The nature and nurture of schizophrenia. Schizophrenia may occur as the result of both genetic (nature) and epigenetic (nurture) factors. That is, an individual with multiple genetic risk factors, combined with multiple stressors causing epigenetic changes, may have abnormal information processing in the form of dysconnectivity, abnormal long-term potentiation (LTP), reduced synaptic plasticity, inadequate synapse strength, dysregulated neurotransmission, and abnormal competitive elimination of synapses. The result may be psychiatric symptoms such as hallucinations, delusions, and thought disorder.

Recent evidence suggests that a portfolio of a few hundred specific genes – each with a small contribution of less than 1% – may together confer risk for schizophrenia (Table 4-7). The function of all of these risk genes is not fully known, but may be to regulate such key aspects of the brain as neurotransmitter systems, synaptogenesis, neuroplasticity, neurodevelopment, cognition, the neurotoxicity of psychosis, and stress vulnerability, amongst other functions (Figure 4-62, upper left). One way to deal with this complexity is to add up all the abnormal genes any individual has amongst the known few hundred risk genes, and compute what is

called a "polygenic risk score" suggesting how much risk there might be for developing schizophrenia. Even with this simplification, the known contribution of all risk genes added together only confers a portion of the risk for schizophrenia. What comprises the remaining risk? In schizophrenia, it is various environmental stressors, specifically, cannabis use, emotionally traumatic experiences such as early childhood adversity, bullying, obstetric events, sleep deprivation, being a migrant, and others (Figure 4-62, upper right). For example, the incidence of psychosis has been shown to be higher in cities with a lot of migrants; in one such city, London, the incidence of psychosis falls by one-third if migrants and their children are excluded from the population studied. Other studies show that there is a high correlation between the frequency of cannabis use and the rate of psychosis across European cities, and that if nobody smoked high-potency cannabis, 12% of all cases of first-episode psychosis across Europe would be prevented. In particular cities, the estimated reduction in first-episode psychosis would be 32% in London and 50% in Amsterdam.

How does the environment unmask schizophrenia in those who have genetic risk for it? The answer is that the environment hypothetically puts a load on the neural circuits where the risk genes are expressed and causes these circuits to malfunction under pressure (Figure 4-62, bottom). Furthermore, these same stressors can even cause normal genes to malfunction and together all of this causes aberrant neuroplasticity and synaptogenesis (Figure 4-62, bottom). How can that be? *Normal* genes causing mental illness? Hypothetically, yes, when environmental stressors (Figure 4-62, upper right) cause various critical normal genes to be expressed when they should be silenced, or silenced when they should be expressed, in a process called epigenetics (Figure 1-30). Some of the best evidence that environmental stressors and normal genes are also involved with abnormal genes in the causation of schizophrenia is that only half of identical twins of patients with schizophrenia also have schizophrenia. Having identical genes is thus not enough to cause schizophrenia and instead epigenetics is also in play, such that the affected twin not only expresses some abnormal genes that the unaffected co-twin might not express, but also expresses some normal genes at the wrong time or silences other normal genes at the wrong time; together these factors may cause schizophrenia in one co-twin but not the other.

In summary, mental illnesses such as schizophrenia are now thought to be due not only to the summed biological action of *abnormal* genes with flawed DNA causing flaws in the structure and function of the proteins and regulators they code (Figure 4–62, upper left), but are also due to the environment, which plays upon both abnormal genes and normal genes that make normal functioning proteins and regulators but are activated or silenced at the wrong times (Figure 4-62, upper right). In other words, schizophrenia results from both nature and nurture (Figure 4-62, bottom).

Table 4-7 Some candidate susceptibility risk genes involved in biological functions implicated in schizophrenia

Genes	Description
Glutamate neurotransmission and synaptic plasticity	
GRIA1	Ionotropic glutamate receptor mediating fast synaptic neurotransmission
GRIN2A	Glutamate gated-ion-channel protein and key mediator of synaptic plasticity
GRM3	Encodes glutamate metabotropic receptor 3, one of the major excitatory neurotransmitter receptors, extensively explored as a potential drug target in schizophrenia
Calcium channel and signaling	
CACNA1C	Encodes an α_1 subunit of voltage-sensitive calcium channels
CACNB2	One of the voltage-sensitive calcium channels
Neurogenesis	
SOX2	Transcription factor essential for neurogenesis
SATB2	Essential for cognitive development and involved in long-term plasticity

Schizophrenia: Problems with Neurodevelopment, Neurodegeneration, or Both?

In the case of schizophrenia, two major questions always arise:

(1) How does the scheming of nature and nurture lead to the full onset of this illness around the time of adolescence?

(2) What kind of neurobiological processes underlie this disorder such that the results of nature and nurture can appear to be neurodevelopmental at the onset of schizophrenia yet neurodegenerative over the lifetime course of this illness?

Both the neurodevelopmental and the neurodegenerative theories of schizophrenia are discussed next.

Neurodevelopment and Schizophrenia

Modern research findings strongly suggest that something is amiss in the way the brain makes, retains, and revises its synaptic connections in schizophrenia, starting from birth. Telltale signs of this include the cognitive deficits, lowering of IQ, oddness, and social deficits of patients before the overt onset of a psychotic break that signals the full diagnostic criteria of schizophrenia. In order to grasp what might be going wrong with neurodevelopment in schizophrenia, it is important to first have an understanding of normal neurodevelopment. An overview of normal neurodevelopment is shown in Figure 4-63. After conception, stem cells differentiate into immature neurons. Only a minority of neurons that are formed are selected for inclusion in the developing brain. The others die off naturally in a process called apoptosis. It remains a mystery why the brain makes so many more neurons than it needs, and how it decides which neurons to select for inclusion in the developing brain, but it is certainly feasible that abnormalities in the process of neuronal selection could be a factor in neurodevelopmental disorders, from autism to intellectual disability (formerly known as mental retardation) to schizophrenia on the severe end of the spectrum, and ADHD (attention deficit hyperactivity disorder) and dyslexia on the mild to moderate end of the spectrum. At any rate, those neurons that are selected migrate and then differentiate into different types of neurons, after which synaptogenesis (making of synaptic connections) occurs (Figure 4-63). Most neurogenesis (i.e., birth of new neurons), neuronal selection, and neuronal migration occur before birth, although new neurons continue to form in some brain areas throughout life. After birth, differentiation and myelination of neurons as well as synaptogenesis also continue throughout a lifetime. All along the way, not just prenatally or even just in childhood but throughout adult life, disruption of this neurodevelopmental process (Figure 4-63) can hypothetically result in various psychiatric symptoms and illnesses.

In the case of schizophrenia, the suspicion is that the neurodevelopmental process of synaptogenesis and brain restructuring has gone awry. Synapses are normally formed at a furious rate between birth and age 6 (Figure 4-64). Although brain restructuring occurs throughout life, it is most active during late childhood and adolescence in a process known as competitive elimination (Figures 4-63 and 4-64). Competitive elimination and restructuring of synapses peak during pubescence and adolescence, normally leaving only about half to two-thirds of the synapses that were present in childhood to survive into adulthood (Figures 4-63 and 4-64). Since the onset of positive symptoms of psychosis (psychotic "breaks") follows this critical neurodevelopmental period of peak competitive elimination and restructuring of synapses, it has thrown suspicion on possible abnormalities in these processes as underlying in part the onset of schizophrenia.

In order to understand how aberrant competitive elimination could contribute to the onset and worsening of schizophrenia, it is important to consider how the brain decides which synapses to keep and which ones to eliminate. Normally, when glutamate synapses are active, their *N*-methyl-D-aspartate (NMDA) receptors trigger an electrical phenomenon known as long-term potentiation (LTP) (shown in Figure 4-65). With the help of gene products that converge upon glutamate synapses and receptors, ion channels, and the processes of neuroplasticity and synaptogenesis, LTP normally leads to structural and functional changes of the synapse that make neurotransmission more efficient, sometimes called "strengthening" of synapses (Figure 4-65, top). This includes changes in synaptic structure such as an increase in the number of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid) receptors for glutamate. AMPA receptors are important for mediating excitatory neurotransmission and depolarization at glutamate synapses. Thus, more AMPA receptors can mean a "strengthened" synapse. Synaptic connections that are frequently used develop frequent LTP and consequential robust neuroplastic influences, thus strengthening them according to the old saying "nerves

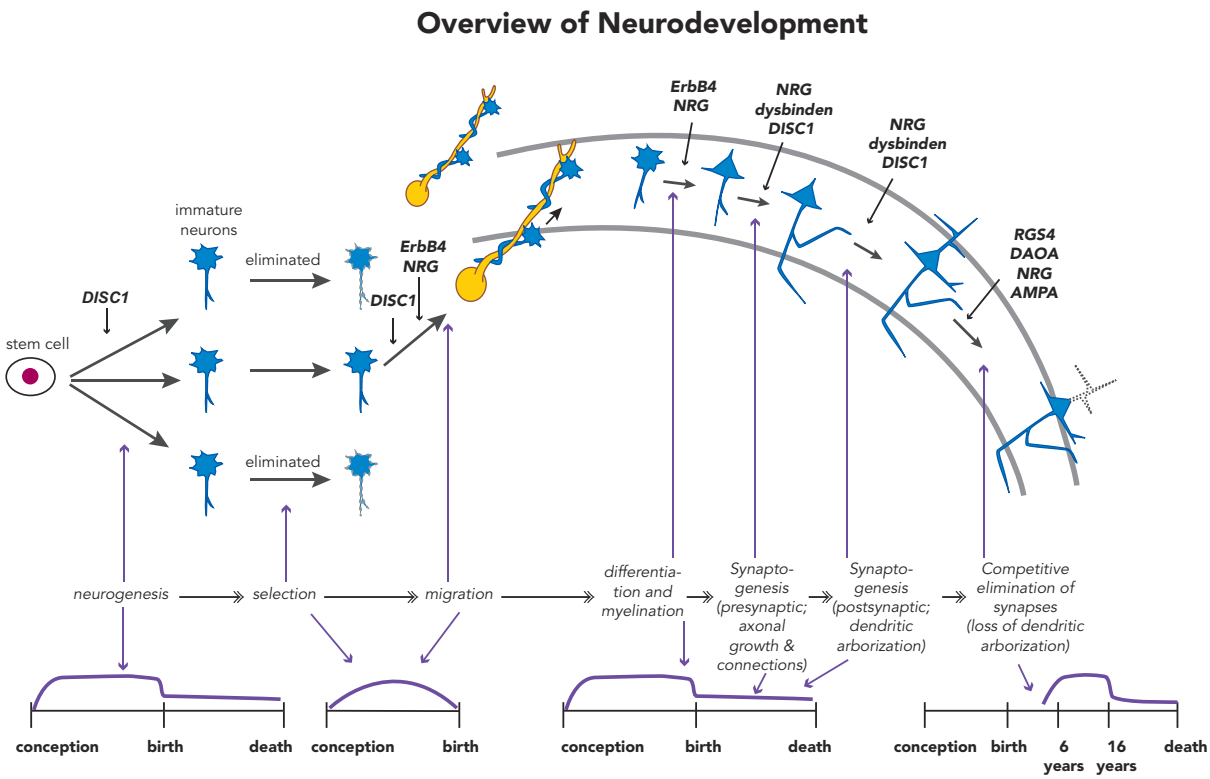


Figure 4-63 Overview of neurodevelopment. The process of brain development is shown here. After conception, stem cells differentiate into immature neurons. Those that are selected migrate and then differentiate into different types of neurons, after which synaptogenesis occurs. Most neurogenesis, neuronal selection, and neuronal migration occur before birth, although new neurons can form in some brain areas even in adults. After birth, differentiation and myelination of neurons as well as synaptogenesis continue throughout a lifetime. Brain restructuring also occurs throughout life, but is most active during childhood and adolescence in a process known as competitive elimination. Key genes involved in the process of neurodevelopment include DISC1 (disrupted in schizophrenia-1), ErbB4, neuregulin (NRG), dysbindin, regulator of G-protein signaling 4 (RGS4), D-amino acid oxidase activator (DAOA), and genes for α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA).

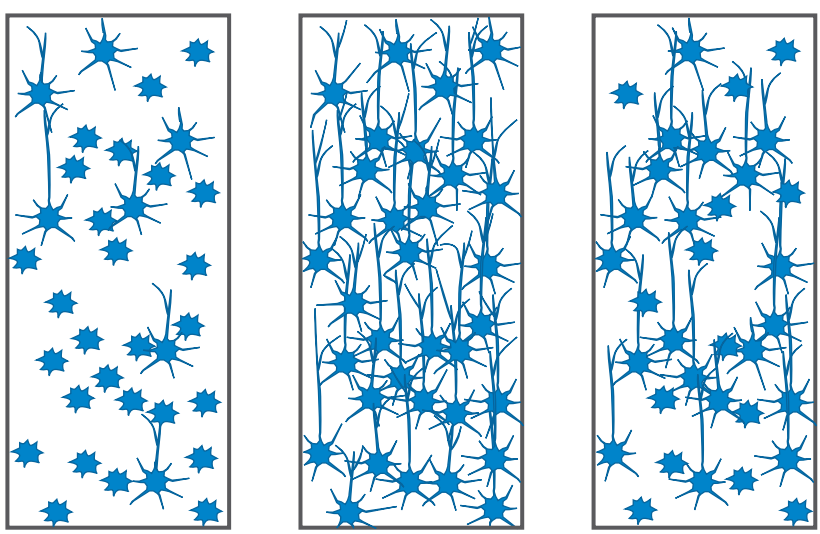


Figure 4-64 Synapse formation by age. Synapses are formed at a furious rate between birth and age 6. Competitive elimination and restructuring of synapses peaks during pubescence and adolescence, leaving about half to two-thirds of the synapses present in childhood to survive into adulthood.

that fire together wire together" (Figure 4-65, top). However, if something is wrong with the genes that regulate synaptic strengthening, it is possible that this causes less effective use of these synapses, makes the NMDA receptors hypoactive (Figure 4-29B), and leads to ineffective LTP and fewer AMPA receptors trafficking into the postsynaptic neuron (Figure 4-65, bottom). Such a synapse would be "weak," theoretically causing inefficient information processing in its circuit and possibly also causing symptoms of schizophrenia.

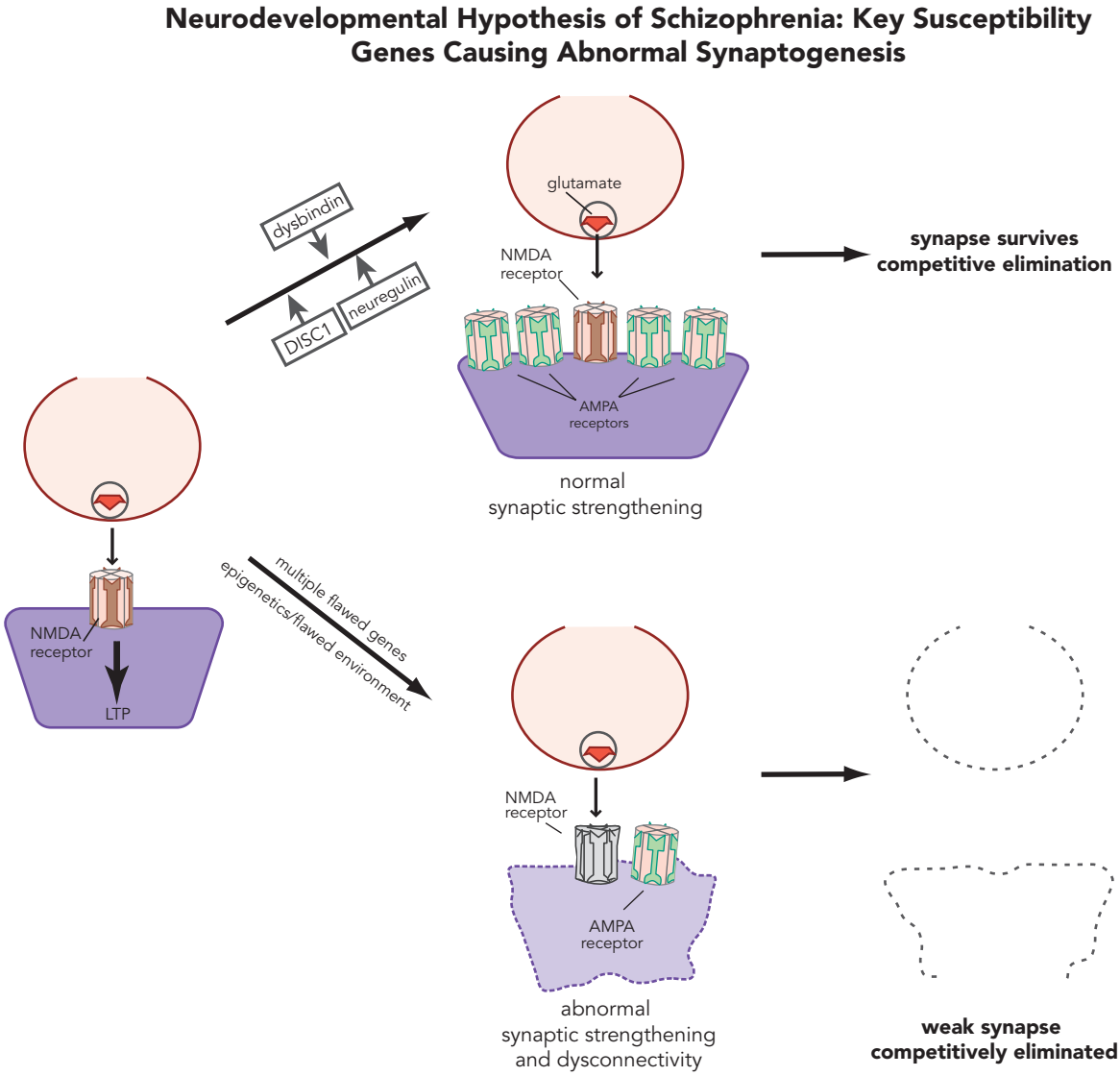


Figure 4-65 Neurodevelopmental hypothesis of schizophrenia. Dysbindin, DISC1 (disrupted in schizophrenia-1), and neuregulin are all involved in "strengthening" of glutamate synapses. Under normal circumstances, *N*-methyl-D-aspartate (NMDA) receptors in active glutamate synapses trigger long-term potentiation (LTP), which leads to structural and functional changes of the synapse to make it more efficient, or "strengthened." In particular, this process leads to an increased number of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors, which are important for mediating glutamatergic neurotransmission. Normal synaptic strengthening means that the synapse will survive during competitive elimination. If the genes that regulate strengthening of glutamate synapses are abnormal, combined with environmental insults, then this could cause hypofunctioning of NMDA receptors, with a resultant decrease in LTP and fewer AMPA receptors. This abnormal synaptic strengthening and dysconnectivity would lead to weak synapses that would not survive competitive elimination. This would theoretically lead to increased risk of developing schizophrenia, and these abnormal synapses could mediate the symptoms of schizophrenia.

Another important aspect of synaptic strength is that this likely determines whether a given synapse is eliminated or maintained. Specifically, "strong" synapses with efficient NMDA neurotransmission and many AMPA receptors survive, whereas "weak" synapses with few AMPA receptors may be targets for elimination (Figure 4-65). This normally shapes the brain's circuits so that the most critical synapses are not only strengthened but also survive the ongoing selection process, keeping the most efficient and most frequently utilized synapses while eliminating inefficient and rarely utilized synapses. However, if critical synapses are not adequately strengthened in schizophrenia, it could lead to their wrongful elimination, causing dysconnectivity that disrupts information flow from circuits now deprived of synaptic connections where communication needs to be efficient (Figure 4-65). Sudden and catastrophic competitive elimination of "weak" but critical synapses during adolescence could even explain why schizophrenia has onset at this time. If abnormalities in genes converging upon the processes of neuroplasticity and synaptogenesis lead to the lack of critical synapses being strengthened, these critical synapses may be mistakenly eliminated during adolescence, with disastrous consequences, namely the onset of symptoms of schizophrenia. This could explain why genetically programmed dysconnectivity present from birth is masked by the presence of many additional weak connections prior to adolescence, acting with exuberance to compensate for defective connectivity, and when that compensation is destroyed by the normal competitive elimination of synapses in adolescence, schizophrenia emerges. Thus, aberrant neurodevelopment of both not forming adequate synapses and competitively and erroneously removing critical synapses during adolescence may provide partial answers both to why schizophrenia has its full catastrophic onset at this critical stage of neurodevelopment, and why schizophrenia has aspects of a neurodevelopmental disorder, especially around the time of full onset of the disorder.

Neurodegeneration and Schizophrenia

Many patients with schizophrenia have a progressive, downhill course, especially when available treatments are not used consistently and there are long durations of untreated psychosis (Figure 4-66). Such observations have led to the notion that this illness may thus be neurodegenerative in nature. If schizophrenia looks as though it begins as aberrant neurodevelopment, it can seemingly appear that as it progresses, it is neurodegenerative. In other words, if the manner in which synapses are made and revised dramatically during adolescence potentially explains how the full onset of schizophrenia can be conceptualized as neurodevelopmental, then the manner in which synapses are made and revised in a more methodical manner throughout adult life could potentially explain how the long-term course of schizophrenia can be conceptualized as neurodegenerative.

As stated earlier, normally, almost half of the brain's synapses are eliminated in adolescence (Figure 4-64). However, what is often not appreciated as well is that, in adulthood, you may lose (and replace elsewhere) about 7% of the synapses in your cortex every week! You can imagine if this process in adulthood runs amok over a long period of time that this could have pervasive cumulative consequences on adult brain development – or lack thereof – and be manifest as a progressively declining clinical course and even brain atrophy (Figure 4-66). That is, the strengthening or weakening of synapses occurs not only when these synapses first form, but continues throughout life as a sort of ongoing remodeling in response to what experiences the individual has, and thus how often that synapse is used or neglected. The strengthening or weakening of glutamate synapses in particular is an example of "activity dependent" or "use dependent" or "experience dependent" regulation of NMDA receptors and functionality at glutamate synapses. The old saying is, "use it or lose it." In schizophrenia, it is possible that abnormal synaptogenesis prevents normal synapses from strengthening even if the patient is "using" that synapse. It is also possible that the "wrong" synapses are "used" and strengthened, while the critical synapses for full functioning are not used and therefore lost along with the function those connections would have provided, yielding a progressive downhill course. Evidence is accumulating that allowing the positive symptoms of psychosis to persist unabated hastens the progressive loss of brain tissue associated with recurrent episodes of psychotic breaks (usually with repeated hospitalizations) in schizophrenia (Figure 4-66).

Abnormalities in these continuing dynamics at NMDA receptors and glutamate synapses in particular may explain why the course of schizophrenia is progressive and changes over time for most patients; namely, from an asymptomatic period to a prodrome (maybe due to laying down deficient synapses initially in the

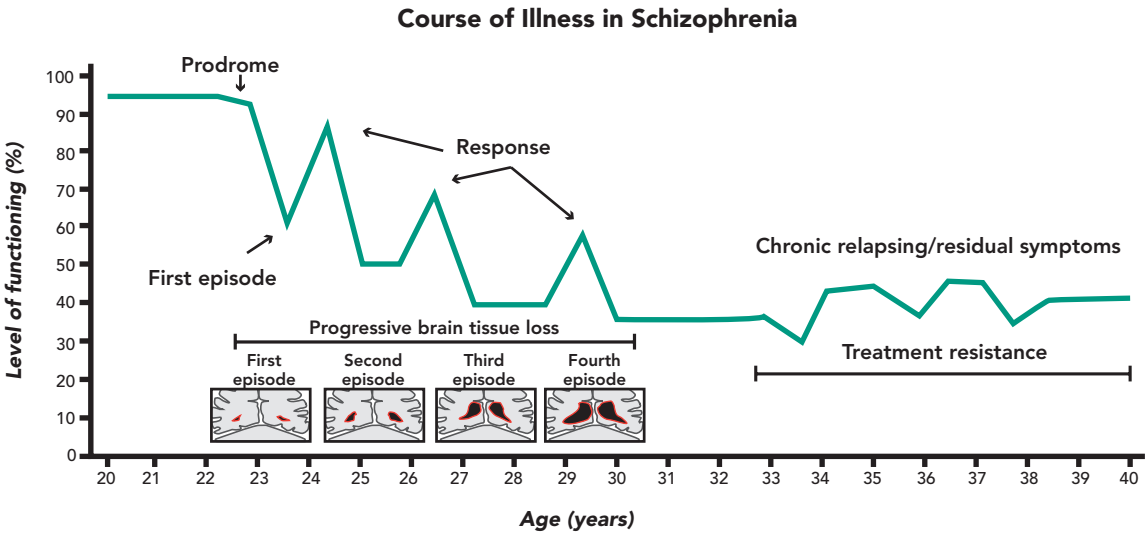


Figure 4-66 Course of illness in schizophrenia. Although schizophrenia may begin as a neurodevelopmental disorder, its progressive nature suggests that it may also be a neurodegenerative disorder. Strengthening and weakening of synapses occurs throughout the lifetime. In schizophrenia, it is possible that abnormal synaptogenesis prevents normal synapses from strengthening even if they are being "used," and/or allows the "wrong" synapses to strengthen and be retained. There is evidence that recurrent episodes of psychotic breaks are associated with progressive loss of brain tissue in schizophrenia and loss of treatment responsiveness.

young brain) to a first-break psychosis (when synaptic remodeling dramatically accelerates and perhaps the wrong synapses are eliminated) (Figure 4-66). One powerful indication of a downhill course in schizophrenia is what happens over time to treatment responsiveness and to the brain's structure. At the time of a first-break psychosis, there is often robust treatment responsiveness to medicines for psychosis, and the brain can appear grossly normal (see first episode brain in Figure 4-66). However, as the number of psychotic episodes mounts, often due to medication discontinuation, this can often be accompanied by declining treatment responsiveness to medications for psychosis and progressive loss of brain tissue observable on structural neuroimaging (see second, third, and fourth episodes and accompanying brain scans in Figure 4-66). Finally, the patient too often can progress to a state of pervasive negative and cognitive symptoms without recovery and with relative resistance to treatment with drugs for psychosis and with even more dramatic signs of brain degeneration observed with neuroimaging.

The good news is that there is evidence that reducing the period of untreated psychosis may slow the progression of schizophrenia, and there is even hope that presymptomatic or prodromal treatments prior to the onset of full psychotic symptoms in schizophrenia may some day prevent or slow the onset of the illness altogether. In fact, there is an emerging concept in psychopharmacology in general that treatments that reduce symptoms can also be disease modifying. Whether or not the same agents that treat the symptoms of schizophrenia could also prevent the emergence of schizophrenia when given to high-risk individuals who are either presymptomatic or in a state with only mild prodromal symptoms remains speculative. However, it already seems quite clear that continuous treatment of patients with schizophrenia once it has begun is now the standard of care in treatment of schizophrenia in order to maximize the chances of preventing or slowing a deteriorating course, brain-tissue loss, a tripling of suicide attempts, and treatment resistance with repetitive relapses after the first episode.

Is the neurodevelopmental onset and neurodegenerative progression of schizophrenia the case for any psychotic illness? Fortunately not. As will be briefly discussed in the following section of this chapter, although schizophrenia is the commonest and best known psychotic illness, it is not synonymous with psychosis, but is just one of many causes of psychosis and each has its own unique onset and course of illness. The natural history and course of illness for schizophrenia are not generally the same for every other psychotic illness, although severe forms of bipolar psychosis are sometimes lumped together with severe forms of

schizophrenia and referred to together as "serious mental illness" or SMI. These forms of psychosis can all have a dismal functional outcome, including homelessness, premature death, and even confinement in the criminal justice system. Schizophrenia affects approximately 1% of the population, and in the United States there are over 300,000 acute schizophrenic episodes annually. Between 25% and 50% of schizophrenia patients attempt suicide, and up to 10% eventually succeed, contributing to a mortality rate eight times greater than that of the general population. Life expectancy of a schizophrenia patient may be 20 to 30 years shorter than the general population, not only due to suicide, but also due to premature cardiovascular disease. Accelerated mortality from premature cardiovascular disease in schizophrenia patients is caused by genetic and lifestyle factors, such as smoking, unhealthy diet, and lack of exercise, leading to obesity and diabetes, but also – sorrily – from treatment with some antipsychotic drugs that themselves cause an increased incidence of obesity and diabetes and thus increased cardiac risk. In the United States, over 20% of all social security benefit days are used for the care of schizophrenia patients. The direct and indirect costs of schizophrenia in the US alone are estimated to be in the tens of billions of dollars every year. Many of these costs in the US are borne by the criminal justice system of courts, jails, prisons, and state and forensic hospitals that provide housing and treatment for patients with schizophrenia due to the lack of adequate outpatient treatment or long-term hospitals, as has already been discussed. This may be changing due to innovative outpatient diversion programs that are beginning to divert patients from the criminal justice system to community housing and treatment, which is far less expensive and possibly more humane and effective than alternating homelessness and no treatment with incarceration in a revolving-door fashion.

OTHER PSYCHOTIC ILLNESSES

Psychotic *disorders* have psychotic *symptoms* as their defining features, but there are several other disorders in which psychotic symptoms may be present but are not necessary for the diagnosis. Those disorders that require the presence of psychosis as a defining feature of the diagnosis include schizophrenia, substance/medication-induced (i.e., drug-induced) psychotic disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to another medical condition, and childhood psychotic disorder (Table 4-8). Disorders that may or may not have psychotic symptoms as an *associated* feature include mood disorders (both bipolar mania and many types of depression), Parkinson's disease (known as Parkinson's disease psychosis or PDP), and several cognitive disorders such as Alzheimer disease and other forms of dementia (Table 4-9).

Table 4-8 Disorders in which psychosis is a defining feature

Schizophrenia
Substance/medication-induced psychotic disorders
Schizophreniform disorder
Schizoaffective disorder
Delusional disorder
Brief psychotic disorder
Shared psychotic disorder
Psychotic disorder due to another medical condition
Childhood psychotic disorder

Table 4-9 Disorders in which psychosis is an associated feature

Mania
Depression
Cognitive disorders
Alzheimer disease and other dementias
Parkinson's disease

Symptoms of schizophrenia are not necessarily unique to schizophrenia. It is important to recognize that several illnesses other than schizophrenia can share some of the same five symptom dimensions described here for schizophrenia and shown in Figure 4-59. Thus, numerous disorders in addition to schizophrenia can have *positive symptoms* (delusions and hallucinations), including Parkinson's disease, bipolar disorder, schizoaffective disorder, psychotic depression, Alzheimer disease and other organic dementias, childhood psychotic illnesses, drug-induced psychoses, and others. *Negative symptoms* can also occur in disorders other than schizophrenia, especially mood disorders and dementias where it can be difficult to distinguish between negative symptoms such as reduced speech, poor eye contact, diminished emotional responsiveness, reduction of interest, and reduced social drive and the cognitive and affective symptoms that occur in these other disorders.

Schizophrenia is certainly not the only disorder with *cognitive symptoms*. Autism, post-stroke (vascular or multi-infarct) dementia, Alzheimer disease, and many other organic dementias (Parkinsonian/Lewy body dementia; frontotemporal/Pick's dementia, etc.), and mood disorders including major depression and bipolar depression can also be associated with various forms of cognitive dysfunction.

Mood-Related Psychosis, Psychotic Depression, Psychotic Mania

Mood disorders, from unipolar depression to bipolar disorder, can have symptoms of psychosis that accompany their mood symptoms. We have already discussed how schizophrenia can have symptoms of depressed mood, anxious mood, guilt, tension, irritability, and worry. Thus, schizophrenia can have affective symptoms and mood disorders can have psychotic symptoms. The point is, whenever psychotic symptoms are encountered, they need to be treated, and whenever affective symptoms are encountered, they too need to be treated, not only to relieve the current affective symptoms, but to prevent suicide, which is unfortunately common in patients with schizophrenia.

Parkinson's Disease Psychosis

Parkinson's disease begins of course with prominent motor symptoms. Motor symptoms are believed to be caused by deposition of Lewy bodies containing α-synuclein in the substantia nigra. However, Parkinson's disease progresses in over half the cases, especially in those with concomitant dementia, to psychosis with delusions and hallucinations, called Parkinson's disease psychosis (PDP). Several causes are proposed for PDP, the most prominent theory being the accumulation of Lewy bodies in the cerebral cortex as well as in serotonin cell bodies in the midbrain raphe (Figures 4-52C and 4-54). Psychosis in Parkinson's disease is a big risk factor for hospital admissions, for nursing-home placement, and for mortality, with mortality after 3 years of about 40% for Parkinson's patients after onset of psychosis.

PDP is not simply schizophrenia in a Parkinson's patient. First, the hallucinations in PDP tend to be visual rather than auditory (e.g., seeing people, animals). Second, the delusions tend to be a particular type of persecutory belief (e.g., the impression that someone, particularly a loved one, is trying to harm, steal from, or deceive), or jealousy (e.g., the impression that your partner is cheating on you). Third, insight into the false nature of these hallucinations and delusions is initially retained, which is not characteristic of psychosis in psychiatric disorders. PDP is conceptualized as an imbalance in serotonin and dopamine with upregulation of $5HT_{2A}$ receptors and treatable with $5HT_{2A}$ antagonists (Figure 4-52C and Figure 4-54).

Dementia-Related Psychosis

As the world's population ages, and without a known disease-modifying target to prevent the relentless march of dementia, the behavioral symptoms of dementia are attaining more and more attention, as dementia patients are surviving longer and as their dementia progresses. Agitation and psychosis are particularly important, common, and disabling behavioral symptoms of dementia and can be difficult to distinguish from each other in dementia. However, it is important to do so whenever possible, as the neuronal pathways for these different behaviors are also different, and so are their evolving treatments. Agitation in dementia is discussed in detail in Chapter 12 on dementia. In this chapter we have only briefly covered psychosis in dementia. Although we have discussed how psychosis is generally defined as the presence of delusions and/or hallucinations, it is delusions that are often more common in many dementias, especially Alzheimer disease, where there is a 5-year-period prevalence of delusions of over 50%. However, in Lewy body dementia, patients often have the same visual hallucinations and delusions characteristic of PDP, not surprising since Lewy body deposition in the cerebral cortex is thought to be a contributing cause of psychosis in both conditions.

From a pharmacological point of view, it may matter little what causes the disruption of brain pathways that brings on the symptoms of psychosis. It may matter far more *where* the pathways are disrupted and *which* pathways are disrupted. That is, whether an amyloid plaque, a tau tangle, a small stroke, or a Lewy body disrupts the glutamate–GABA connections or the serotonin–glutamate connections in the cerebral cortex, it may not matter as long as the disruption leads to downstream dopamine hyperactivity and the symptoms of delusions and hallucinations (Figure 4-52D and 4-55). When those same pathological conditions occur in other pathways, presumably those patients do not experience psychosis, but perhaps the other symptoms of dementia, such as memory disturbances and agitation.

Alzheimer disease dementia patients may have a serotonin component to their psychosis, since serotonin in presubiculum of the cerebral cortex is reported

to be low in patients with psychotic compared with nonpsychotic dementia. Furthermore, the *C102* allele of the $5HT_{2A}$ receptor gene may also be associated with psychosis in Alzheimer disease. In addition, Alzheimer patients with psychosis have significantly more plaques and tangles in the medial temporal-presubicular area and middle frontal cortex and five times higher levels of abnormal paired helical filament-tau protein in entorhinal and temporal cortices. If these lesions disrupt regulation of glutamate–GABA–serotonin–dopamine circuits, they would be expected to be the cause of psychosis (Figure 4-52D and 4-55).

SUMMARY

This chapter has provided a brief description of psychosis and an extensive explanation of the three principal theories of psychosis, namely those linked to dopamine, glutamate, and serotonin (5HT). The major dopamine, glutamate, and serotonin pathways in the brain have all been described. Overactivity of the mesolimbic dopamine system may mediate the positive symptoms of psychosis and may be linked to hypofunctioning NMDA glutamate receptors in parvalbumin-containing GABA interneurons in the prefrontal cortex and hippocampus in some psychotic disorders such as schizophrenia. Underactivity of the mesocortical dopamine system may mediate the negative, cognitive, and affective symptoms of schizophrenia and could also be linked to hypofunctioning NMDA receptors at different GABA interneurons. Imbalance in serotonin neurotransmission, particularly excessive activity at $5HT_{2A}$ receptors in the cortex, may explain psychosis in Parkinson's disease. Imbalance between serotonin and GABA neurotransmission at glutamate neurons in the cerebral cortex due to neurodegenerative processes knocking out GABA inhibition may lead to excessive excitation of glutamate neurons by serotonin acting at $5HT_{2A}$ receptors and that can be relieved by $5HT_{2A}$ antagonists.

The synthesis, metabolism, reuptake, and receptors for dopamine, glutamate, and serotonin are all described in this chapter. D_2 receptors are targets for drugs that treat psychosis, as are $5HT_{2A}$ receptors specifically for the psychosis associated with Parkinson's disease and with dementias. NMDA glutamate receptors require interaction not only with the neurotransmitter glutamate, but also with the cotransmitters glycine or D-serine.

Dysconnectivity of NMDA-receptor-containing synapses caused by genetic and environmental/epigenetic influences is a major hypothesis for the cause of schizophrenia, including its upstream glutamate hyperactivity and NMDA receptor hypofunction, as well as its downstream increases in mesolimbic dopamine but decreases in mesocortical dopamine. A whole host of susceptibility genes that regulate neuronal connectivity and synapse formation may represent a hypothetical central biological flaw in schizophrenia.

5 Targeting Dopamine and Serotonin Receptors for Psychosis, Mood, and Beyond: So-Called "Antipsychotics"

Targeting Mesolimbic/Mesostriatal Dopamine D_2 Receptors Causes Antipsychotic Actions 161
Targeting Dopamine D_2 Receptors in Mesolimbic/Mesostriatal and Mesocortical Pathways Causes Secondary Negative Symptoms 162
Secondary Negative Symptoms Due to Targeting Mesolimbic Dopamine D_2 Receptors 162
Secondary Negative Symptoms Due to Targeting Mesocortical Dopamine D_2 Receptors 163
Targeting Tuberoinfundibular Dopamine D_2 Receptors Causes Elevation of Prolactin 164
Targeting Nigrostriatal Dopamine D_2 Receptors Causes Motor Side Effects 165
Drug-Induced Parkinsonism 166
Drug-Induced Acute Dystonia 169
Akathisia 169
Neuroleptic Malignant Syndrome 169
Tardive Dyskinesia 170
Drugs Targeting Dopamine D_2 Receptors: So-Called First Generation or Conventional "Antipsychotics" 179
Drugs Targeting Serotonin 2A Receptors with or without Simultaneously Targeting Dopamine D_2 Receptors 183
$5HT_{2A}$ Receptor Regulation of Dopamine Release in Three Downstream Pathways 184
Drugs Targeting Serotonin 1A Receptors and Dopamine D_2 Receptors as Partial Agonists 189
D_2 Partial Agonism 189
How Does D_2 Partial Agonism Cause Fewer Motor Side Effects than D_2 Antagonism? 192
$5HT_{1A}$ Partial Agonism 193
Links between Receptor Binding Properties of Drugs Used to Treat Psychosis and Other Therapeutic Actions and Side Effects 195
Mania 195
Antidepressant Actions in Bipolar and Unipolar Depression 195
Anxiolytic Actions 196
Agitation in Dementia 197
Sedative Hypnotic and Sedating Actions 197
Cardiometabolic Actions 198
Pharmacological Properties of Selected Individual First-Generation D_2 Antagonists 201
Chlorpromazine 201
Fluphenazine 202
Haloperidol 202
Sulpiride 202
Amisulpride 203
An Overview of the Pharmacological Properties of Individual $5HT_{2A}$/ D_2 Antagonists and D_2/$5HT_{1A}$ Partial Agonists: The Pines (Peens), Many Dones and a Rone, Two Pips and a Rip 204
The Pines (Peens) 222
Many Dones and a Rone 234
Two Pips and a Rip 239
Selective $5HT_{2A}$ Antagonist 240
The Others 240
Future Treatments for Schizophrenia 241
Roluperidone (MIN-101) 241
D_3 Antagonists 241
Trace Amine Receptor Agonists and SEP-363856 241
Cholinergic Agonists 242
A Few Other Ideas 242
Summary 242

This chapter explores drugs that target dopamine receptors, serotonin receptors, or both, for the treatment of psychosis, mania, and depression. It also explores myriad additional neurotransmitter receptors that these agents engage. The drugs covered in this chapter have classically been called "antipsychotics," but this terminology is now considered out of date and confusing since these same agents are used even more frequently for mood disorders than for psychosis, yet are not classified as "antidepressants." As mentioned earlier, throughout this textbook we strive to utilize modern neuroscience-based nomenclature, where drugs are named for their pharmacological mechanism of action and not for their clinical indication. Thus, drugs discussed in this chapter have "antipsychotic action" but are not called "antipsychotics"; they also have "antidepressant action"

but are not called "antidepressants." Instead, this chapter reviews one of the most extensively prescribed classes of psychotropic agents in psychiatry today, namely, those that target dopamine and serotonin receptors, and that began as drugs for psychosis, and later extended their use even more frequently as drugs for mania, bipolar depression, and treatment-resistant unipolar depression. On the horizon is the use of at least some of these agents in PTSD (posttraumatic stress disorder), agitation in dementia, and beyond. We discuss how the pharmacological properties of these agents form not only a single large class of many agents, but in many ways, how each individual agent has binding properties that render every agent unique from all the others. The reader is referred to standard reference manuals and textbooks for practical prescribing information because this chapter on drugs for psychosis and mood emphasizes basic pharmacological concepts of mechanism of action and not practical issues such as how to prescribe these drugs (for that information, see, for example, *Stahl's Essential Psychopharmacology: the Prescriber's Guide*, which is a companion to this textbook).

The pharmacological concepts developed here should help the reader understand the rationale for how to use each of the different agents, based first and foremost upon their interactions with the dopamine and serotonin receptor systems, and secondarily with other neurotransmitter systems. Such interactions can often explain both the therapeutic actions and the side effects of the various drugs in this group. Understanding the full range of receptor interactions for each individual drug also sets the stage for differentiating one drug from another, and thus for tailoring the selection of a drug treatment by matching the pharmacological mechanisms of a specific drug to the therapeutic and tolerability needs of an individual patient.

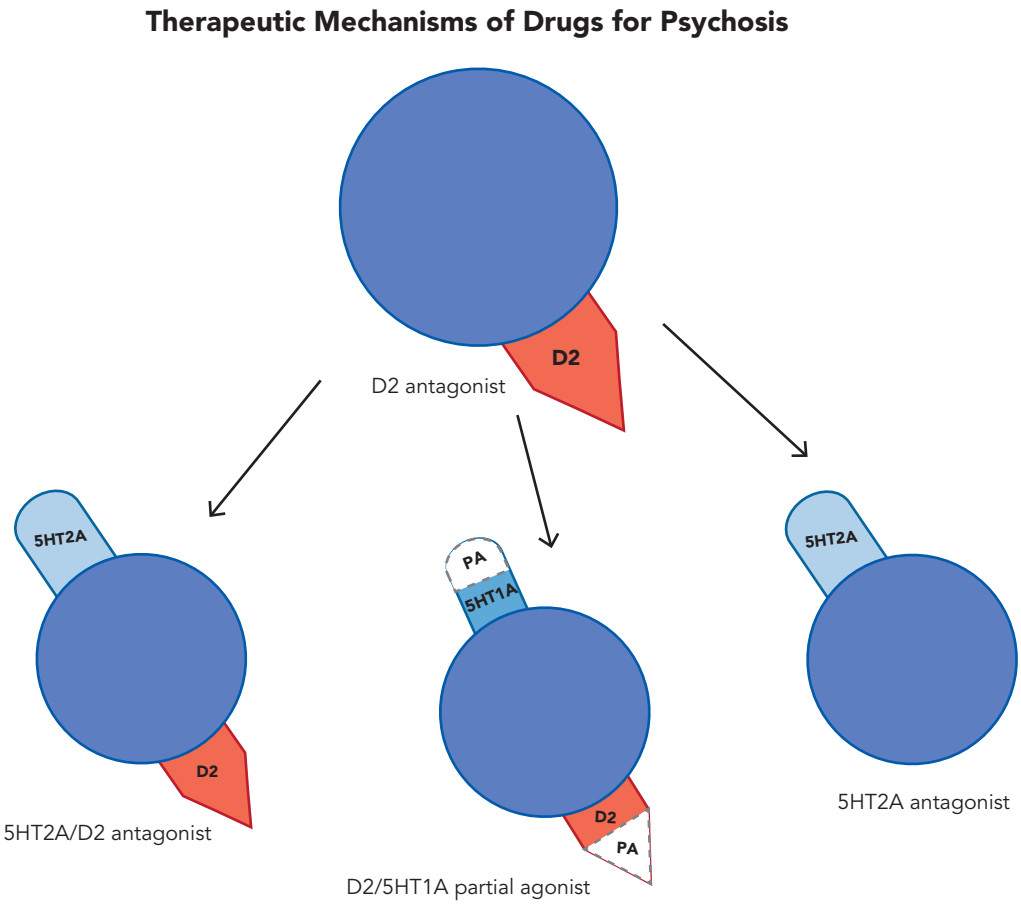


Figure 5-1 Therapeutic mechanisms of drugs for psychosis. The first mechanism identified to treat psychosis was dopamine-2 (D_2) antagonism, and for several decades all available medications to treat psychosis were D_2 antagonists. Today, there are many agents available with additional mechanisms, including D_2 antagonism combined with serotonin (5HT) 2A ($5HT_{2A}$) antagonism, D_2 partial agonism (PA) combined with serotonin 1A ($5HT_{1A}$) partial agonism, and $5HT_{2A}$ antagonism alone.

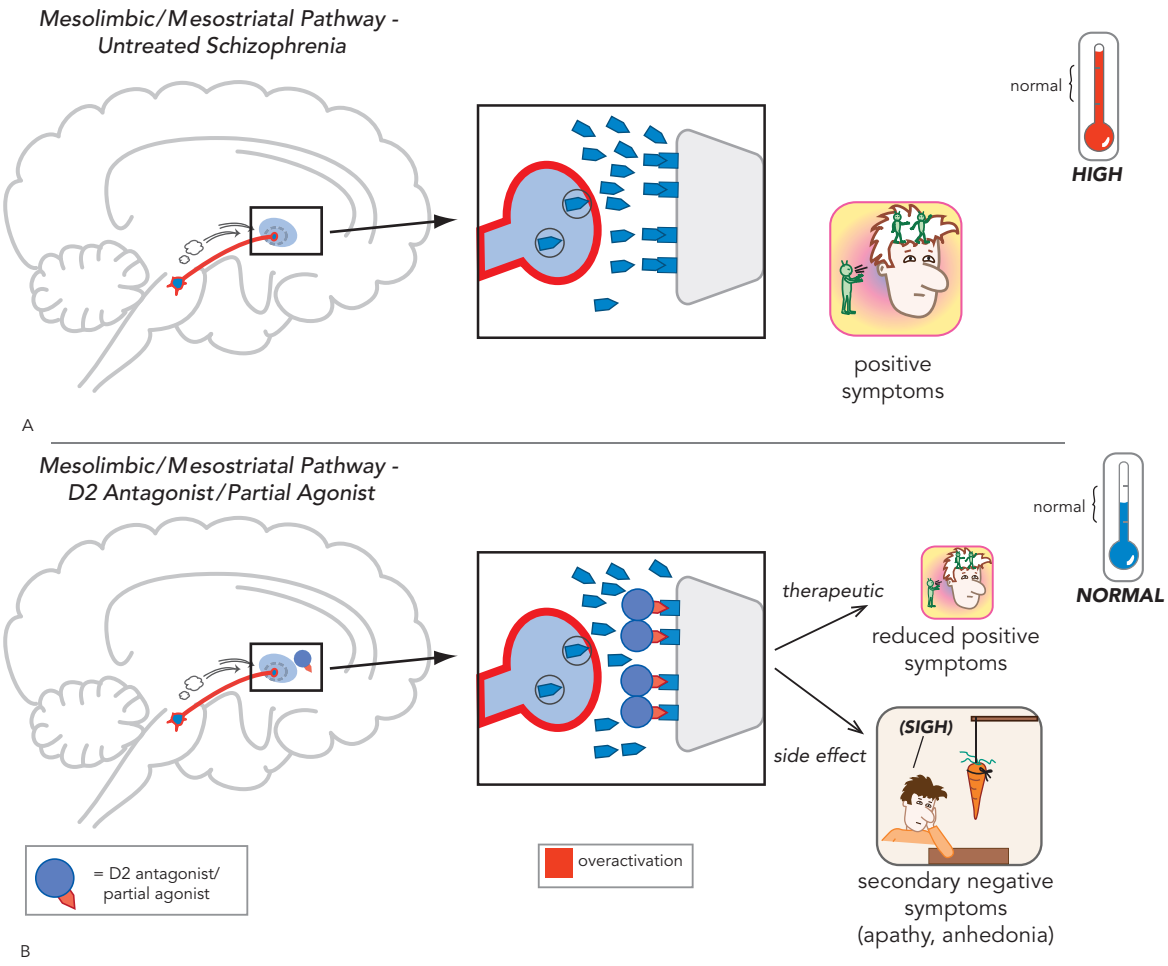


Figure 5-2 Mesolimbic/mesostriatal dopamine pathway and D_2 antagonists. (A) In untreated schizophrenia, the mesolimbic/mesostriatal dopamine pathway is hypothesized to be hyperactive, indicated here by the pathway appearing red as well as by the excess dopamine in the synapse. This leads to positive symptoms such as delusions and hallucinations. (B) Administration of a D_2 antagonist or partial agonist blocks dopamine from binding to the D_2 receptor, which reduces hyperactivity in this pathway and thereby reduces positive symptoms as well. However, because the mesolimbic/mesostriatal dopamine pathway also plays a role in regulating motivation and reward, blockade of D_2 receptors can cause secondary negative symptoms such as apathy and anhedonia.

TARGETING MESOLIMBIC/MESOSTRIATAL DOPAMINE D_2 RECEPTORS CAUSES ANTIPSYCHOTIC ACTIONS

How do the drugs approved for treating psychosis, especially in schizophrenia, work? The earliest effective treatments for schizophrenia and other psychotic illnesses arose from serendipitous clinical observations approximately 70 years ago, rather than from scientific knowledge of the neurobiological basis of psychosis, or of the mechanism of action of effective drugs that empirically treated psychosis. Thus, the first truly effective drugs for psychosis other than sedating tranquilizers were discovered by accident in the 1950s when a drug with antihistamine properties (chlorpromazine) was observed to improve psychosis when this putative antihistamine was tested in schizophrenia patients. Chlorpromazine indeed has antihistaminic activity, but its therapeutic actions in schizophrenia are not mediated by this property. Once chlorpromazine was observed to be an effective drug for treating psychosis out of proportion to its ability to cause sedation, it was tested experimentally to uncover its mechanism of antipsychotic action, which was identified as dopamine D_2 receptor antagonism (Figures 5-1 and 5-2).

Early in the testing process, chlorpromazine and other drugs for psychosis of this era were all found to cause "neurolepsis," known as an extreme form of slowness

or absence of motor movements as well as behavioral indifference in experimental animals. The original drugs for psychosis in fact were first discovered largely by their ability to produce this effect in experimental animals, and thus sometimes drugs with antipsychotic properties are called "neuroleptics." A human counterpart of neurolepsis is also caused by these drugs and is characterized by psychomotor slowing, emotional quieting, and affective indifference, sometimes also called "secondary" negative symptoms because they mimic the primary negative symptoms associated with the untreated illness itself (see Figures 4-56 through 4-59 and Tables 4-4 and 4-5). We know today that neurolepsis and secondary negative symptoms are likely caused at least in part by blocking D_2 receptors that normally mediate motivation and reward (Figure 5-2B) as an undesired "cost of doing business" in order to simultaneously block D_2 receptors that are thought to mediate the positive symptoms of psychosis due to excessive release of dopamine (see Figure 5-2A).

By the 1970s it was widely recognized that the key pharmacological property of all "neuroleptics" with antipsychotic properties was their ability to block D_2 receptors (Figure 5-1 and Figure 5-2B), specifically those in the mesolimbic/mesostriatal dopamine pathway (Figure 5-2B; see also Figure 4-15). This pharmacological property has been retained by many of the newer agents, some of which add highly potent serotonin 2A ($5HT_{2A}$) antagonism and/or $5HT_{1A}$ partial agonism to D_2 antagonism, others of which substitute D_2 partial agonism for D_2 antagonism, and, most recently, still others which only have $5HT_{2A}$ antagonism and drop the D_2 targeting entirely (Figure 5-1). The effects of serotonin-receptor-targeting of the newer agents and of partial agonism are discussed in detail below. Also explained in the following sections are how targeting serotonin and dopamine receptors in various brain circuits mediates not only therapeutic effects in psychosis and other conditions, but also side effects. These drugs are first classified into several general groups and then each individual drug is discussed.

TARGETING DOPAMINE D_2 RECEPTORS IN MESOLIMBIC/MESOSTRIATAL AND MESOCORTICAL PATHWAYS CAUSES SECONDARY NEGATIVE SYMPTOMS

Secondary Negative Symptoms Due to Targeting Mesolimbic Dopamine D_2 Receptors

Dopamine 2 (D_2) receptors in the mesolimbic/mesostriatal dopamine pathway are postulated not only to mediate the positive symptoms of psychosis from excessive release of dopamine in the pathway (see Figures 4-14, 4-15, and 5-2A), but also to have a major role in regulating motivation and reward (Figures 4-14 and 5-2B). In fact, the nucleus accumbens, a major target of mesolimbic/mesostriatal dopamine neurons in the ventral emotional striatum, is widely considered to be the "pleasure center" of the brain. The mesolimbic dopamine pathway to the nucleus accumbens is often considered the final common pathway of all reward and reinforcement (even if this is an oversimplification), including not only normal reward (such as the pleasure of eating good food, orgasm, listening to music) but also the artificial reward of substance abuse (see the discussion on drugs of abuse in Chapter 13).

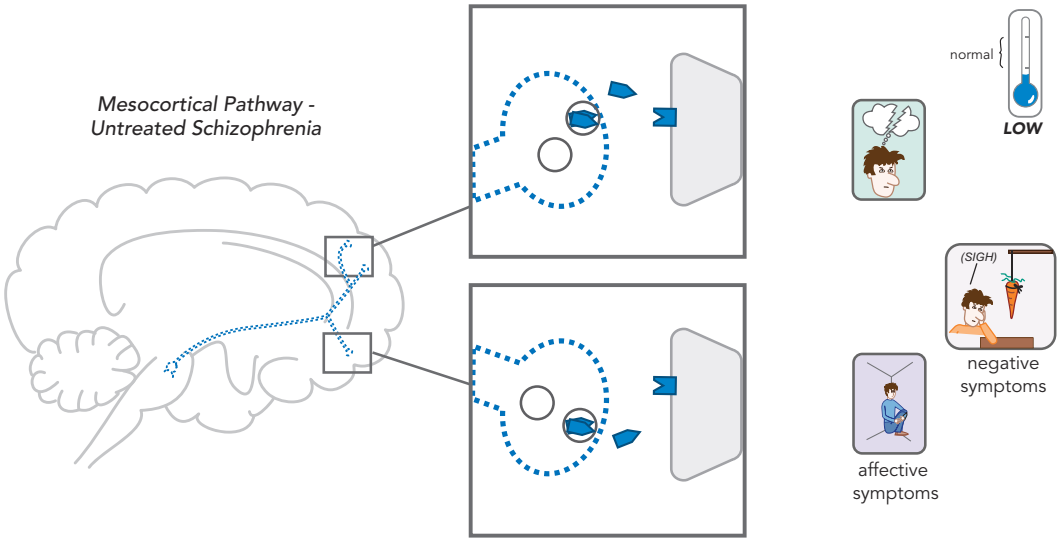
If normal mesolimbic D_2 receptor stimulation is associated with the experience of pleasure (Figure 4-14) and excessive mesolimbic D_2 receptor stimulation is associated with the positive symptoms of psychosis (Figure 5-2A), D_2 antagonism/partial agonism may not only reduce the positive symptoms of schizophrenia, but at the same time block reward mechanisms (both shown in Figure 5-2B). When this happens, it can leave patients feeling apathetic, anhedonic, and lacking motivation, interest, or joy from social interactions, a state very similar to that of negative symptoms of schizophrenia. However, these negative symptoms are caused by the drug, not the illness and thus are termed "secondary" negative symptoms. When D_2 blockers are administered, as has already been mentioned above, an adverse behavioral state can thus be simultaneously produced by D_2 antagonist/partial agonists, sometimes called the "neuroleptic-induced deficit syndrome" because it looks so much like the negative symptoms produced by schizophrenia itself, and this is reminiscent of "neurolepsis" in animals. The near shut-down of the mesolimbic dopamine pathway, sometimes necessary to improve the positive symptoms of psychosis (Figure 5-2A), may exact a heavy "cost of doing business" to the patient by causing a worsening of anhedonia, apathy, and other negative symptoms (Figure 5-2B). Worsening negative symptoms with loss of pleasure caused by treatment with drugs for psychosis is a plausible partial explanation for the high incidence of smoking and drug abuse in schizophrenia as patients may attempt to overcome this anhedonia and lack of pleasurable experiences. The emotional flattening and worsening of negative symptoms may contribute to patients stopping their given D_2 blockers.

Treatment of negative symptoms includes reducing the dose of the D_2 blocker or switching to a D_2 blocker that is better tolerated; some adjunct medications can be helpful

in reducing negative symptoms, including drugs that treat depression. Several other agents are in various stages of development for negative symptoms and include $5HT_{2A}$ antagonists as well as dopamine 3 (D_3) partial agonists, as discussed below in the section on individual agents.

Secondary Negative Symptoms Due to Targeting Mesocortical Dopamine D_2 Receptors

Negative symptoms (Figure 5-3A) can also be worsened by D_2 antagonist/partial agonist actions in the mesocortical dopamine pathway (Figure 5-3B).



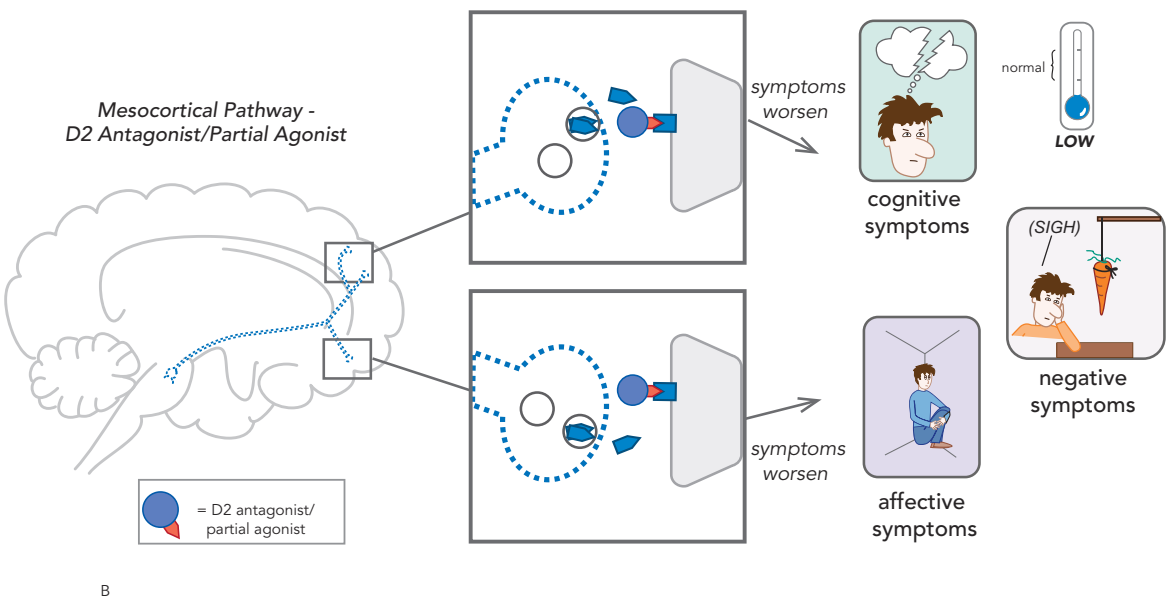


Figure 5-3 Mesocortical dopamine pathway and D_2 antagonists. (A) In untreated schizophrenia, the mesocortical dopamine pathways to the dorsolateral prefrontal cortex (DLPFC) and to the ventromedial prefrontal cortex (VMPFC) are hypothesized to be hypoactive, indicated here by the dotted outlines of the pathway. This hypoactivity is related to cognitive symptoms (in the DLPFC), negative symptoms (in the DLPFC and VMPFC), and affective symptoms of schizophrenia (in the VMPFC). (B) Administration of a D_2 antagonist or partial agonist could further reduce activity in this pathway and thus potentially worsen these symptoms.

Drugs for psychosis also block those D_2 receptors that are present in the mesocortical dopamine pathway (Figure 5-3B) where dopamine is already hypothetically deficient in schizophrenia (see Figures 4-17 through 4-19). This can cause or worsen not only negative symptoms of schizophrenia, but also cognitive and affective symptoms related to dopamine action in the mesocortical dopamine pathway, even though there is only a low density of D_2 receptors in the cortex (Figure 5-3B).

TARGETING TUBEROINFUNDIBULAR DOPAMINE D_2 RECEPTORS CAUSES ELEVATION OF PROLACTIN

Dopamine 2 receptors in the tuberoinfundibular dopamine pathway are also blocked when D_2 antagonists are administered and this causes plasma prolactin concentrations to rise, a condition called

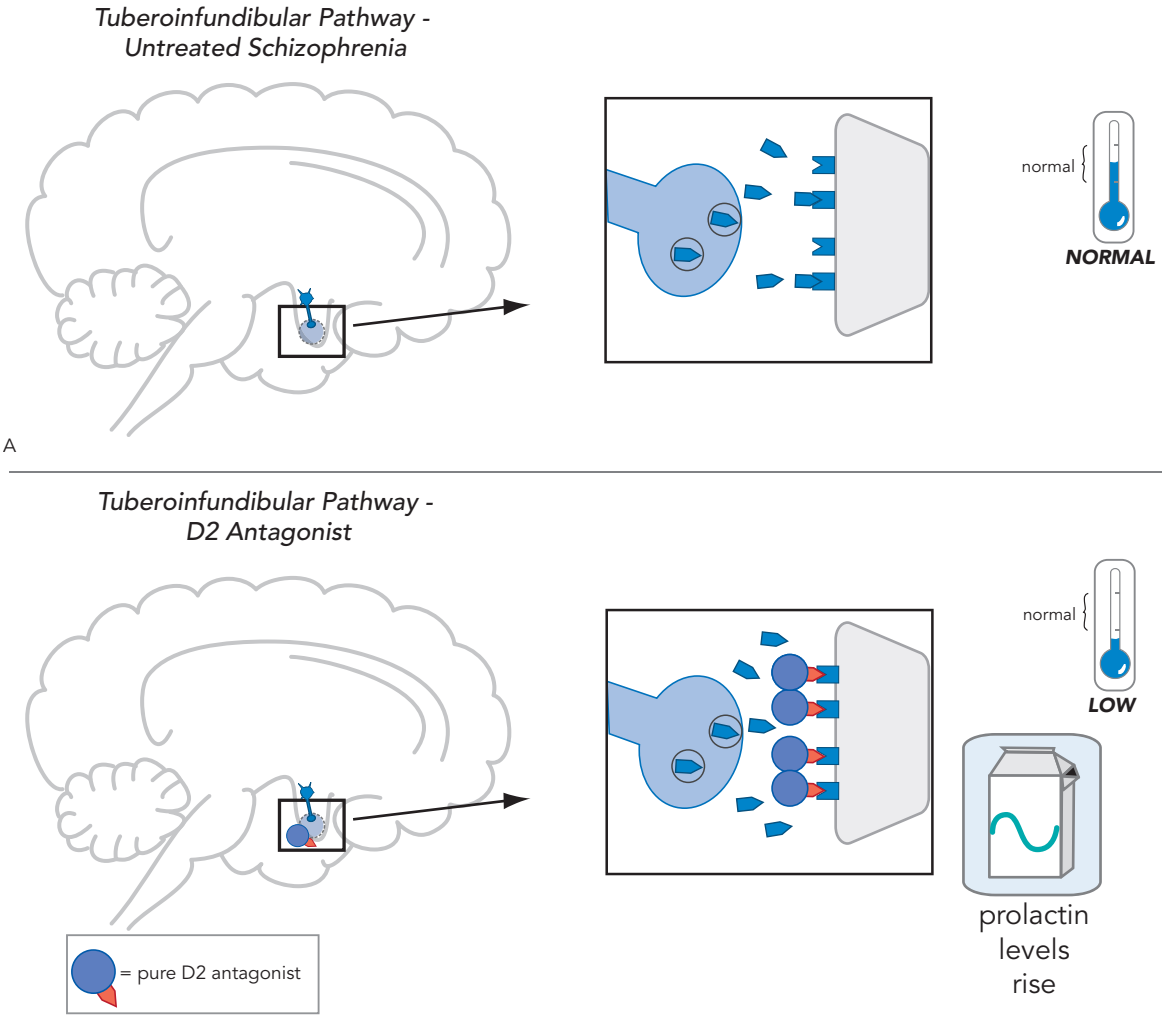


Figure 5-4 Tuberoinfundibular dopamine pathway and D_2 antagonists. (A) The tuberoinfundibular dopamine pathway, which projects from the hypothalamus to the pituitary gland, is theoretically "normal" in untreated schizophrenia. (B) D_2 antagonists reduce activity in this pathway by preventing dopamine from binding to D_2 receptors. This causes prolactin levels to rise, which is associated with side effects such as galactorrhea (breast secretions) and amenorrhea (irregular menstrual periods).

hyperprolactinemia (Figure 5-4). This can be associated with a condition called gynecomastia, or enlargement of the breasts, in men as well as women, and another condition called galactorrhea (i.e., breast secretions) and amenorrhea (i.e., irregular or lack of menstrual periods) in women. Hyperprolactinemia may thus interfere with fertility, especially in women. Hyperprolactinemia might lead to more rapid demineralization of bones, especially in postmenopausal women who are not taking estrogen replacement therapy. Other possible problems associated with elevated prolactin levels may include sexual dysfunction and weight gain, although the role of prolactin in causing such problems is not clear.

TARGETING NIGROSTRIATAL DOPAMINE D_2 RECEPTORS CAUSES MOTOR SIDE EFFECTS

Motor side effects are caused by D_2 antagonists/partial agonists blocking D_2 receptors in the nigrostriatal motor pathway (Figure 5-5). When D_2 receptors are blocked *acutely* in the nigrostriatal pathway – the same pathway that degenerates in Parkinson's disease – this can cause a condition known as drug-induced parkinsonism (DIP) because it looks similar to Parkinson's disease with tremor, muscular rigidity, and slowing of movements (bradykinesia) or loss of movement (akinesia) (Figure 5-5B). Often, any abnormal motor symptoms caused

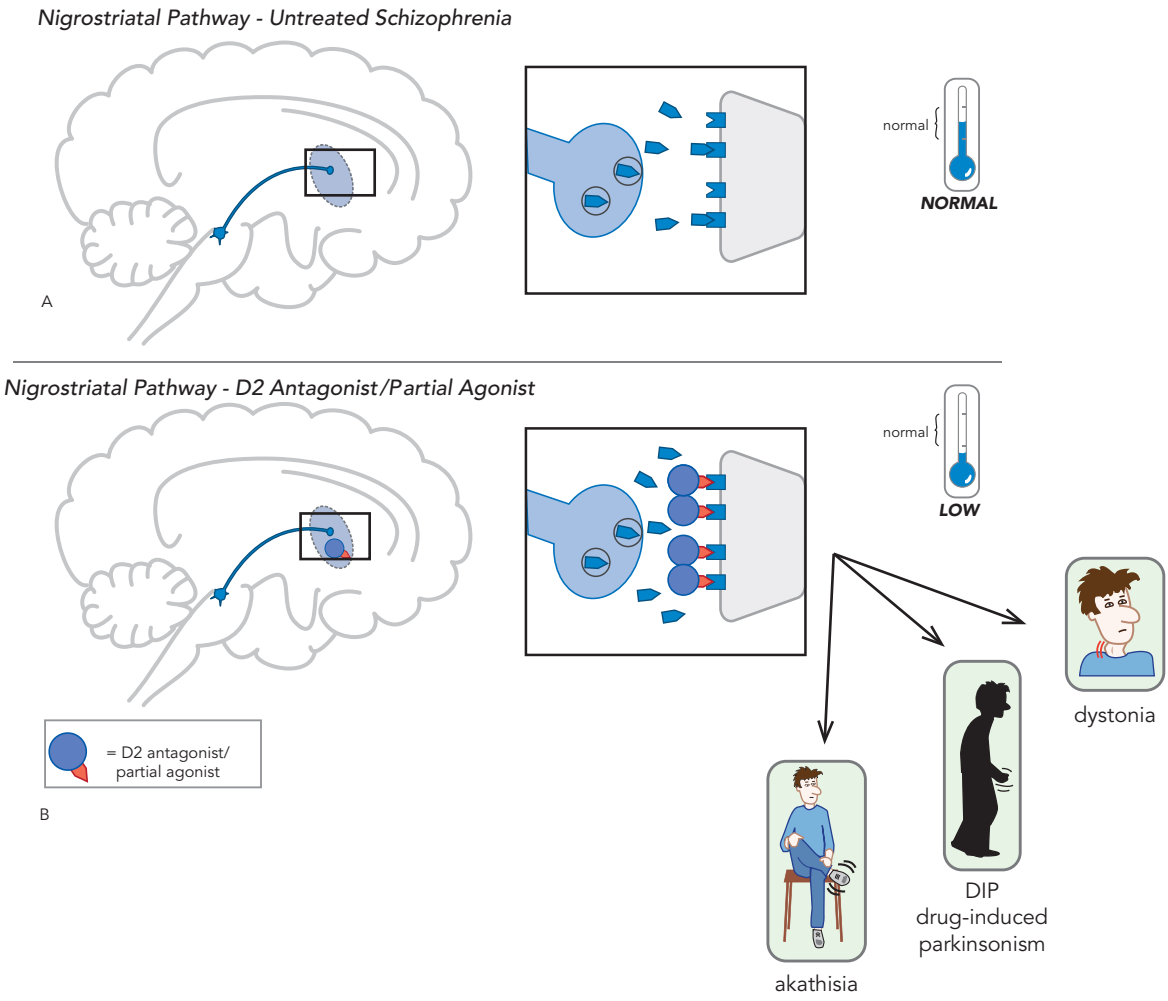


Figure 5-5 Nigrostriatal dopamine pathway and D_2 antagonists. (A) The nigrostriatal dopamine pathway is theoretically unaffected in untreated schizophrenia. (B) Blockade of D_2 receptors prevents dopamine from binding there and can cause motor side effects such as drug-induced parkinsonism (tremor, muscle rigidity, slowing or loss of movement), akathisia (motor restlessness), and dystonia (involuntary twisting and contractions).

by D_2 receptor blockers are lumped together and called collectively extrapyramidal symptoms (EPS), but EPS is an old-fashioned and relatively imprecise term for describing the motor side effects of D_2 antagonists/partial agonists. A practical consequence of lumping all D_2-blocker-induced movements together as EPS is to miss the fact that different motor symptoms can have different clinical manifestations and – importantly – vastly different treatments. More precise terms than EPS include not only DIP but also akathisia (motor restlessness) and dystonia (involuntary twisting and contractions), which can also be caused by the acute administration of D_2 antagonists/partial agonists and are discussed below.

Yet another abnormal involuntary movement disorder can be caused by the *chronic* blockade of D_2 receptors in the nigrostriatal dopamine pathway, namely tardive dyskinesia (TD) ("tardive" because, unlike the other motor symptoms caused by D_2 blockade, these abnormal involuntary movements are late and delayed in onset, often after months to years of treatment) (Figure 5-6). TD emerges only after chronic treatment with D_2 blockers, and can be irreversible. It consists of involuntary continuous movements, often about the face and tongue, such as constant chewing, tongue protrusions, facial grimacing, but also limb movements that can be quick, jerky, or choreiform (dancing). Unfortunately, DIP and TD are often lumped together as EPS, leading to the failure to differentiate one versus the other despite the fact that they have essentially opposite pharmacologies and vastly different treatments, as discussed below. Now that treatments exist for both DIP and TD, it is more important than ever to make this differentiation so that proper treatment can be given. Inadequate relief of motor side effects of D_2 blockers is a major reason why patients stop their medication.

Drug-Induced Parkinsonism

The most common side effect of drugs that target D_2 receptors for psychosis is drug-induced parkinsonism, explained above as the presence of tremor, muscular rigidity, and slowing of movements (bradykinesia) or loss of movement (akinesia). Classic treatment for DIP is the use of "anticholinergics," namely drugs that block muscarinic cholinergic receptors, especially the postsynaptic M_1 receptor. This approach exploits the normal reciprocal balance between dopamine and acetylcholine in the striatum (Figure 5-7A). Dopamine

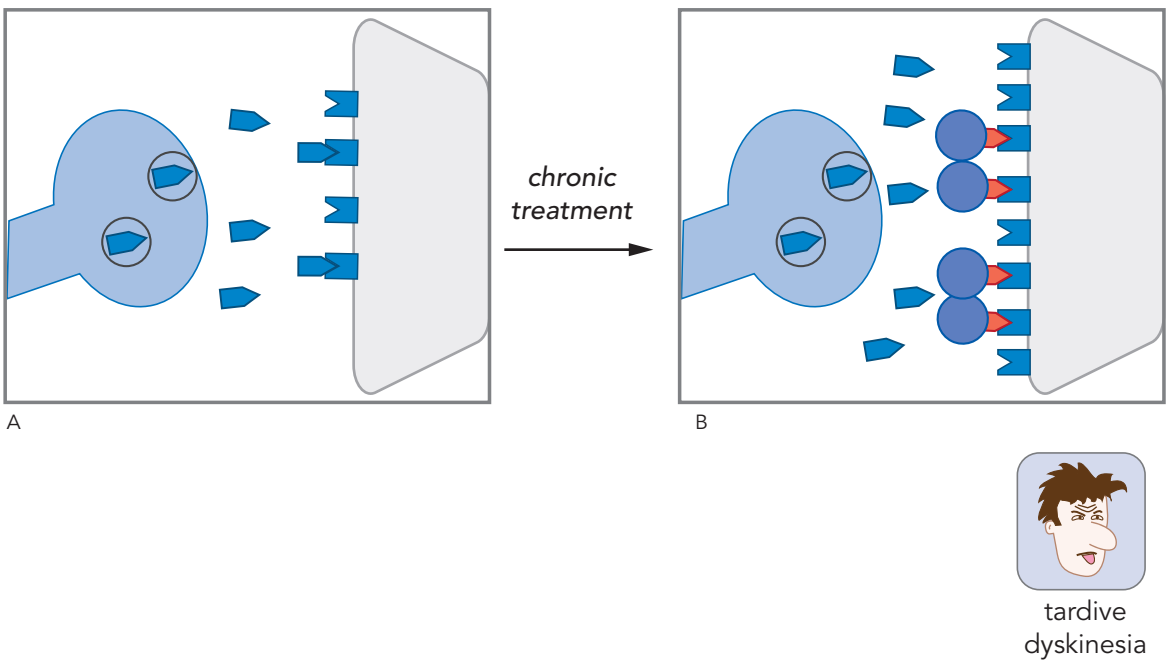


Figure 5-6 Tardive dyskinesia. (A) Dopamine binds to D_2 receptors in the nigrostriatal pathway. (B) Chronic blockade of D_2 receptors in the nigrostriatal dopamine pathway can cause upregulation of those receptors, which can lead to a hyperkinetic motor condition known as tardive dyskinesia, characterized by facial and tongue movements (e.g., tongue protrusions, facial grimaces, chewing) as well as quick, jerky limb movements.

neurons in the nigrostriatal motor pathway make postsynaptic connections on cholinergic interneurons (Figure 5-7A). Dopamine acting at D_2 receptors normally *inhibits* acetylcholine release from postsynaptic nigrostriatal cholinergic neurons (Figure 5-7A). When D_2 blockers are given, dopamine can no longer suppress acetylcholine release, thus disinhibiting acetylcholine release from cholinergic neurons (see enhanced acetylcholine release in Figure 5-7B). This in turn leads to more excitation of postsynaptic muscarinic cholinergic receptors on medium spiny GABAergic neurons, which hypothetically leads in part to inhibition of movements and to the symptoms of DIP (akinesia, bradykinesia, rigidity, and tremor). However, when the enhanced downstream release of acetylcholine is blocked by anticholinergics at muscarinic cholinergic receptors, this hypothetically restores in part the normal balance between dopamine and acetylcholine in the striatum, and DIP is reduced (Figure 5-7C).

Empirically, anticholinergics do work in clinical practice to reduce DIP, especially the DIP caused by some of the older D_2 blockers that lack serotonergic actions. On the other hand, there are many potential problems with administering anticholinergics (such as the commonly used benztropine); namely, peripheral side effects, such as dry mouth, blurred vision, urinary retention, and constipation, as well as central side effects including drowsiness and cognitive dysfunction, such as problems with memory, concentration, and slowing of cognitive processing (Figure 5-8). To compound matters, many drugs for psychosis themselves have anticholinergic properties as will be discussed below for each individual agent. Furthermore, many patients are on concomitant psychotropic and nonpsychotropic medications that have anticholinergic properties. Thus, the clinician must be alert to the total anticholinergic burden for a given patient and also be wary of the side effects that can interfere with normal cognitive functioning and can lead to life-threatening decrease in bowel motility called paralytic ileus. On balance, today many patients administered D_2 blockers are overmedicated with total anticholinergic burden. Alternatives to using these agents should often be sought, such as use of a different drug for psychosis that lacks anticholinergic properties,

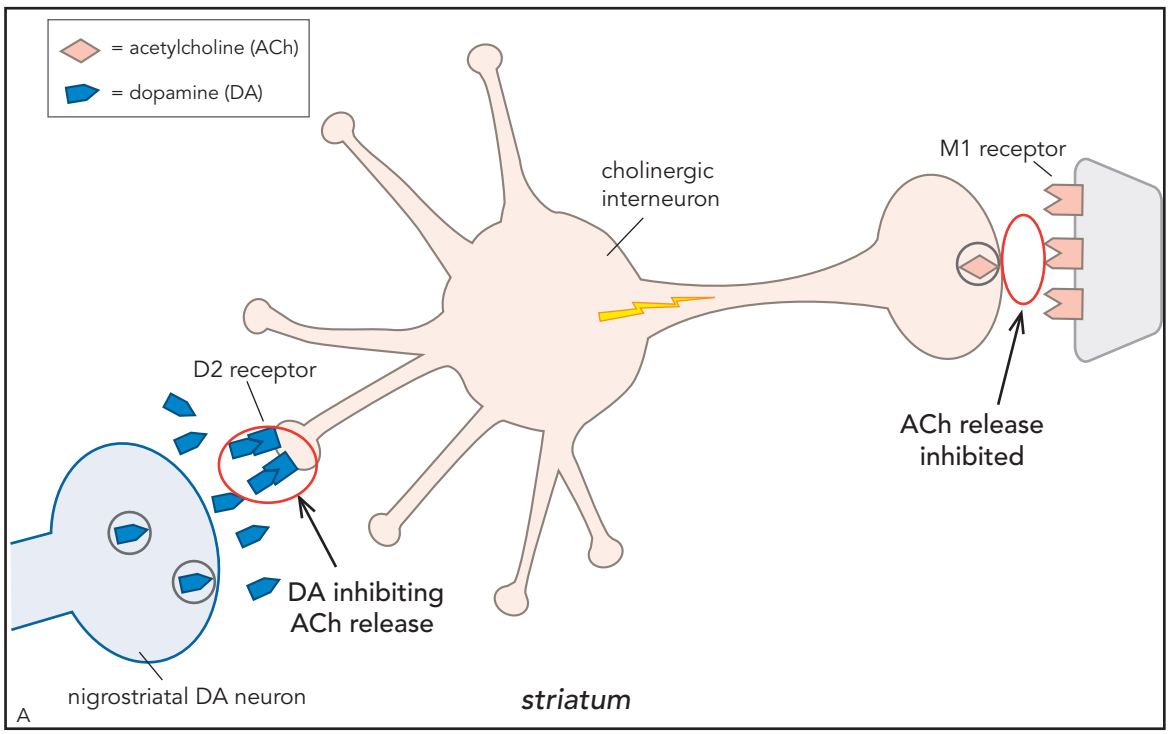


Figure 5-7A Reciprocal relationship of dopamine and acetylcholine. Dopamine and acetylcholine have a reciprocal relationship in the nigrostriatal dopamine pathway. Dopamine neurons here make postsynaptic connections with the dendrite of a cholinergic neuron. Normally, dopamine binding at D_2 receptors suppresses acetylcholine activity (no acetylcholine being released from the cholinergic axon on the right).

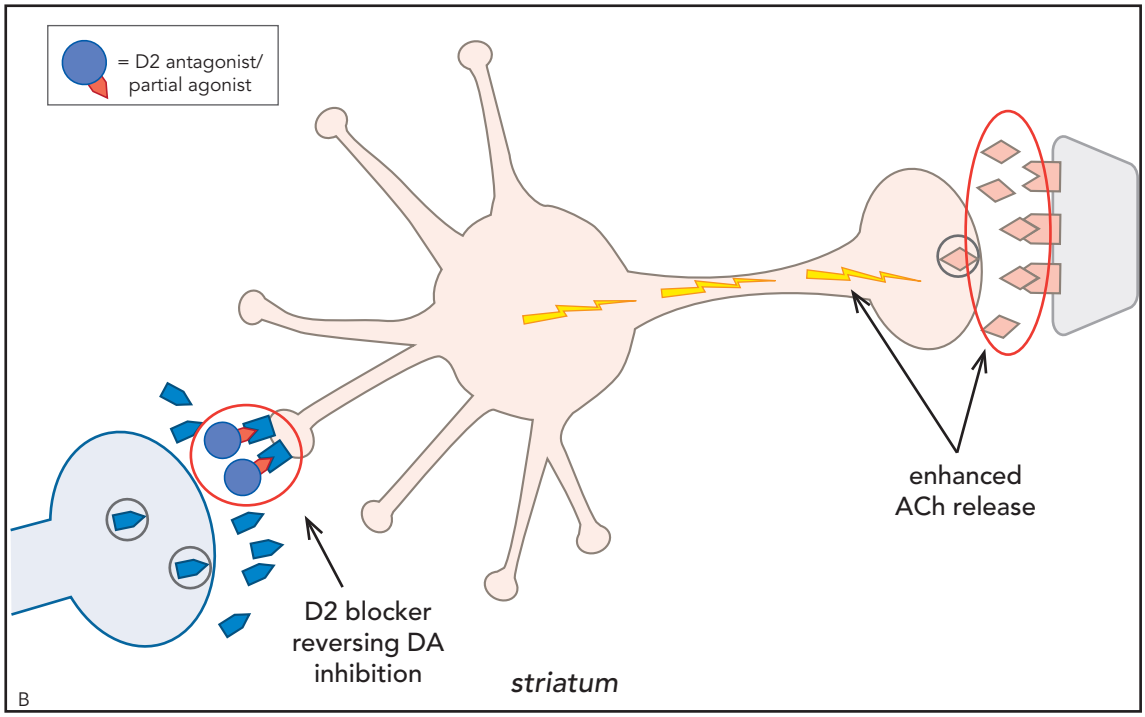


Figure 5-7B Dopamine, acetylcholine, and D_2 antagonism. Since dopamine normally suppresses acetylcholine activity, removal of dopamine inhibition causes an increase in acetylcholine activity. As shown here, if D_2 receptors are blocked on the cholinergic dendrite on the left, then acetylcholine release from the cholinergic axon on the right is enhanced. This is associated with the production of drug-induced parkinsonism.

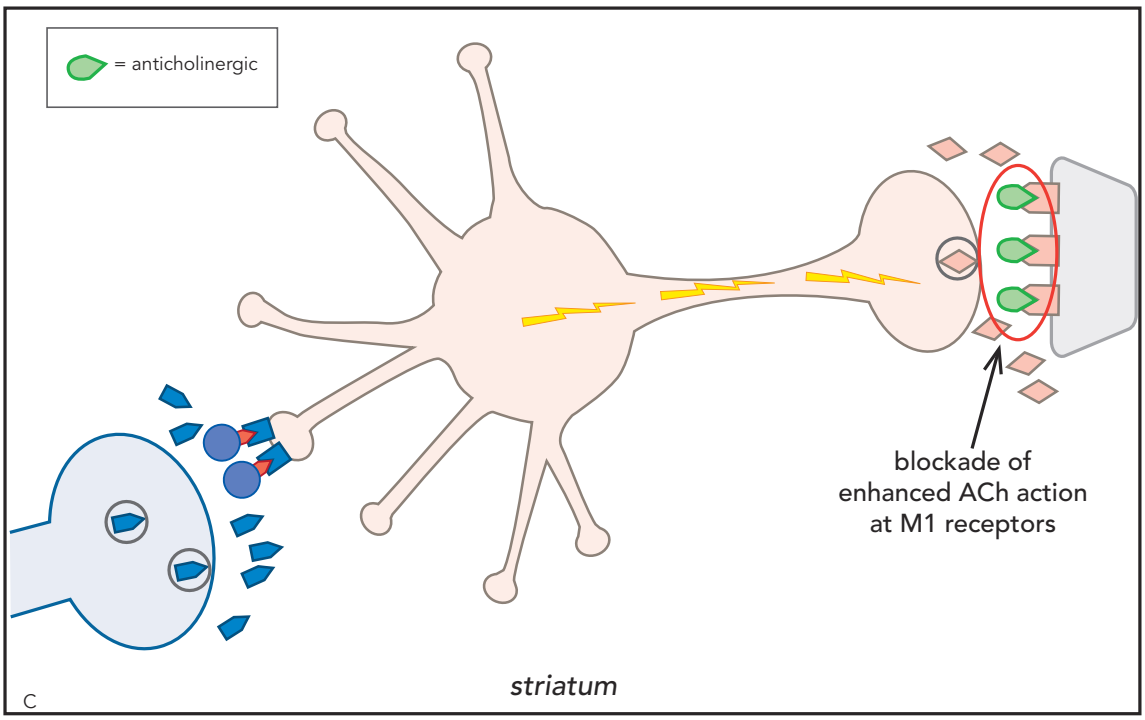


Figure 5-7C D_2 antagonism and anticholinergic agents. One compensation for the overactivity that occurs when D_2 receptors are blocked is to block the muscarinic cholinergic receptors with an anticholinergic agent (M_1 receptors being blocked by an anticholinergic on the far right). This hypothetically restores in part the normal balance between dopamine and acetylcholine and can reduce symptoms of drug-induced parkinsonism.

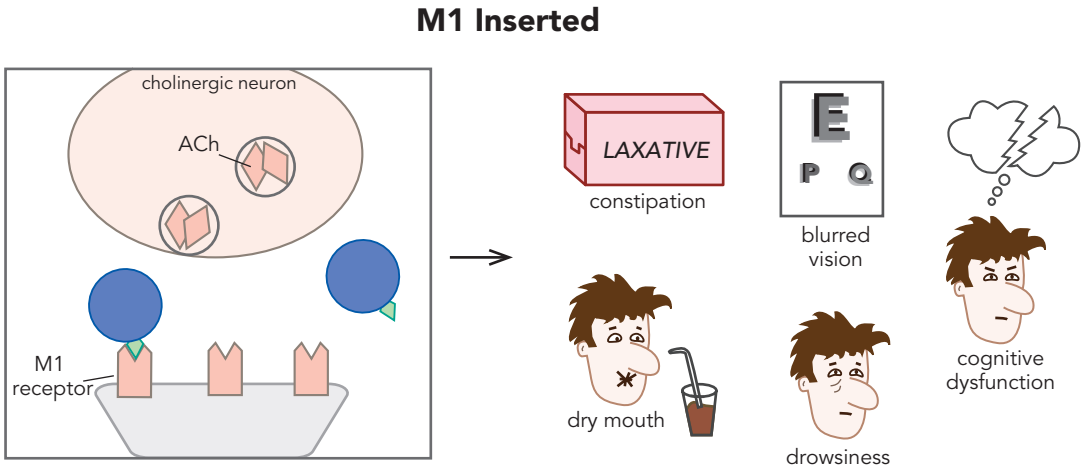


Figure 5-8 Side effects of muscarinic cholinergic receptor blockade. Blockade of muscarinic cholinergic receptors can reduce drug-induced parkinsonism, but can also induce side effects such as constipation, blurred vision, dry mouth, drowsiness, and cognitive dysfunction (problems with memory and concentration, slowed cognitive processing).

or stopping anticholinergic medications, or use of amantadine, which lacks anticholinergic properties but can mitigate the symptoms of DIP.

Amantadine's mechanism of action is thought to be weak antagonism of NMDA (*N*-methyl-D-aspartate) glutamate receptors, possibly leading to downstream changes in the activity of dopamine in both the direct and indirect striatal motor pathways. No matter what its actual mechanism of action, amantadine can be useful for improving DIP and also has some evidence of being useful in TD and levodopa-induced dyskinesias caused by levodopa treatment of Parkinson's disease.

Drug-Induced Acute Dystonia

Occasionally, exposure to D_2 blockers, especially those with neither serotonergic nor anticholinergic properties, can cause a condition called dystonia, often upon first exposure to the D_2 blocker. Dystonia is intermittent spasmodic or sustained involuntary contraction of the muscles in the face, neck, trunk, pelvis, extremities, or even the eyes. Drug-induced dystonias can be frightening and severe; fortunately, administration of an intramuscular injection of an anticholinergic is nearly always effective within 20 minutes. The cause and the treatment of this condition are other examples of the clinical significance of the balance between dopamine and acetylcholine in the motor striatum for the regulation of movements (Figures 5-7A, 5-7B, and 5-7C).

Chronic treatment with D_2 blockers can also cause late-onset dystonia as a manifestation of tardive dyskinesia, sometimes also called tardive dystonia. This requires TD treatment, as anticholinergics rarely work for this condition and can even make this form of dystonia worse.

Akathisia

Akathisia is a syndrome of motor restlessness seen commonly after treatment with D_2 blockers. Akathisia has both subjective and objective features. Subjectively, there is a sense of inner restlessness, mental unease, or dysphoria. Objectively, there are restless movements, most typical being lower-limb movements such as rocking from foot to foot, walking or marching in place when standing, or pacing. Sometimes drug-induced akathisia can be difficult to distinguish from the agitation and repetitive restless movements that are part of the underlying psychiatric disorder. Akathisia is not particularly effectively treated with anticholinergic medication, but instead is often more effectively treated with either β-adrenergic blockers or benzodiazepines. Serotonin 2A antagonists can also be helpful.

Neuroleptic Malignant Syndrome

A rare but potentially fatal complication can occur with D_2 receptor blockade, possibly due in part to D_2 receptor blockade specifically in the nigrostriatal motor pathway. This is called the "neuroleptic malignant syndrome," associated with extreme muscular rigidity, high fevers, coma, and even death. Some consider neuroleptic malignant syndrome to be the most extreme form of DIP; others theorize that this is a toxic complication of D_2 blocking drugs on cell membranes, including muscle. It constitutes a medical emergency that requires withdrawal of the D_2 blocker, muscle-relaxing agents such

as dantrolene and dopamine agonists, as well as intensive supportive medical treatment.

Tardive Dyskinesia

Pathophysiology

Overall, about 5% of patients maintained on D_2 antagonists that have little or no serotonin receptor action will develop TD every year (i.e., about 25% of patients by 5 years), not a very encouraging prospect for an illness starting in the early 20s and requiring lifelong treatment. The risk of developing TD in elderly subjects may be as high as 25% within the first year of exposure to D_2 antagonists. Estimates for the newer D_2 drugs for psychosis that have serotonergic receptor action are more difficult to obtain since many patients taking them have taken the older drugs as well in the past. Nevertheless, for those likely to have taken only newer D_2 antagonists/$5HT_{2A}$ antagonists or D_2/$5HT_{1A}$ partial agonists, the rate of TD may be about half the rate of the older drugs. These newer agents may mitigate DIP as well by the mechanisms discussed in detail below. Those mechanisms are both $5HT_{2A}$ antagonism and $5HT_{1A}$ partial agonism. Perhaps these mechanisms by which they mitigate DIP serve also to mitigate the chances of getting TD.

Who amongst all those who receive drugs for psychosis will get TD and how does this happen? Some evidence suggests that those who are most vulnerable to having DIP with acute D_2 blockade may also be those who are the most vulnerable to getting TD with chronic D_2 blockade. One theory is that nigrostriatal D_2 receptors most sensitive to blockade trigger a form of undesirable neuroplasticity called supersensitivity in reaction to D_2 receptor blockade (Figures 5-6). If D_2 receptor blockade is removed early enough, TD may reverse. This reversal is theoretically due to a "resetting" of supersensitive D_2 receptors by an appropriate return to normal in the number or sensitivity of D_2 receptors in the nigrostriatal pathway once the antipsychotic drug that had been blocking these receptors is removed. However, after long-term treatment, sometimes the D_2 receptors apparently cannot reset back to normal, even when D_2 blocking drugs are discontinued. This leads to TD that is irreversible, persisting whether or not D_2 blockers are administered.

Interestingly, D_2 receptors in the motor striatum also appear to react in much the same way to chronic *stimulation* by levodopa in Parkinson's disease as they do to chronic *blockade* by D_2 antagonists/partial agonists in schizophrenia. That is, chronic levodopa administration in Parkinson's disease can lead to levodopa-induced dyskinesias that look very similar to TD, and may share a similar pathophysiology of aberrant striatal plasticity and abnormal neuronal "learning." Perhaps the lesson here is not to mess with your dopamine receptors in the motor striatum or consequences may ensue!

A more detailed view of D_2 antagonist/partial agonist effects in the nigrostriatal dopamine system is shown in Figures 5-9A, 5-9B, and 5-9C. This view was introduced in Chapter 4 and illustrated in Figures 4-13B, 4-13C, 4-13D, 4-13E, and 4-13F. Some fibers of the nigrostriatal dopamine pathway, particularly those projecting medially to the associative striatum, may be hyperactive as part of the limbic (emotional) system and contribute to the positive symptoms of psychosis (see Figure 4-16B). Other nigrostriatal dopamine projections, particularly those projecting to the sensorimotor striatum, are part of the extrapyramidal nervous system and control motor movements and those are the nigrostriatal dopaminergic neurons depicted in Figures 5-9A, 5-9B, and 5-9C.

Normally, dopamine acts at D_2 receptors in the indirect motor pathway, which is the receptor subtype present in this pathway. The so-called indirect pathway is also the pathway for "stop" actions (Figures 4-13F and 5-9A). Since D_2 receptors are inhibitory, dopamine causes inhibition of the stop pathway; a fancy way for dopamine to say "go" in this pathway (Figures 4-13B and 5-9A). Thus, dopamine at D_2 receptors in the indirect pathway triggers a "go" signal.

What happens when this action of dopamine is blocked? When acute D_2 antagonists/partial agonists are administered, this blocks the ability of dopamine to say "go" because these drugs inhibit dopamine's action in the "stop" pathway. Another way to say this is that D_2 antagonists say "stop" in the indirect pathway (Figure 5-9B). If there is too much "stop," this can result in DIP (Figure 5-9B). In technical terms, when "stop" is not inhibited by dopamine action at D_2 receptors in the indirect pathway because of the presence of a D_2 blocker, then movements are "stopped" – sometimes so much so that the slow, rigid movements of DIP are produced (Figure 5-9B).

If this situation is allowed to persist, D_2 receptors in the indirect pathway of the motor striatum hypothetically react to the acute D_2 receptor blockade shown in Figure 5-9B by "learning" to have TD when D_2 blockade becomes chronic (Figure 5-9C). The theoretical mechanism for this is a proliferation of excess numbers

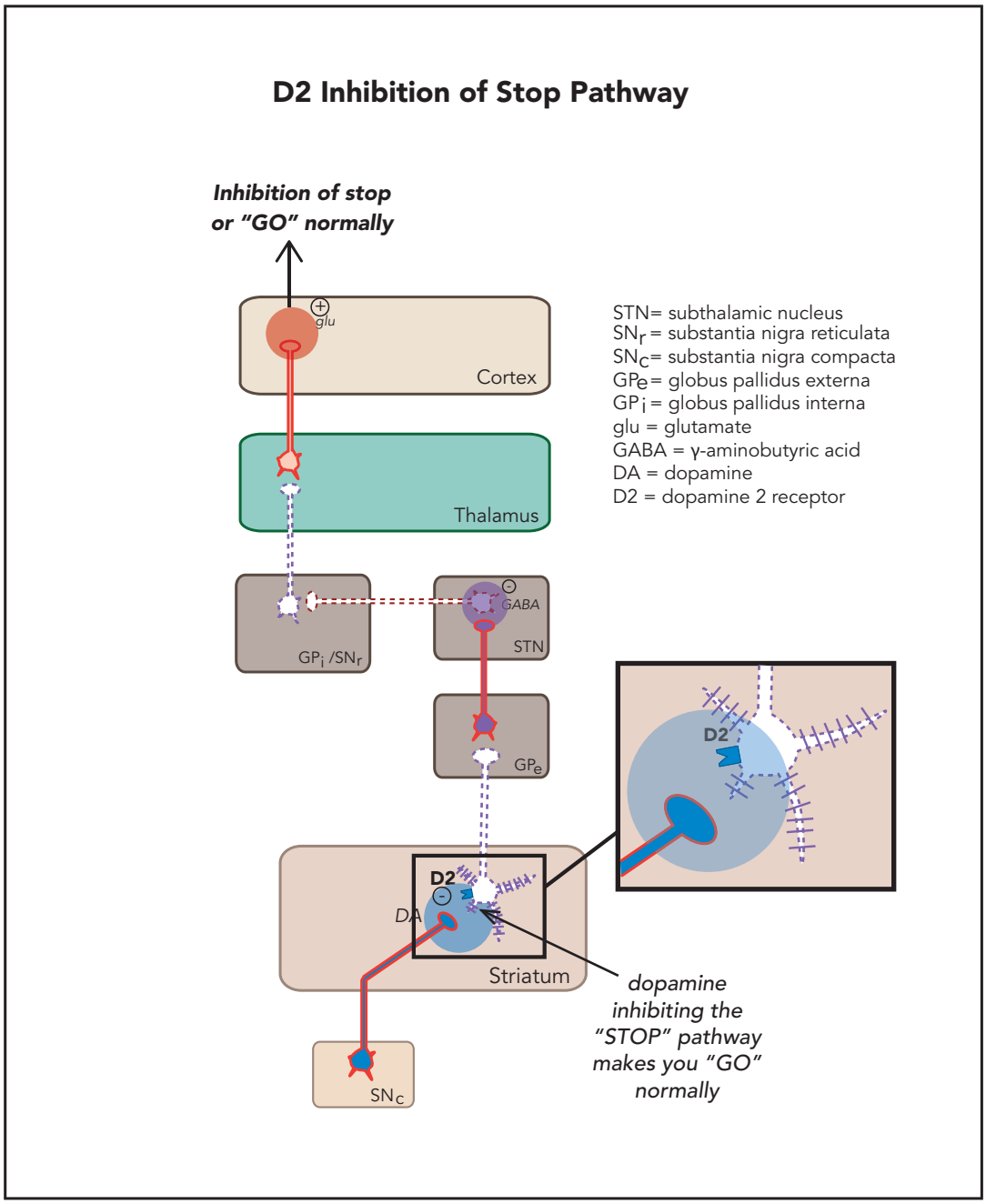


Figure 5-9A **D_2 receptor inhibition of the stop pathway.** Dopamine released from the nigrostriatal pathway binds to postsynaptic D_2 receptors on a γ-aminobutyric acid (GABA) neuron projecting to the globus pallidus externa. This causes inhibition of the indirect (stop) pathway, thus instead telling it to "go."

of D_2 receptors in the indirect motor pathway (Figure 5-9C). Perhaps the dopamine system becomes engaged in a futile attempt to overcome drug-induced blockade by making more D_2 receptors (Figure 5-9C). The result is supersensitivity of the indirect pathway to dopamine. It has been difficult to prove, but animal models and positron emission tomography (PET) scans in patients with schizophrenia do indeed suggest that chronic D_2

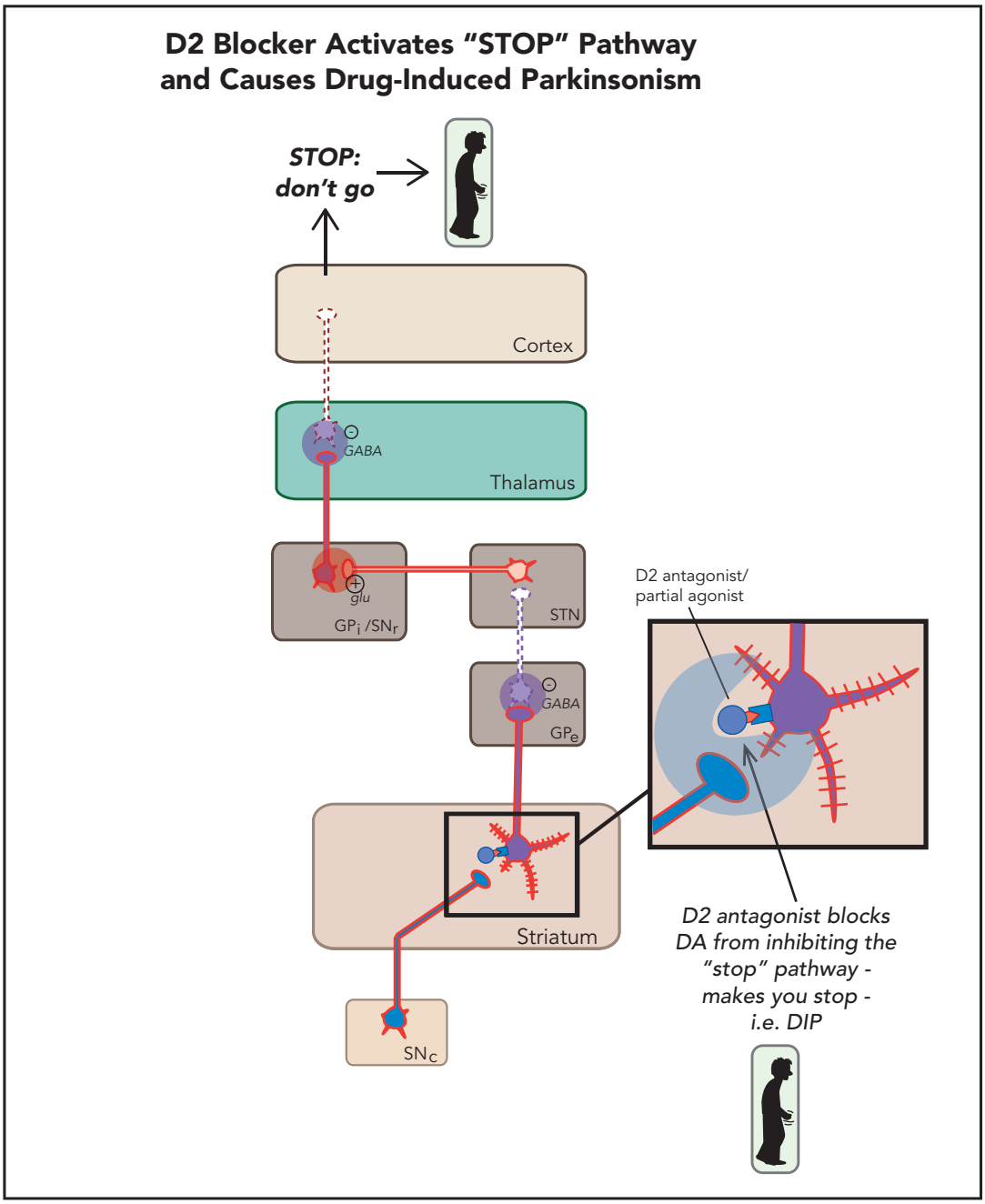


Figure 5-9B **D_2 receptor blockade activates the stop pathway.** Dopamine released from the nigrostriatal pathway is blocked from binding to postsynaptic D_2 receptors on a γ-aminobutyric acid (GABA) neuron projecting to the globus pallidus externa. This prevents inhibition of the indirect (stop) pathway; in other words, D_2 antagonists activate the indirect (stop) pathway. Too much stop can result in drug-induced parkinsonism.

blockade in the motor striatum causes upregulated, supersensitive D_2 receptors, and this happens to the greatest extent in patients with TD. Whatever is happening, it leads to the opposite situation (Figure 5-9C) to what was just described for acute blockade of D_2 receptors (Figure 5-9B). Namely, instead of not enough

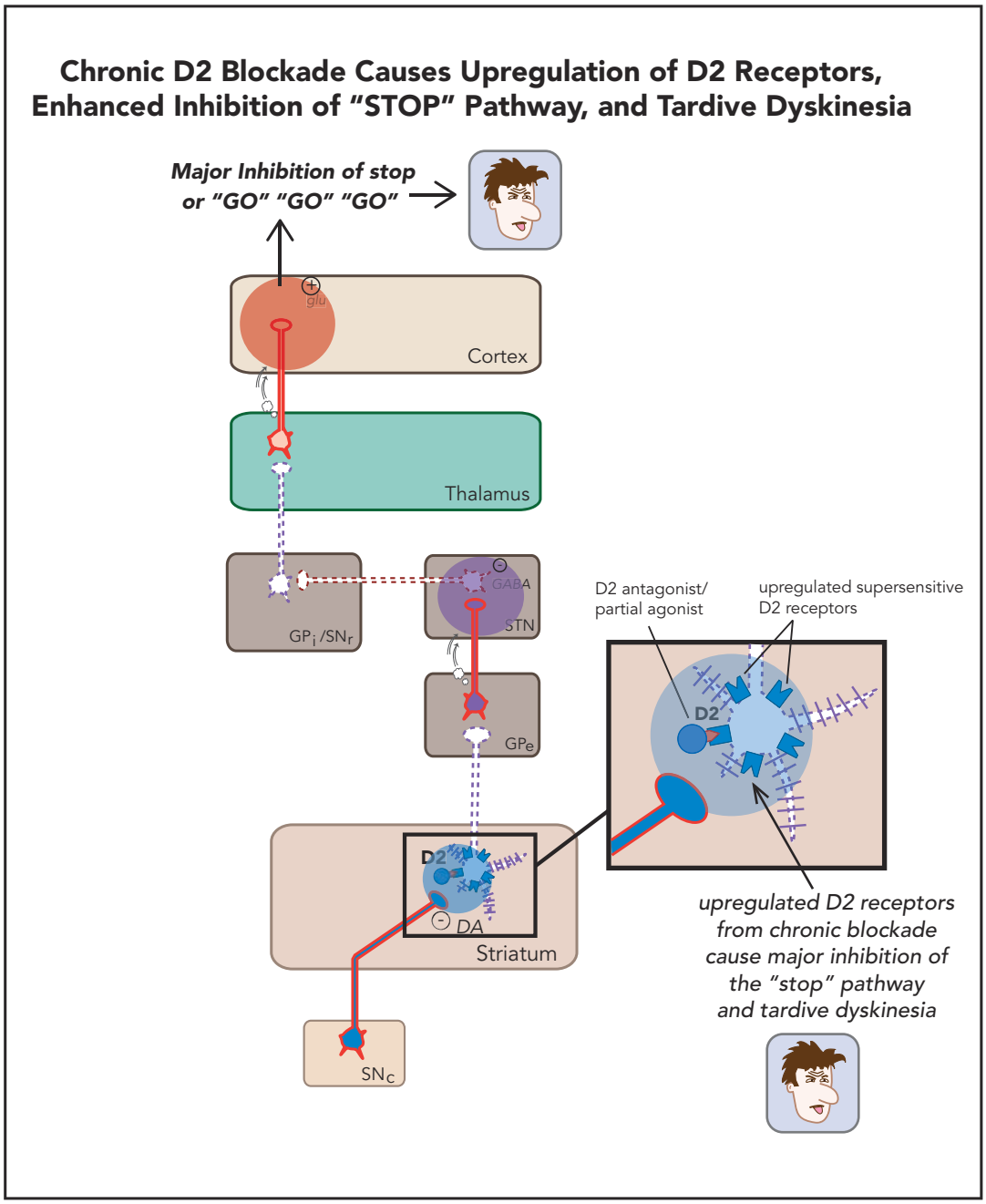


Figure 5-9C Chronic D_2 receptor blockade and overinhibition of the stop pathway. Dopamine released from the nigrostriatal pathway is blocked from binding to postsynaptic D_2 receptors on a γ-aminobutyric acid (GABA) neuron projecting to the globus pallidus externa. Chronic blockade of these receptors can lead to their upregulation; the upregulated receptors may also be "supersensitive" to dopamine. Dopamine can now exert its inhibitory effects in the indirect (stop) pathway, and in fact cause so much inhibition of the "stop" signal that the "go" signal is overactive, leading to the hyperkinetic involuntary movements of tardive dyskinesia.

inhibition of stop signals from acute D_2 blockade (Figure 5-9B), there is now too much inhibition of stop signals from chronic D_2 blockade (Figure 5-9C). The situation has flipped from slow rigid movements of DIP (Figure 5-9B) to rapid hyperkinetic involuntary movements of TD (Figure 5-9C).

What is the mechanism that causes the indirect pathway to flip from too much stop to too much go? The answer may be abnormal neuronal plasticity causing the proliferation of too many and too sensitive D_2 receptors in the indirect pathway (Figure 5-9C). Now, all of a sudden, instead of not enough dopamine at D_2 receptors (Figure 5-9B), there is too much dopamine at too many D_2 receptors (Figure 5-9C). The motor striatum translates this into excessive inhibition of the "stop" signal; thus, "not enough stop" and "too much go." Therefore, neuronal impulse traffic out of the striatum no longer has an enforced speed limit, and thus, the involuntary hyperkinetic movements of TD emerge.

The emergence of abnormal involuntary movements of TD should be specifically monitored, using a neurological examination and a rating scale such as the AIMS (Abnormal Involuntary Movement scale) periodically. Best practices are to monitor movements in anyone taking any of these drugs, although it is frequently not done, and especially not done in patients being treated for depression, unfortunately. If anything, patients with mood disorders may be at greater risk for TD. Remember, these are the same drugs no matter in whom they are used.

Treatment

If the brain has literally "learned" to have TD in an aberrant attempt to compensate for chronic D_2 blockade and this has resulted in unwanted dopamine overstimulation in the indirect pathway, then TD would seem to be a disorder ideally set up to respond to interventions that lower dopamine neurotransmission. How can this be done?

One way is to raise the dose of D_2 antagonist to block those numerous new upregulated and supersensitive D_2 receptors. Although this might work short-term in some patients, it is done at the expense of more immediate side effects and the prospects of making TD even worse down the road. Another treatment possibility is to stop the offending D_2 antagonist with the hope that the motor system will readjust back to normal on its own and that the movement disorder will reverse. Many patients who do not have an underlying psychotic disorder may be able to tolerate the discontinuation of their D_2 antagonist/partial agonist, but most patients with psychosis may not be able to tolerate D_2 antagonist/partial agonist discontinuation. Furthermore, it does not seem that the TD brain can "forget" its aberrant neuroplastic learning very well, and only some patients – particularly those who discontinue D_2 blockade soon after the onset of their TD movements – will likely enjoy reversal of their TD. In fact, most patients experience an immediate worsening of their movements when D_2 blockade is eliminated, due to the completely unblocked actions of dopamine in the absence of any D_2 antagonist therapy at all. Thus, D_2 antagonist drug discontinuation is often not an option in the treatment of TD.

Recent developments show that TD can now be successfully treated by inhibiting the vesicular monoamine transporter type 2 (VMAT2). Presynaptic transporters for neurotransmitters released into the synapse were discussed in Chapter 2 (see Table 2-3 and Figures 2-2A and 2-2B). These transporters are localized on the presynaptic axon terminal and are well known as "reuptake pumps" targeted by many drugs for depression (Figures 2-2A and 2-2B; see also discussion of monoamine reuptake blockers in Chapter 6 on drugs for depression). Transporters also exist for neurotransmitters that are inside neurons; these intraneuronal transporters are located on synaptic vesicles and called vesicular transporters. Several types of vesicular transporters have been identified, including different ones for GABA (γ-aminobutyric acid), glutamate, glycine, acetylcholine, monoamines, and others (see Chapter 2 and Figures 2-2A and 2-2B). The specific transporter known as VMAT2 is located on synaptic vesicles inside dopamine, norepinephrine, serotonin, and histamine neurons. VMAT2 acts to store intraneuronal neurotransmitters until they are needed for release during neurotransmission (Figure 5-10A). VMAT2 can also transport certain drugs as "false" substrates, such as amphetamine and "Ecstasy" (MDMA; 3,4-methylene-dioxymethamphetamine), and these false substrates can compete with the "true" natural neurotransmitter and block it from being transported. This is discussed in further detail in Chapter 11 on stimulant treatment for attention deficit hyperactivity disorder, and in Chapter 13 on substance abuse. Synaptic vesicles create low pH in their lumens (interiors) with an energy-requiring proton pump there (Chapter 2 and Figures 2-2A and 2-2B). Low pH in turn serves as the driving force to sequester neurotransmitter in synaptic vesicles.

There are actually two types of VMATs: VMAT1 localized on synaptic vesicles of neurons in both the peripheral and central nervous system, and VMAT2, located only on synaptic vesicles within central nervous system neurons. There are also two known types of VMAT inhibitors: reserpine, which irreversibly inhibits

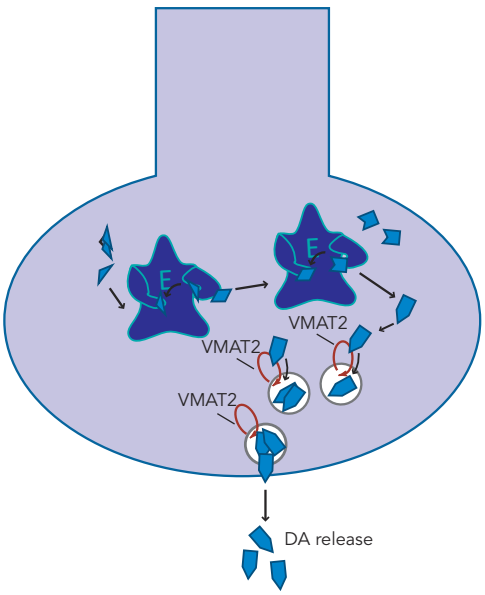


Figure 5-10A Vesicular monoamine transporter 2 (VMAT2) and dopamine. The VMAT2 is an intraneuronal transporter located on synaptic vesicles. VMAT2 takes intraneuronal monoamines, including dopamine, up into the synaptic vesicles so that they can be stored until they are needed for release during neurotransmission.

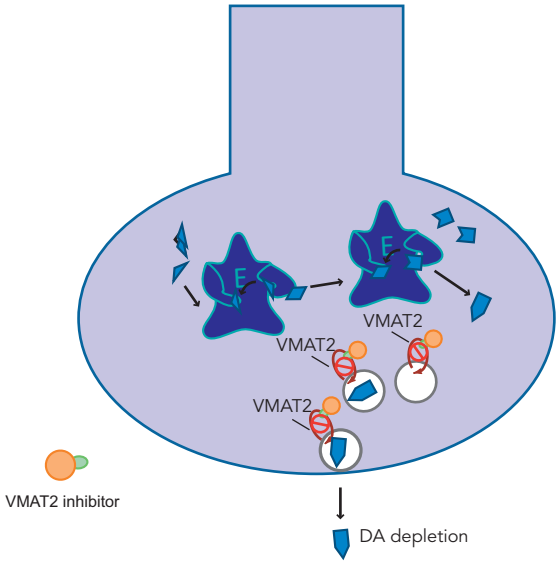


Figure 5-10B Dopamine depletion by VMAT2 inhibition. Inhibition of VMAT2 prevents dopamine from being taken up into synaptic vesicles. The intraneuronal dopamine is therefore metabolized, leading to depletion of dopamine stores.

both VMAT1 and VMAT2; and tetrabenazine-related drugs, which reversibly inhibit only VMAT2. That is why reserpine, but not tetrabenazine-related drugs, is associated with frequent peripheral side effects, such as orthostatic hypotension (reserpine was once used for hypertension), stuffy nose, itching, and gastrointestinal side effects. Although VMAT2 transports multiple neurotransmitters into synaptic vesicles (dopamine, norepinephrine, serotonin, and histamine), tetrabenazine preferentially affects dopamine transport at clinical doses (Figure 5-10B). When tetrabenazine-related drugs block the transport of dopamine into presynaptic vesicles, dopamine is rapidly degraded by monoamine oxidase (MAO) within the presynaptic neuron, leading to depletion of presynaptic dopamine proportional to the degree of VMAT2 inhibition (Figure 5-10B).

Tetrabenazine itself is actually an inactive prodrug converted into four active dihydro metabolites by the enzyme carbonyl reductase, and all four are inactivated by CYP450 2D6 (Figure 5-11A). Most of the inhibition of VMAT2 by tetrabenazine is ultimately done by the +β-dihydro enantiomer because it has the greatest potency for VMAT2 of those metabolites that inhibit VMAT2 (Figure 5-11A). Tetrabenazine is not approved for the treatment of TD, but is approved for the treatment of a related hyperkinetic movement disorder, namely, the chorea of Huntington's disease. Tetrabenazine's disadvantages are its short half-life and thus need for three times a day dosing; its peak-dose side effects, including sedation and drug-induced parkinsonism; the need to do genetic testing for poor metabolizers of CYP450 2D6 in order to go to higher doses; and the risk of depression and even suicide when used to treat Huntington's disease.

A clever trick called deuteration has recently been discovered that converts a drug that is a good substrate for CYP450 2D6 into a poorer substrate for CYP450 2D6; this allows for a longer half-life, less frequent dosing, and lower peak plasma levels. Deuteration is the process of substituting some of the hydrogen atoms in a drug with deuterium, also called heavy hydrogen. Deuterium is a stable isotope of hydrogen with a nucleus consisting of one proton and one neutron, which is double the mass of the nucleus of ordinary hydrogen that contains only one proton. This substitution causes the drug to be a less favorable substrate for CYP450 2D6,

resulting in the predicted increased half-life, decreased dosing frequency (twice rather than three times a day), and reduced peak-dose side effects, all problems with non-deuterated tetrabenazine mentioned above. For commercial considerations, deuteration can also restart the patent life of the non-deuterated drug, creating incentives for drug development. Other advantages of deuterated tetrabenazine, also called deutetrabenazine, are specific regulatory approval for the treatment of TD as well as Huntington's disease, no longer needing to do genetic testing in order to administer the full dose range, and the lack of a suicide warning for treatment of TD. Disadvantages include need for twice daily administration and dosing with food.

The metabolites of deutetrabenazine (Figure 5-11B) are the same as those of nondeuterated tetrabenazine (Figure 5-11A). In addition to the +β-dihydro enantiomer, both tetrabenazine and deutetrabenazine have substantial concentrations of the –α- and the –β-dihydro enantiomers, which carry additional receptor actions, especially antagonism of $5HT_7$ receptors and to a lesser extent antagonism of D_2 receptors (Figures 5-11A and 5-11B).

Another form of tetrabenazine is called valbenazine, named because the amino acid valine is linked to the +α enantiomer of tetrabenazine. When swallowed, valbenazine is hydrolyzed into valine and +α-tetrabenazine, which is rapidly converted by carbonyl reductase to just the +α dihydro enantiomer of tetrabenazine, the most selective and potent inhibitor of VMAT2 amongst the four active enantiomers (Figure 5-11C). The slow hydrolysis of valbenazine results in a long half-life and once-daily administration. Valbenazine is approved for the treatment of TD, has no need for genetic testing, no need for dosing with food, once-daily dosing, and no suicide warning.

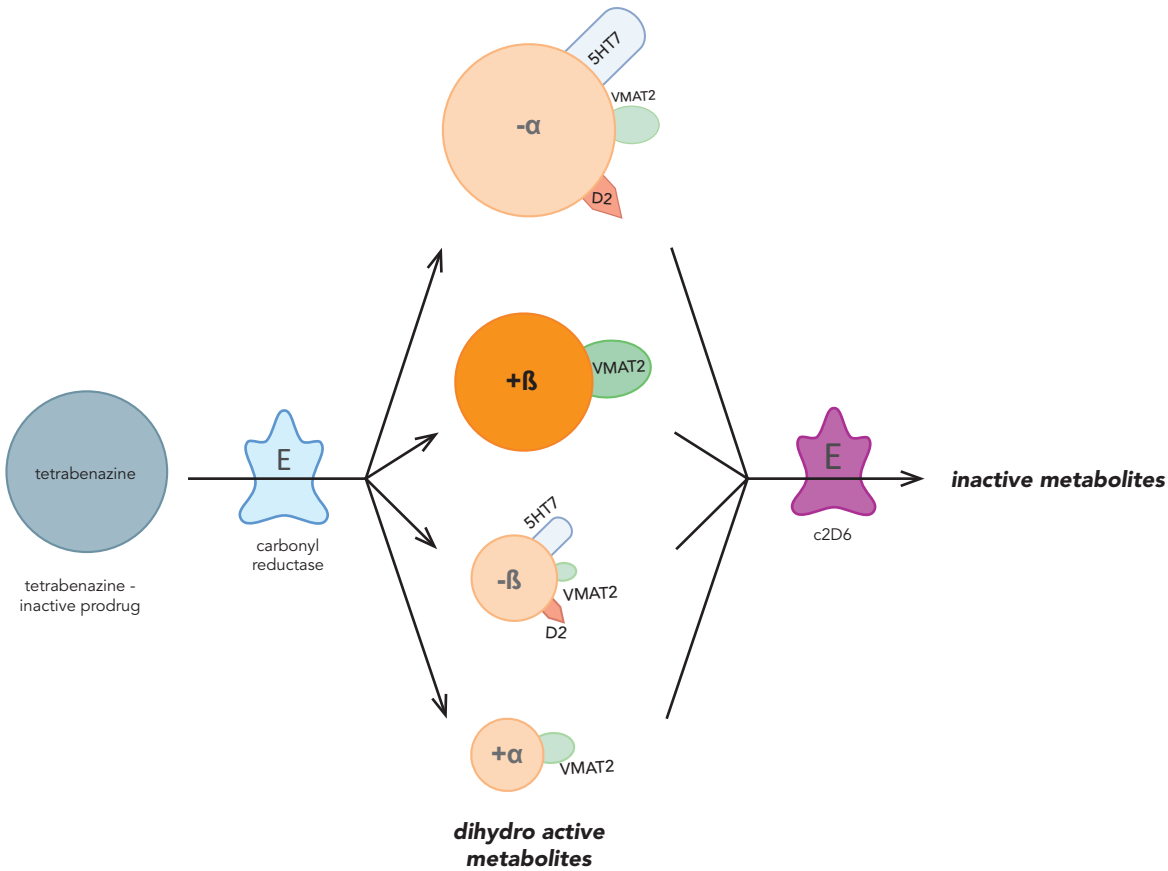


Figure 5-11A Tetrabenazine potency. Tetrabenazine is an inactive prodrug; its metabolism by carbonyl reductase results in four active dihyro metabolites, all of which are converted into inactive metabolites by CYP450 2D6. Of the four active metabolites, the +β-dihydro enantiomer has the greatest potency for VMAT2 and thus is responsible for most of tetrabenazine's therapeutic effects. The other active metabolites have additional receptor actions, as shown.

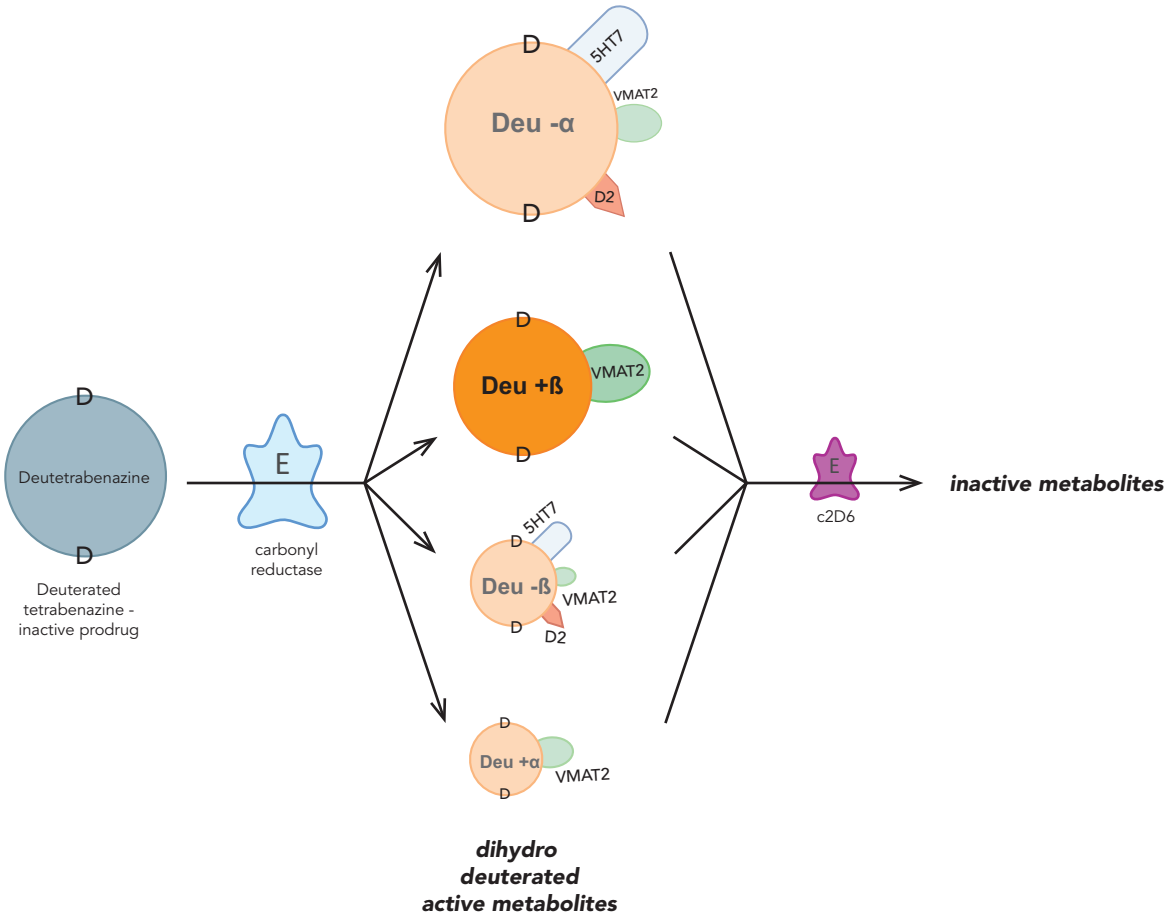


Figure 5-11B Deutetrabenazine potency. Deuteration is the process of substituting some of the hydrogen atoms in a drug with deuterium. Deuterium has one proton and one neutron and is thus double the mass of hydrogen. The substitution of deuterium for hydrogen makes it a less favorable substrate for CYP450 2D6 (shown with the smaller c2D6 enzyme compared to Figure 5-11A). This allows for a longer half-life, decreased dosing frequency, and reduced peak-dose side effects.

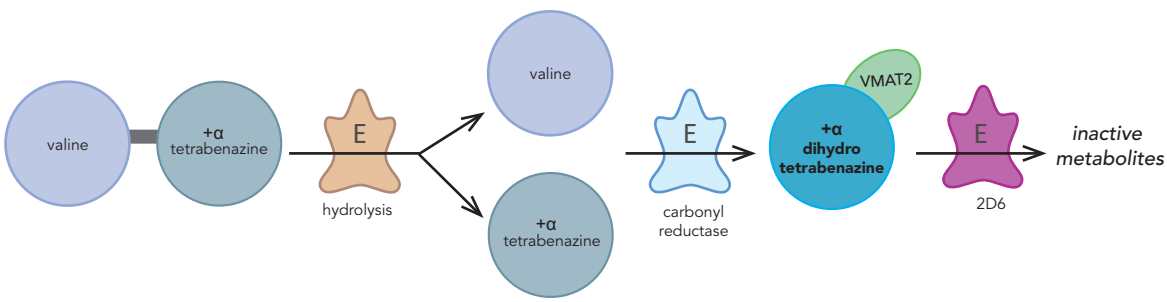


Figure 5-11C Valbenazine potency. Valbenazine is tetrabenazine with the amino acid valine linked to the +α enantiomer of tetrabenazine. When swallowed, valbenazine is hydrolyzed into valine and +α tetrabenazine and then rapidly converted by carbonyl reductase into +α-dihydrotetrabenazine. The slow hydrolysis results in a long half-life and once-daily dosing.

A more detailed explanation of the mechanism of action of VMAT2 inhibition on TD is shown in Figures 5-12A through 5-12D within both the direct and indirect pathways. The state of normal movements condition is shown in Figure 5-12A, where dopamine at the bottom left is enhancing "go" in the direct pathway at

D_1 receptors and at the bottom right where dopamine is inhibiting "stop" in the indirect pathway at D_2 receptors. The striatum regulates normal motor movements by facilitating or diminishing dopamine release at the direct and indirect pathways as it orchestrates the smooth execution of movements and postures that require muscles to go or to stop, often in sequence and in changing ways over time (Figure 5-12A).

Figure 5-12B shows the situation when TD develops, with the upregulation of D_2 receptors on the bottom right in the indirect pathway causing far too much inhibition of stop, and thus the message "go, go, go," with the result being the hyperkinetic involuntary movements of TD. This was also explained above and shown in Figure 5-9C.

Figures 5-12C and 5-12D show the mechanism of action of VMAT2 inhibition in TD. No matter what form of tetrabenazine is chosen to block VMAT2 in order to treat TD, it appears that a high degree, perhaps >90%, of VMAT2 inhibition may often be required for the best balance between efficacy for TD and tolerability. VMAT2 inhibition is a mechanism that reduces dopamine stimulation without blocking D_2 receptors. Thus, this action reduces the overstimulation of D_2 receptors in the indirect pathway (bottom right in Figure 5-12C), resulting in less inhibition of the stop signal there. However, there is also a benefit of VMAT2 inhibition in the direct pathway, where "go" signals are being amplified normally by dopamine at D_1 receptors (Figure 5-12A). Even though these D_1 receptors and this direct extrapyramidal pathway (Figure 5-12A) may not be the site of pathology in TD (see Figures 5-9C and 5-12B), they do drive "go" signals for movement normally (Figure 5-12A), and thus lowering dopamine there by

Normal Regulation of Motor Movements by Dopamine: Enhancing "Go" at D1 Receptors in the Direct Pathway and Inhibiting "Stop" at D2 Receptors in the Indirect Pathway

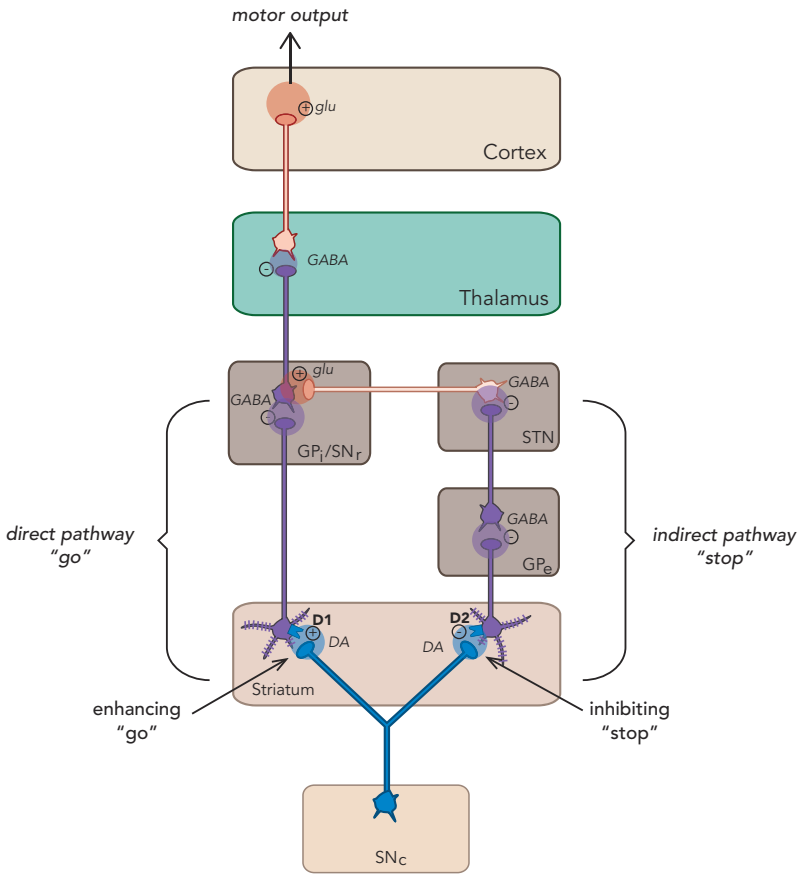


Figure 5-12A Normal regulation of motor movements by dopamine. Dopamine regulates motor movements through both the direct (go) and indirect (stop) pathways. In the direct pathway (shown on the left), dopamine released into the striatum binds to D_1 receptors on GABA neurons. This stimulates GABA release, which ultimately leads to glutamate release in the cortex and thus enhances motor output. In the indirect pathway (shown on the right), dopamine released into the striatum binds to D_2 receptors on GABA neurons. This inhibits GABA release, thus inhibiting the "stop" pathway, and therefore also enhancing motor output.

Tardive Dyskinesia: Upregulated D2 Receptors in the Indirect Pathway and Too Much "GO"

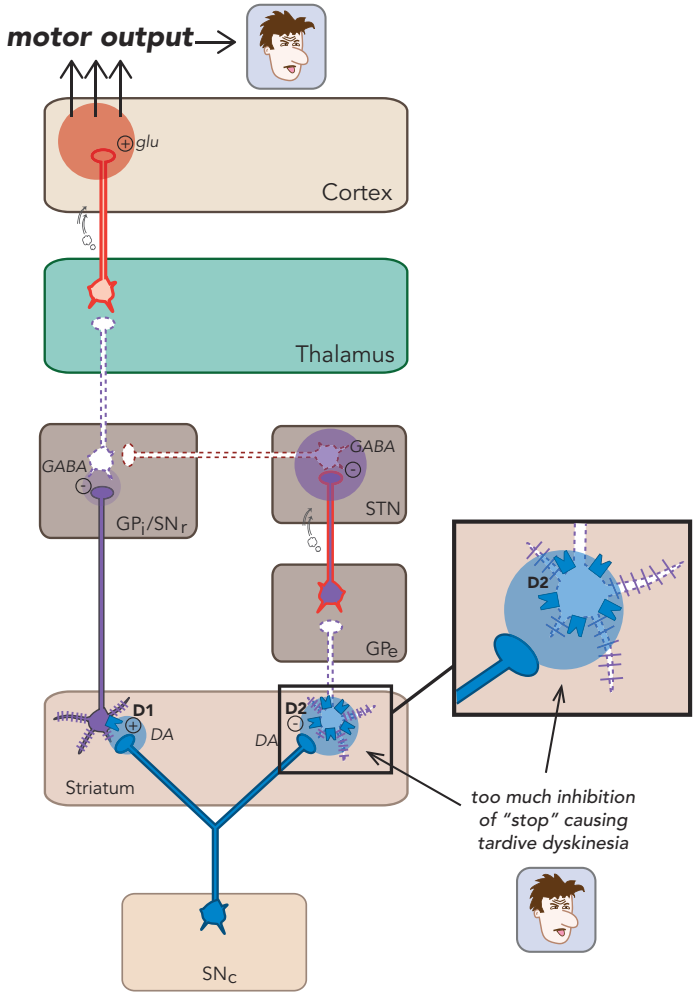


Figure 5-12B Upregulation of dopamine 2 receptors in the indirect pathway. Chronic blockade of D_2 receptors can lead to their upregulation; the upregulated receptors may also be supersensitive to dopamine. In the indirect (stop) pathway, this can lead to so much inhibition of the "stop" signal that the "go" signal is overactive, leading to the hyperkinetic involuntary movements of tardive dyskinesia.

VMAT2 inhibition would be expected to lower the "go" signals arising from the direct pathway (Figure 5-12D). Combined with more "stop" signals from the indirect pathway (Figure 5-12C), motor output to drive abnormal involuntary hyperkinetic movements is therefore robustly reduced by this combination of effects of dopamine depletion in both pathways (Figures 5-12C and 5-12D). So, it appears that VMAT2 inhibition "trims" the "go" drives of dopamine in both direct and indirect motor pathways (Figures 5-12C and 5-12D) to compensate for the abnormal "learning" just in the indirect pathway after chronic D_2 receptor blockade (Figures 5-9C and 5-12B). Whether this will be disease modifying in the long run, and reverse rather than only treat movements symptomatically, must be determined by long-term studies of VMAT2 inhibition in TD.

DRUGS TARGETING DOPAMINE D_2 RECEPTORS: SO-CALLED FIRST GENERATION OR CONVENTIONAL "ANTIPSYCHOTICS"

A list of many of the earliest agents used to treat psychosis is given in Table 5-1. Several of these remain in clinical use today. Although not generally used first line, conventional D_2 antagonists are still used in patients who do not respond to the newer drugs for psychosis and

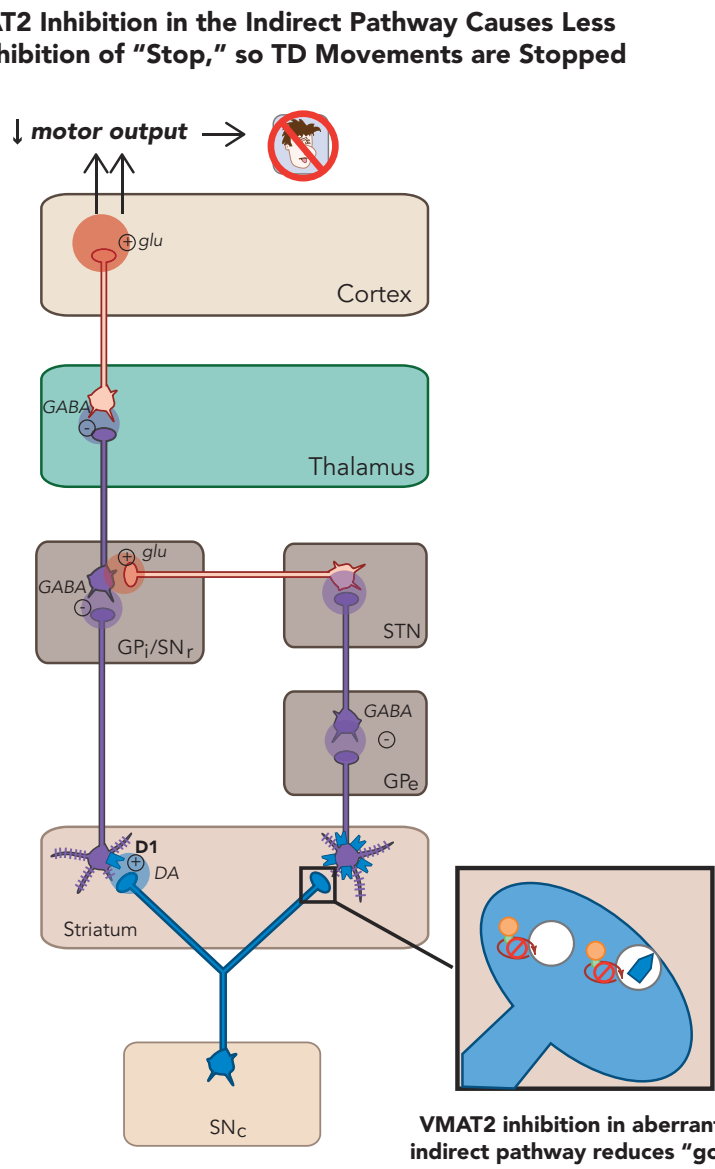


Figure 5-12C VMAT2 inhibition in the indirect (stop) pathway. VMAT2 inhibition reduces dopaminergic output; thus, it can reduce the overstimulation of inhibitory D_2 receptors in the indirect (stop) pathway. This disinhibits the indirect (stop) pathway and therefore can reduce the hyperkinetic movements of tardive dyskinesia.

in patients requiring injections, both immediate-onset and long-acting injections. Several of the first-generation drugs for psychosis are available both orally and as injections and many clinicians still have experience with them, even preferring them in treatment-resistant and difficult cases. Although these original drugs for psychosis (Table 5-1) are often called "conventional," "classic," or "first-generation" antipsychotics, we will continue to refer to drugs as "having antipsychotic actions" and not as "antipsychotics," to reduce confusion, since many of these same agents are used to treat many other conditions, including bipolar mania, psychotic mania, psychotic depression, Tourette syndrome, and even for gastrointestinal problems including gastroesophageal reflux, gastroparesis from diabetes, and to prevent/treat nausea and vomiting including from cancer chemotherapy. So, not just antipsychotic actions! Modern nomenclature for the drugs in this group of original agents for psychosis is "D_2 antagonists" because this is the common pharmacological mechanism for all uses, not just for antipsychotic actions.

D_2 antagonists have various other pharmacological properties, including muscarinic cholinergic antagonism (discussed above, see Figure 5-8), antihistaminic actions (H_1 antagonism), and α_1-adrenergic antagonism (Figure 5-13). These additional pharmacological

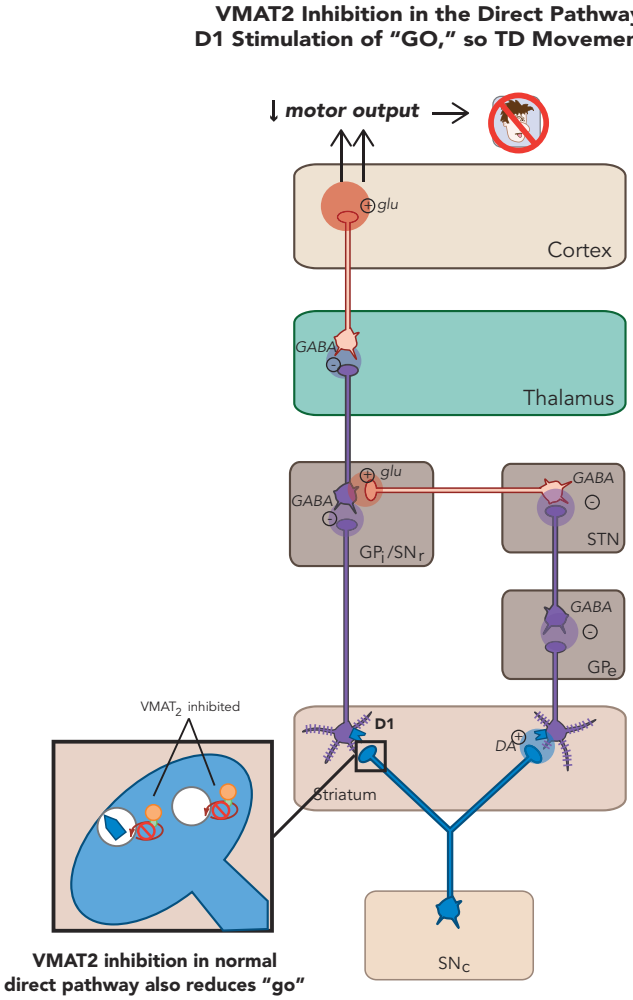


Figure 5-12D VMAT2 inhibition in the direct (go) pathway. VMAT2 inhibition reduces dopaminergic output; thus, it can reduce activation of excitatory D_1 receptors in the direct (go) pathway. This inhibits the direct (go) pathway and therefore can reduce the hyperkinetic movements of tardive dyskinesia.

properties are linked much more to side effects than to therapeutic effects. Blockade of muscarinic cholinergic receptors is associated with dry mouth, blurred vision, and risk of paralytic ileus as discussed earlier (Figure 5-8); blocking H_1 histamine receptors is associated with weight gain and sedation (Figure 5-13A); and blockade of α_1-adrenergic receptors is associated with sedation as well as cardiovascular side effects such as orthostatic hypotension (Figure 5-13B). As many D_2 antagonists have all three actions, anticholinergic, antihistaminic, and α_1 antagonist, they can combine to contribute to a great deal of sedation by simultaneously blocking several of the neurotransmitters in the arousal pathway; namely, acetylcholine, histamine, and norepinephrine (Figure 5-14). Agents with particularly strong binding at these three receptors (such as chlorpromazine) are sometimes administered when sedation is needed on top of antipsychotic action. However, even if sedation is needed in some clinical situations, it is not always desirable. Conventional D_2 antagonists (Table 5-1) differ in terms of their ability to block muscarinic, histaminic, and α_1-adrenergic receptors. For example, the popular conventional antipsychotic haloperidol has relatively little anticholinergic or antihistaminic binding activity. Because of this, conventional D_2 antagonists differ somewhat in their side-effect profiles, even if they do not differ overall in their therapeutic profiles. That is, some D_2 blockers are more sedating than others; some have more ability to cause cardiovascular side effects than others, some have more ability to cause DIP and other movement disorders than others. Differing degrees of muscarinic cholinergic blockade may explain why some D_2 antagonists have a lesser propensity to produce DIP than others. That is, those D_2 antagonists that are more likely to cause DIP are generally the agents that have only *weak* anticholinergic properties, whereas those D_2

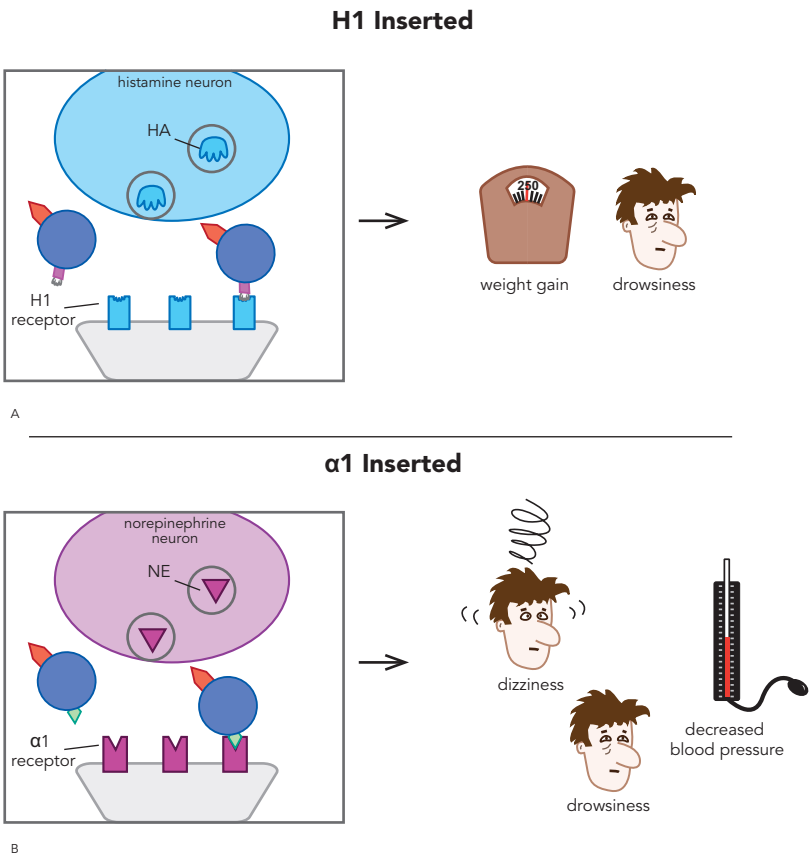


Figure 5-13 Blockade of histamine 1 and α_1-adrenergic receptors. The majority of D_2 antagonists have additional pharmacological properties; the specific receptor profiles differ for each agent and contribute to divergent side-effect profiles. Many of the early D_2 antagonists also block H_1 receptors (A), which can contribute to weight gain and drowsiness, and/or α_1-adrenergic receptors (B), which can contribute to dizziness, drowsiness, and decreased blood pressure.

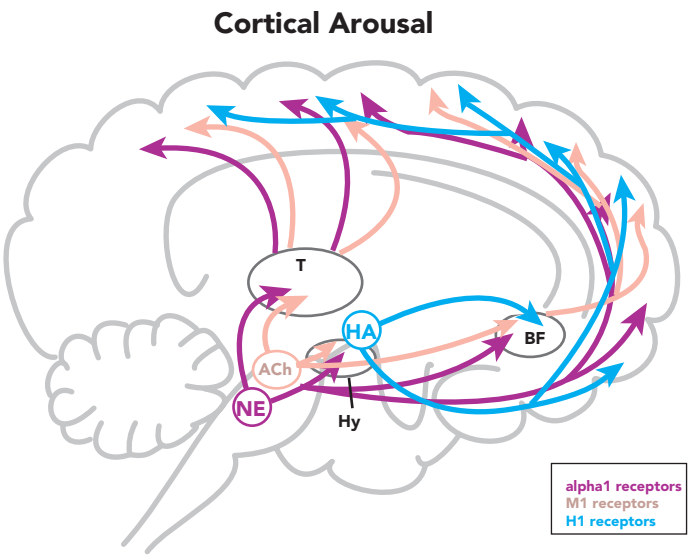


Figure 5-14 Neurotransmitters of cortical arousal. The neurotransmitters acetylcholine (ACh), histamine (HA), and norepinephrine (NE) are all involved in arousal pathways connecting neurotransmitter centers with the thalamus (T), hypothalamus (Hy), basal forebrain (BF), and cortex. Thus, pharmacological actions at their receptors could influence arousal. In particular, antagonism of muscarinic M_1, histamine H_1, and α_1-adrenergic receptors are all associated with sedating effects.

Table 5-1 Earliest agents used to treat psychosis

Generic name	Trade name	Comment
Chlorpromazine	Thorazine	Low potency
Cyamemazine	Tercian	Popular in France; not available in the US
Flupenthixol	Depixol	Depot; not available in the US
Fluphenazine	Prolixin	High potency; depot
Haloperidol	Haldol	High potency; depot
Loxapine	Loxitane	
Mesoridazine	Serentil	Low potency; QTc issues; discontinued
Perphenazine	Trilafon	High potency
Pimozide	Orap	High potency; Tourette syndrome; QTc issues; second line
Pipothiazine	Piportil	Depot; not available in the US
Sulpiride	Dolmatil	Not available in the US
Thioridazine	Mellaril	Low potency; QTc issues; second line
Thiothixene	Navane	High potency
Trifluoperazine	Stelazine	High potency
Zuclopenthixol	Clopixol	Depot; not available in the US

blockers that cause DIP less frequently are the agents that have *stronger* anticholinergic properties. These latter agents have a sort of "inbuilt" anticholinergic property that accompanies their D_2 antagonist property. Although DIP may occur less frequently with such agents, the risk of constipation and potential for life-threatening paralytic ileus is higher, especially when combined with other drugs with anticholinergic properties, and requires more monitoring of gastrointestinal status and bowel movements. A few selected agents from the first-generation class of D_2 antagonists are discussed in more detail below.

DRUGS TARGETING SEROTONIN 2A RECEPTORS WITH OR WITHOUT SIMULTANEOUSLY TARGETING DOPAMINE D_2 RECEPTORS

In an attempt to improve the efficacy and the tolerability of the first-generation classic drugs for psychosis with D_2 antagonist properties, a newer class of drugs with antipsychotic action combines D_2 antagonism with serotonin (5HT) 2A antagonism, so-called second-generation antipsychotics or atypical antipsychotics. We will refer to them as $5HT_{2A}$ antagonists/D_2 antagonists with antipsychotic properties, and not as "antipsychotics" or "atypical antipsychotics." An even newer class of drugs with antipsychotic properties are agents with $5HT_{2A}$ antagonism without any D_2 antagonism. Some preclinical studies suggest that all known $5HT_{2A}$ antagonists may actually be inverse agonists (see Chapter 2 and Figures 2-9 and 2-10) rather than antagonists at $5HT_{2A}$ receptors (Figure 5-15). Since it is not clear what clinical distinction there is between an inverse agonist (Chapter 2 and Figures 2-9 and 2-10) and an antagonist (Figures 2-6 and 2-10) at $5HT_{2A}$ receptors, we will continue to refer to these agents using the simpler term "antagonist."

Antagonism of serotonin $5HT_{2A}$ receptors appears to improve both the efficacy and the side effects of D_2 antagonism:

Schizophrenia. Clinical trials show that adding selective $5HT_{2A}$ antagonists to drugs with D_2 antagonism/partial agonism may improve positive symptoms of psychosis in schizophrenia. Also, there is some indication that the more potent a $5HT_{2A}/D_2$ antagonist is for $5HT_{2A}$ receptors compared to potency for D_2 receptors, the lower the degree of D_2 antagonism that may be necessary to treat positive symptoms, and also the better tolerated the drug might be. More research is necessary on this possibility.

Parkinson's disease psychosis and dementia-related psychosis. Antagonism of serotonin $5HT_{2A}$ receptors alone appears to provide sufficient antipsychotic action to be useful as monotherapy for other causes of psychosis, such as Parkinson's disease psychosis and dementia-related psychosis, allowing D_2 antagonism and its side effects to be avoided entirely.

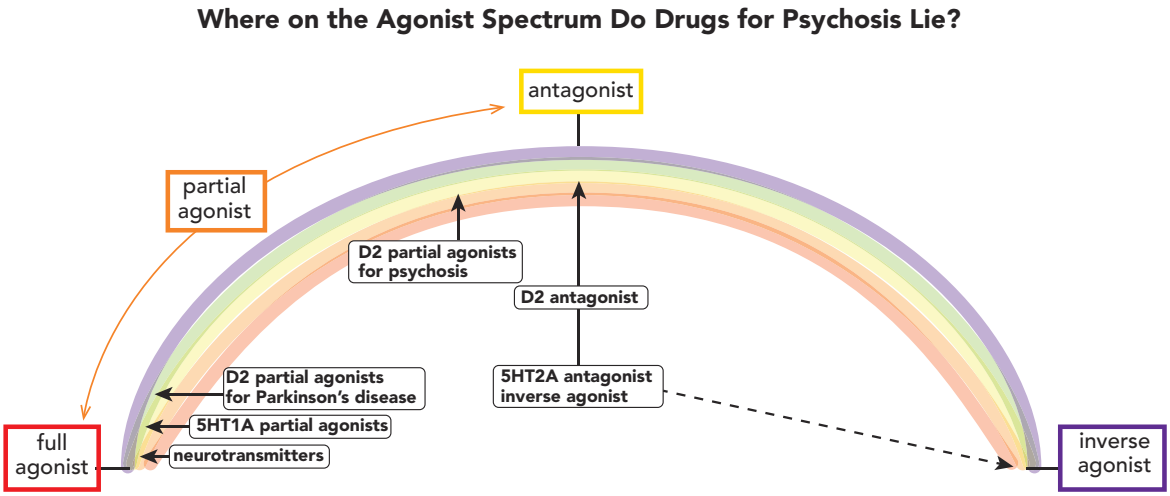


Figure 5-15 Agonist spectrum for drugs to treat psychosis. Drugs used to treat psychosis may fall along a spectrum, with some having actions closer to a silent antagonist and others having actions closer to a full agonist. For dopamine 2 (D_2) binding, agents with too much agonism may be psychotomimetic and thus not ideal for treating psychosis, but may be useful within Parkinson's disease. D_2 partial agonists that are closer to the antagonist end of the spectrum may be preferred for treating psychosis, as are D_2 antagonists. Many drugs used to treat psychosis are serotonin $5HT_{2A}$ antagonists, either in conjunction with D_2 binding or without D_2 binding. Some preclinical data suggest that they may actually be inverse agonists, but the clinical significance of this distinction is unclear. $5HT_{1A}$ partial agonism is also a common property of many drugs used to treat psychosis, in particular many D_2 partial agonists.

Negative symptoms of psychosis in schizophrenia. Clinical trials show that administering selective $5HT_{2A}$ antagonists by themselves, or adding selective $5HT_{2A}$ antagonists to drugs with D_2 antagonism/partial agonism, may improve negative symptoms in schizophrenia.

Motor side effects. Adding $5HT_{2A}$ antagonist actions to D_2 antagonism has also proven to lessen unwanted motor side effects such as drug-induced parkinsonism.

Hyperprolactinemia. Adding $5HT_{2A}$ antagonist actions to D_2 antagonism lessens the elevation of prolactin caused by D_2 receptor blockade.

Why would adding $5HT_{2A}$ antagonism improve side effects of D_2 blockade and enhance the antipsychotic efficacy of D_2 blockade? The short answer may be that $5HT_{2A}$ antagonism *opposes* D_2 antagonism in some pathways by causing more dopamine release in these sites and thus reversing some of the unwanted D_2 antagonism that causes side effects. On the other hand, because of the differing configuration of other brain circuits, $5HT_{2A}$ antagonism can *enhance* the efficacy of D_2 antagonism in another circuit and thus improve positive symptoms. Let's now explain this.

$5HT_{2A}$ Receptor Regulation of Dopamine Release in Three Downstream Pathways

The key to understanding why adding $5HT_{2A}$ antagonism creates entirely new classes of drugs to treat psychosis with reduced side-effect burden is to grasp the pharmacology of $5HT_{2A}$ receptors, where they are located, and what happens to dopamine when $5HT_{2A}$ receptors are blocked. All $5HT_{2A}$ receptors are postsynaptic and excitatory. The $5HT_{2A}$ receptors critical to this discussion are the ones located on three separate populations of cortical glutamatergic pyramidal neurons that are all naturally stimulated by serotonin at their $5HT_{2A}$ receptors to release glutamate downstream. These three separate populations of descending glutamate neurons regulate three distinct dopamine pathways (Figure 5-16).

One population of glutamatergic pyramidal neurons *directly* innervates mesolimbic/mesostriatal dopamine neurons projecting to the *emotional striatum* that mediates the positive symptoms of psychosis (Figure 5-16A). This very same pathway was discussed extensively in Chapter 4 and illustrated in Figures 4-29A–C through 4-45. The glutamate neuron depicted in Figure 5-16A is that same glutamate neuron in the final common pathway of positive symptoms of psychosis (Figures 4-29B, 4-52C, 4-52D, 4-54, and 4-55). Specifically, this neuron is the hypothetical final common pathway downstream from all causes of positive symptoms of psychosis, whether in schizophrenia from hypofunctioning glutamate receptors on GABA interneurons (Figure 4-29B), in dementia-related psychosis from loss of these same GABA interneurons (Figure 4-52D and Figure 4-55), in Parkinson's disease

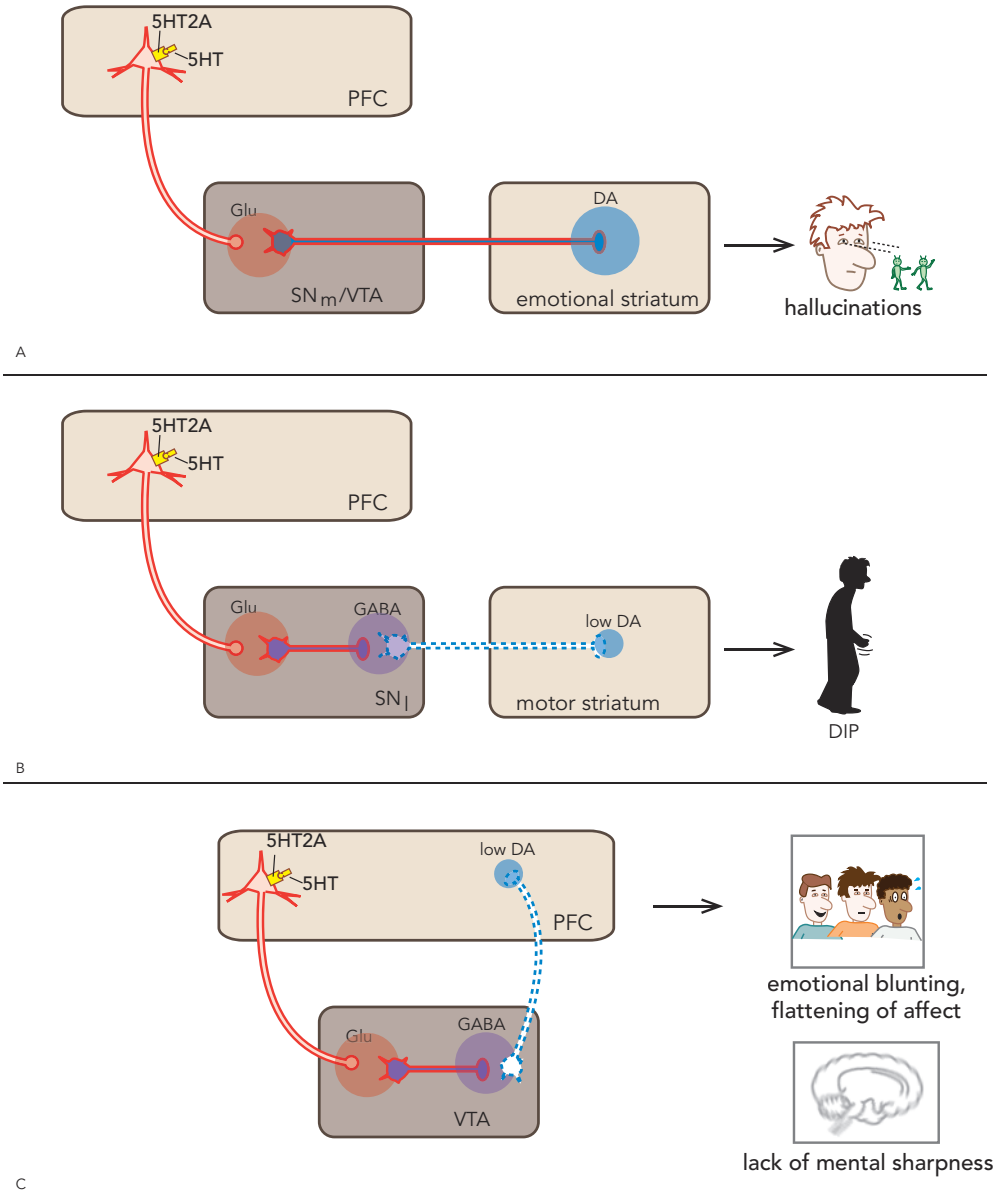


Figure 5-16 **5HT$_{2A}$ receptor regulation of downstream dopamine (DA) release.** 5HT$_{2A}$ receptors, which are postsynaptic and excitatory, are relevant to the treatment of psychosis because of their presence on three separate populations of descending glutamate neurons. (A) 5HT$_{2A}$ receptors are located on descending glutamatergic pyramidal neurons that directly innervate mesolimbic/mesostriatal dopamine neurons projecting to the emotional striatum. Excessive activity in this pathway can lead to the positive symptoms of psychosis. (B) 5HT$_{2A}$ receptors are located on descending glutamatergic pyramidal neurons that indirectly innervate nigrostriatal dopamine neurons via a GABAergic interneuron in the substantia nigra. Excessive stimulation of these 5HT$_{2A}$ receptors leads to a reduction in dopamine release in the motor striatum and can cause side effects such as drug-induced parkinsonism. (C) 5HT$_{2A}$ receptors are located on descending glutamatergic pyramidal neurons that indirectly innervate mesocortical dopamine neurons via a GABAergic interneuron in the ventral tegmental area. Excessive stimulation of these 5HT$_{2A}$ receptors leads to a reduction in dopamine release in the prefrontal cortex (PFC), which could lead to cognitive dysfunction as well as negative symptoms such as emotional blunting and flattened affect. SN$_m$, medial substantia nigra; VTA, ventral tegmental area; SN$_l$, lateral substantia nigra.

psychosis from excessive actions of serotonin (Figure 4-52C and Figure 4-54), or in hallucinogen psychosis from excessive stimulation of serotonin receptors (Figure 4-52B and Figure 4-53). In all cases, anything that increases the activity of this population of glutamate neurons will hypothetically lead to downstream release of dopamine from mesolimbic/mesostriatal dopamine neurons to cause the positive symptoms of psychosis (Figure 5-16A).

The most common treatment of course is to block excessive dopamine release at the end of this circuit, namely at D_2 receptors in the emotional striatum. However, one can also reduce the excitatory tone of serotonin at $5HT_{2A}$ receptors at the beginning of

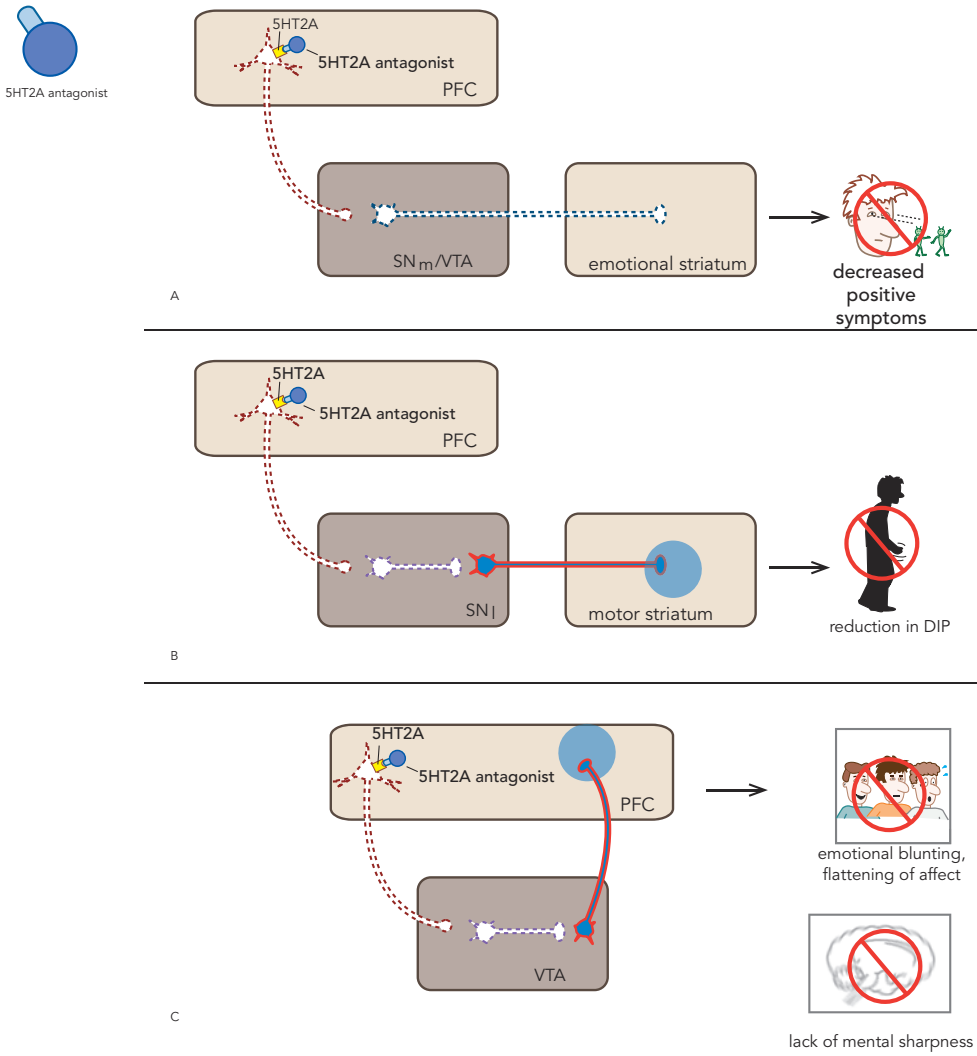


Figure 5-17 $5HT_{2A}$ receptor antagonism and downstream dopamine release. $5HT_{2A}$ antagonism can modulate downstream dopamine release via three key pathways. (A) $5HT_{2A}$ antagonism reduces glutamatergic output from a descending neuron that directly innervates mesolimbic/mesostriatal dopamine neurons. This in turn reduces dopamine output in the emotional striatum and can therefore decrease the positive symptoms of psychosis. (B) $5HT_{2A}$ antagonism reduces glutamatergic output in the substantia nigra, leading to reduced activity of the GABA interneuron and therefore disinhibition of the nigrostriatal dopamine pathway. The increased dopamine release in the motor striatum can reduce motor side effects caused by D_2 antagonism because there is more dopamine to compete with the D_2 antagonist. (C) $5HT_{2A}$ antagonism reduces glutamatergic output in the ventral tegmental area, leading to reduced activity of the GABA interneuron and therefore disinhibition of the mesocortical dopamine pathway. Increased dopamine release in the prefrontal cortex (PFC) can potentially reduce cognitive and negative symptoms of psychosis. SN_m, medial substantia nigra; VTA, ventral tegmental area; SN_l, lateral substantia nigra.

this circuit (Figure 5-17A, top left) by blocking them here with a $5HT_{2A}$ antagonist, using either an agent having both D_2 and $5HT_{2A}$ antagonist properties or an agent selective for just $5HT_{2A}$ antagonist properties (Figure 5-1). When this happens at the specific glutamate neurons shown in Figure 5-16A, this theoretically reduces release of dopamine in the emotional striatum (Figure 5-17A, right) and this in turn causes a mechanistically independent antipsychotic action, different from direct D_2 receptor blocking.

In the case of schizophrenia being treated with agents that have combined $5HT_{2A}/D_2$ antagonism, any simultaneous D_2 antagonism would theoretically become even more effective in treating positive symptoms of psychosis. Clinical trials are in progress adding a selective $5HT_{2A}$ antagonist to the other agents with antipsychotic properties to determine if ramping up $5HT_{2A}$ antagonism will consistently improve positive symptoms of psychosis or if it will allow reduction of dose, to lower D_2 antagonism, in order to improve side effects without losing therapeutic effects. There are indeed suggestions that drugs with very potent $5HT_{2A}$ antagonism might require less D_2 antagonism to treat positive symptoms of psychosis (see discussion of lumateperone, clozapine, quetiapine, and others below).

In the case of psychosis in dementia or in Parkinson's disease, where D_2 antagonism can cause problematic side effects or even be dangerous, $5HT_{2A}$ antagonist action alone can produce a sufficiently robust antipsychotic effect even in the absence of any D_2 antagonism.

A second population of glutamatergic pyramidal neurons *indirectly* innervate those nigrostriatal dopamine neurons that project to the *motor striatum* and mediate the motor side effects of D_2 antagonism (Figure 5-16B). This is a parallel pathway to the pathway just discussed in Figure 5-16A, and involves a different population of glutamate neurons that not only project to the substantia nigra rather than to the ventral tegmental area (VTA)/mesostriatum/integrative hub, but do so *indirectly*, namely, first to a GABA interneuron in the substantia nigra and then to the nigrostriatal dopamine motor pathway (compare Figure 5-16A and B). This has the effect of changing the polarity of upstream glutamate release from stimulating dopamine release (Figure 5-16A) to inhibiting dopamine release downstream (Figure 5-16B). Therefore, blocking $5HT_{2A}$ receptors on the specific glutamate neurons shown in Figure 5-16B (upper left) leads to disinhibiting (i.e., increasing) dopamine release downstream in the motor striatum (Figure 5-17B, right). That is precisely what is needed to reduce motor side effects! Namely, more dopamine is available to compete with a D_2 antagonist in the motor striatum that otherwise would cause motor side effects. And that is exactly what is observed with $5HT_{2A}$ antagonist/D_2 antagonist drugs: i.e., fewer motor side effects compared to D_2 antagonists without $5HT_{2A}$ antagonism. This has indeed been repeatedly observed for $5HT_{2A}/D_2$ antagonists, and has reduced the need for anticholinergic medication administration to treat motor side effects compared to D_2 antagonists without $5HT_{2A}$ antagonist actions (see Figure 5-1 and compare icons on the top with the bottom left).

A third population of glutamatergic pyramidal neurons *indirectly* innervate those mesocortical dopamine neurons that project to the *prefrontal cortex* and mediate in part the negative, cognitive, and affective symptoms of schizophrenia (Figure 5-16C). This is yet another parallel pathway to the pathways just discussed, and involves yet different glutamate neurons that project indirectly via a GABA interneuron to those dopamine neurons in the VTA destined to innervate the prefrontal cortex. As discussed above for the nigrostriatal pathway (Figure 5-16B), this arrangement in Figure 5-16B also has the effect of upstream glutamate release leading to inhibiting dopamine release downstream (see Figure 5-16C). Thus, blocking $5HT_{2A}$ receptors on these specific glutamate neurons (Figure 5-17C, top left) will lead to disinhibiting (i.e., increasing) dopamine release in the prefrontal cortex (Figure 5-17C, top right). This is just what you need to improve negative symptoms of schizophrenia, and that is what has been observed in trials of $5HT_{2A}$ selective agents, either alone or augmenting other D_2 antagonist and $5HT_{2A}/D_2$ antagonist drugs. Increasing dopamine release in the prefrontal cortex also has the potential of improving cognitive and affective/depressive symptoms (Figure 5-17C). This effect is not consistent or robust across all $5HT_{2A}/D_2$ antagonist drugs that treat psychosis, in part because of different potencies of $5HT_{2A}$ antagonism compared to D_2 antagonism, and because of the presence of additional interfering pharmacological properties in some agents, such as anticholinergic and antihistaminic actions. A better approach may ultimately prove to be adding a selective $5HT_{2A}$ antagonist to drugs with D_2 antagonist action.

How Do $5HT_{2A}$ Antagonist Actions Reduce Hyperprolactinemia?

The pituitary lactotroph is responsible for secretion of prolactin and both D_2 receptors and $5HT_{2A}$ receptors

are located on the membranes of these cells. Serotonin and dopamine have reciprocal roles in the regulation of prolactin secretion, with dopamine inhibiting prolactin release via stimulation of D_2 receptors (Figure 5-18A) and serotonin promoting prolactin release via stimulation of $5HT_{2A}$ receptors (Figure 5-18B). Thus, when D_2 receptors alone are blocked by D_2 antagonism, dopamine can no longer inhibit prolactin release, so prolactin levels rise (Figure 5-18C). However, in the case of a drug that has both D_2 antagonism and $5HT_{2A}$ antagonism, there is simultaneous inhibition of $5HT_{2A}$ receptors, so serotonin can no longer stimulate prolactin release (Figure 5-18D). This mitigates the hyperprolactinemia of D_2 receptor blockade. Although this is interesting theoretical pharmacology, in practice, not all $5HT_{2A}/D_2$ antagonists reduce prolactin secretion to the same extent, and others do not reduce prolactin elevations at all, possibly due to other off-target receptor properties.

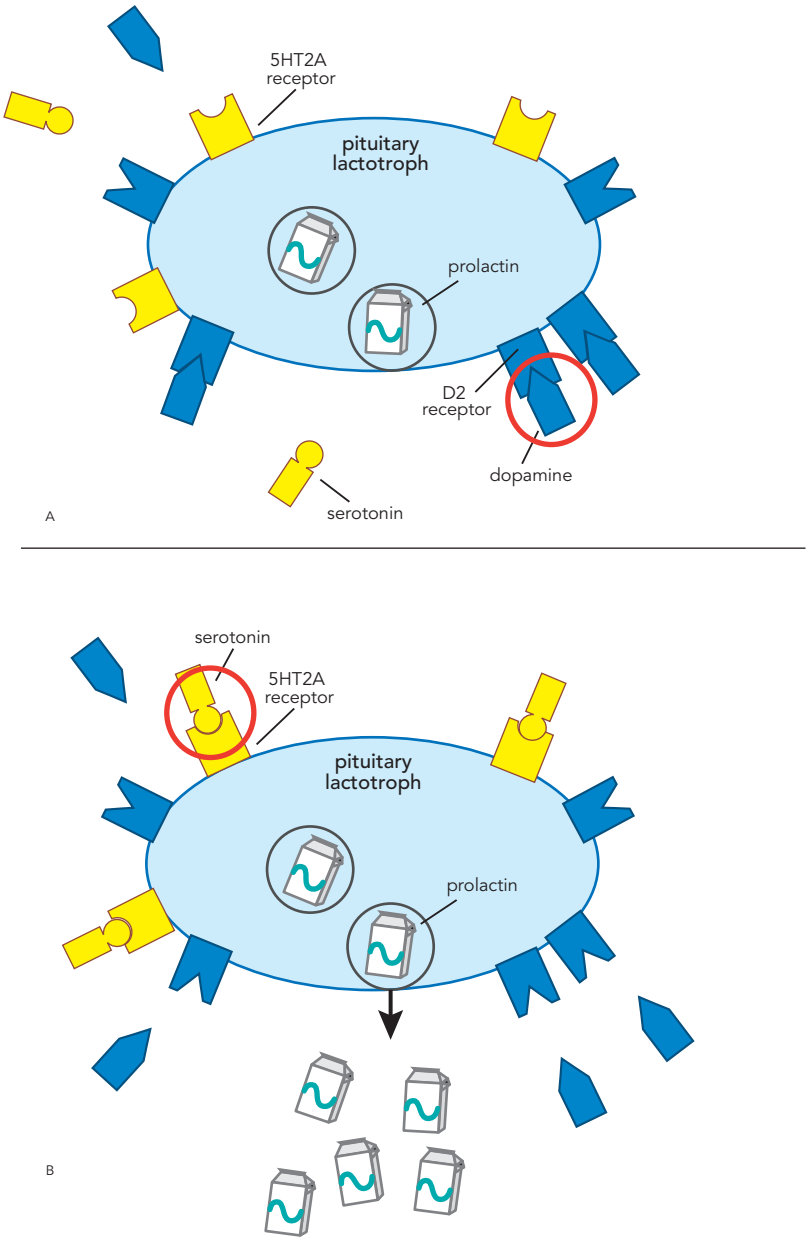


Figure 5-18A, B Dopamine and serotonin regulate prolactin release, part 1. (A) Dopamine binding at inhibitory D_2 receptors (red circle) prevents prolactin release from pituitary lactotroph cells in the pituitary gland. (B) Serotonin (5HT) binding at excitatory $5HT_{2A}$ receptors (red circle) stimulates prolactin release from pituitary lactotroph cells in the pituitary gland. Thus, dopamine and serotonin have a reciprocal regulatory action on prolactin release.

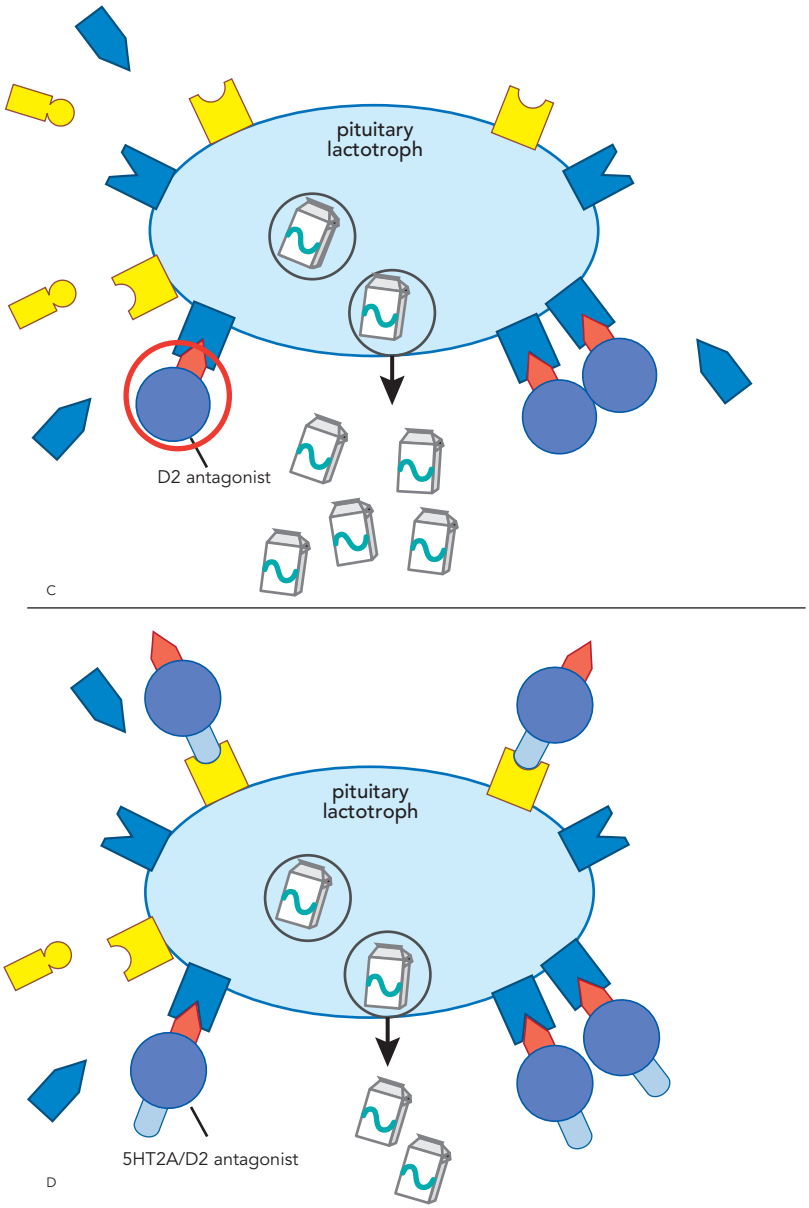


Figure 5-18C, D Dopamine and serotonin regulate prolactin release, part 2. (C) D_2 antagonism (red circle) blocks dopamine's inhibitory effect on prolactin secretion from pituitary lactotrophs. Thus, these drugs increase prolactin levels. (D) As dopamine and serotonin have reciprocal regulatory roles in the control of prolactin secretion, one cancels the other. Thus, $5HT_{2A}$ antagonism reverses the ability of D_2 antagonism to increase prolactin secretion.

DRUGS TARGETING SEROTONIN 1A RECEPTORS AND DOPAMINE D_2 RECEPTORS AS PARTIAL AGONISTS

Another attempt to improve first-generation drugs for psychosis with D_2 antagonist properties substitutes D_2 partial agonism for D_2 antagonism, and adds serotonin $5HT_{1A}$ partial agonism.

D_2 Partial Agonism

Some antipsychotics act to stabilize dopamine neurotransmission at D_2 receptors in a state between complete silent antagonism (see Chapter 2, Figures 2-6 and 2-10) and full stimulation/agonist action (Chapter 2, Figures 2-5 and 2-10). This intermediate position is illustrated here in Figures 5-19 through 5-22 and is called partial agonism. This was also discussed and illustrated in Chapter 2 (see Figures 2-7 and 2-10).

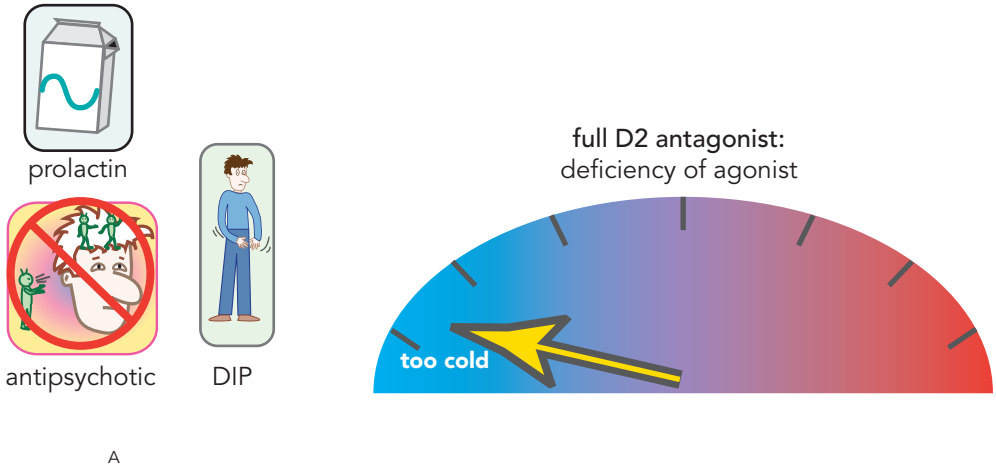


Figure 5-19 Spectrum of dopamine neurotransmission. Simplified explanation of actions on dopamine. (A) Full D_2 antagonists bind to the D_2 receptor in a manner that is "too cold"; that is, they have powerful antagonist actions while preventing agonist actions and thus can reduce positive symptoms of psychosis but also cause drug-induced parkinsonism (DIP) and prolactin elevation. (B) D_2 receptor agonists, such as dopamine itself, are "too hot" and can therefore lead to positive symptoms. (C) D_2 partial agonists bind in an intermediary manner to the D_2 receptor and are therefore "just right," with antipsychotic actions but without DIP or prolactin elevation.

An oversimplified explanation of partial agonist action at the D_2 receptor is illustrated in Figure 5-19. Namely, D_2 antagonist action is "too cold," with antipsychotic actions but elevated prolactin and motor symptoms such as DIP (Figure 5-19A). On the other hand, maximally stimulating full agonist actions of dopamine itself (or amphetamine, which releases dopamine) are "too hot" with positive symptoms of psychosis (Figure 5-19B). Instead, a partial agonist binds in an intermediary manner, hopefully "just right," with antipsychotic actions but lower DIP and lesser prolactin elevations (Figure 5-19C). For this reason, partial agonists are sometimes called "Goldilocks" drugs if they get the balance "just right" between full agonism and complete antagonism. However, as we shall see, this explanation is an oversimplification; the balance is slightly different for each drug in the D_2 partial agonist class and there is no perfect "Goldilocks" solution.

A more sophisticated explanation is that partial agonists have the intrinsic ability to bind to receptors in a manner that causes signal transduction from the receptor to be intermediate between full output and no output (Figure 5-20). The naturally occurring neurotransmitter generally functions as a full agonist, and causes maximum signal transduction from the receptor it occupies (volume blaring in Figure 5-20, top), whereas antagonists essentially shut down all output from the receptor they occupy and make them "silent" in terms of communicating with downstream signal transduction cascades (volume essentially turned off in Figure 5-20, middle). By contrast, partial agonists (Figure 5-20, bottom) cause receptor output that is more than

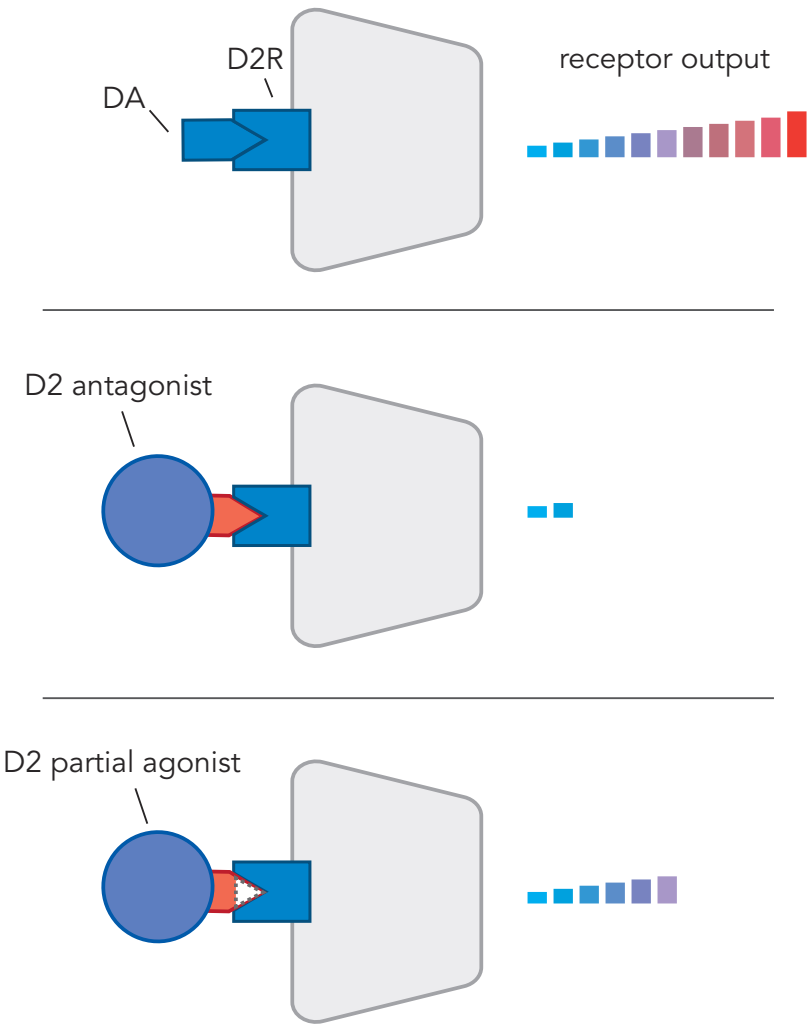


Figure 5-20 Dopamine receptor output. Dopamine (DA) itself is a full agonist and causes full receptor output (top). D_2 antagonists allow little if any receptor output (middle). However, D_2 partial agonists can partially activate dopamine receptor output and cause a stabilizing balance between stimulation and blockade of dopamine receptors (bottom).

the silent antagonist (Figure 5-20, middle), but less than the full agonist (Figure 5-20, top). Thus, many degrees of partial agonism are possible between these two extremes. Full agonists, silent antagonists, and partial agonists may all cause different changes in receptor conformation that lead to a corresponding range of signal transduction output from the receptor (Figure 5-21).

Where on the agonist spectrum do D_2 partial agonists for psychosis lie? This is illustrated in Figure 5-15, showing that the D_2 partial agonists under discussion here for the treatment of psychosis are very close to the antagonist end of the spectrum, where all the D_2 antagonists discussed so far lie (Figure 5-15). That is because these D_2 partial agonists for the treatment of psychosis are "almost" antagonists with just a whiff of intrinsic agonist activity. By contrast, other dopamine partial agonists useful for the treatment of Parkinson's disease and classified as dopamine partial agonists lie very close to the agonist end of the spectrum (Figure 5-15). They are almost full agonists. Using these agents at the full agonist end of the spectrum for the treatment of psychosis would make the psychosis worse, just as using agents at the other end of the spectrum near to antagonist for the treatment of Parkinson's disease would make their motor movements worse. Thus, it is important not to lump all partial agonists together and to understand where on the spectrum a given agent lies in order to understand its pharmacological mechanism of action because very small changes in the amount of partial agonism and placement on this spectrum (Figure 5-15) can have profound clinical effects.

How Does D_2 Partial Agonism Cause Fewer Motor Side Effects than D_2 Antagonism?

It seems that it takes only a very small amount of signal transduction through D_2 receptors in the striatum in

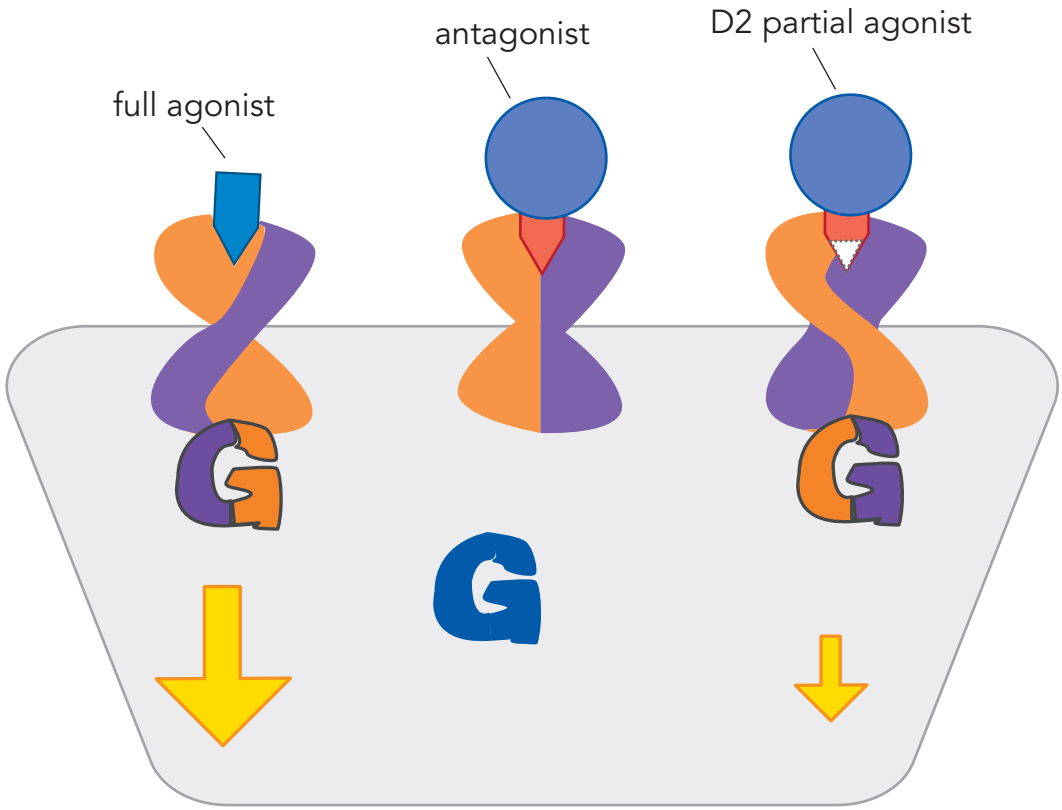


Figure 5-21 Agonist spectrum and receptor conformation. This figure shows an artist's depiction of changes in receptor conformation in response to full agonists versus antagonists versus partial agonists. With full agonists, the receptor conformation is such that there is robust signal transduction through the G-protein-linked second-messenger system of D_2 receptors (left). Antagonists, on the other hand, bind to the D_2 receptor in a manner that produces a receptor conformation that is not capable of any signal transduction (middle). Partial agonists, such as a dopamine partial agonist, cause a receptor conformation such that there is an intermediate amount of signal transduction (right). However, the partial agonist does not induce as much signal transduction (right) as a full agonist (left).

order for a D_2 partial agonist to have reduced propensity to cause motor side effects, especially drug-induced parkinsonism. Thus, a very slight degree of agonism, sometimes called "intrinsic activity," can have a very different set of clinical consequences compared to a fully silent and completely blocked D_2 receptor, which is what D_2 antagonists and $5HT_{2A}/D_2$ antagonists do. D_2 partial agonists capable of treating psychosis lie very close to antagonists on the agonist spectrum (Figure 5-15), as more dopamine antagonism than agonist action is what is needed for the treatment of psychosis.

What is so interesting is how very small movements up and down the partial agonist spectrum (Figure 5-15) can have profound effects upon the clinical properties. Just slightly too close to a pure agonist and such agents may have reduced motor side effects and prolactin elevations and be sufficiently activating to improve negative symptoms but be too activating so that there is lessened efficacy for positive symptoms, or even worsening of positive symptoms, as well as nausea and vomiting. Fairly extensive testing has been made of several D_2 partial agonists in schizophrenia and three of these are approved. OPC4392 (structurally and pharmacologically related to both aripiprazole and brexpiprazole, which were tested later) turned out to be too much of an agonist; it had relatively little intrinsic activity and improved negative symptoms of schizophrenia, with little in the way of motor side effects, but its intrinsic activity was nevertheless too great because this drug also activated and worsened positive symptoms of schizophrenia, so it was never marketed. Another D_2 partial agonist, bifeprunox, is less of an agonist than OPC4392 but turned out to be still too much of an agonist since it caused nausea and vomiting; although it did have some efficacy for positive symptoms and did not cause motor side effects, it was less robust in improving positive symptoms than other agents and also had more gastrointestinal side effects, so the US Food and Drug Administration (FDA) did not approve it. Next, investigators threw another dart closer to the antagonist end of the spectrum and it landed as aripiprazole (the original "pip" – see below). This agent indeed improves positive symptoms without severe motor side effects, but does cause some akathisia and some clinicians question if it is as efficacious as D_2 antagonists for the most severely psychotic patients, although this has never been proven. Finally, two more D_2 partial agonists have been approved: a second "pip" called brexpiprazole and a "rip" called cariprazine. Both are similar on the D_2 partial agonist spectrum to aripiprazole, have antipsychotic efficacy and low motor side effects but some akathisia, and differ mostly in secondary binding properties of receptors other than the D_2 receptor, as will be discussed in detail in the section on individual drugs below.

How Does D_2 Partial Agonist Action Reduce Hyperprolactinemia?

The pituitary lactotrophs' D_2 receptors have proven to be more sensitive to the intrinsic activity of D_2 partial agonists than the other dopamine pathways and targets. Specifically, the three partial agonists in clinical use all actually reduce prolactin levels, rather than raise them. It is hypothesized that this is due to the D_2 receptors on the lactotrophs detecting these drugs more as agonists than as antagonists, and thus these drugs shut down prolactin secretion rather than stimulate it. In fact, co-administration of one of the D_2 partial agonists to a patient who is experiencing hyperprolactinemia while taking one of the D_2 antagonists can actually reverse that hyperprolactinemia.

$5HT_{1A}$ Partial Agonism

Why would adding $5HT_{1A}$ partial agonism to D_2 partial agonism improve the side effects and enhance efficacy for affective and negative symptoms compared to D_2 blockade? There is a simple answer, easy to understand if you have grasped the reason why $5HT_{2A}$ antagonism does much the same thing. That is, $5HT_{1A}$ partial agonism, especially if closer to full agonism than to antagonism on the partial agonist spectrum (Figure 5-15), has similar effects to those of $5HT_{2A}$ antagonism. Just like $5HT_{2A}$ antagonism shown in Figure 5-17, $5HT_{1A}$ partial agonism/full agonism also *opposes* D_2 antagonism in side-effect pathways by causing more dopamine release in these sites, reversing some of the unwanted effects of D_2 antagonism/partial agonism and improving negative and affective symptoms (Figure 5-22).

How does this happen? $5HT_{1A}$ receptors are always inhibitory and they can be both presynaptic on serotonin neurons and postsynaptic on many neurons, including the same glutamatergic pyramidal neurons that have $5HT_{2A}$ receptors (compare the glutamate neurons upper left in both Figure 5-16A and 5-22A). One can think of the situation as the pyramidal neuron having both an accelerator ($5HT_{2A}$ receptors) and a brake ($5HT_{1A}$ receptors). Taking your foot off the accelerator ($5HT_{2A}$ antagonism) should have a similar effect as stepping on the brake ($5HT_{1A}$ partial agonism), especially if they are done at the same time. Thus, $5HT_{1A}$ partial agonism

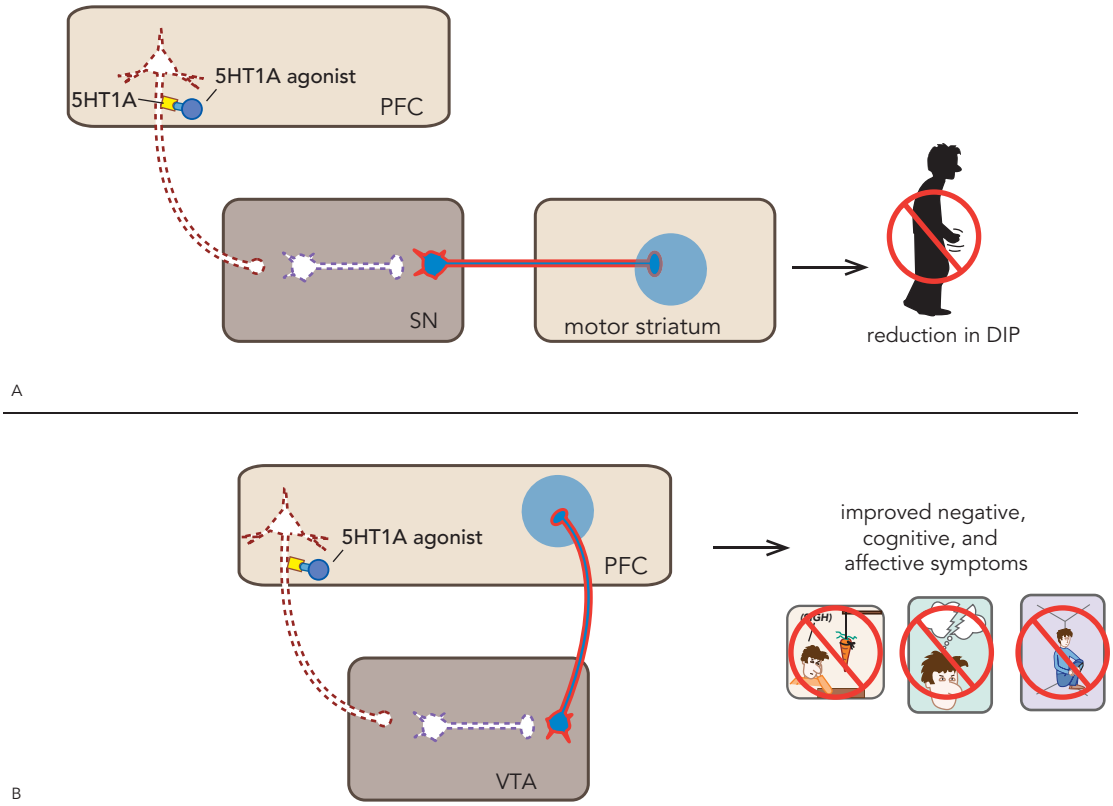


Figure 5-22 $5HT_{1A}$ receptor partial agonism and downstream dopamine release. $5HT_{1A}$ receptors are inhibitory and can be located both presynaptically on serotonin neurons and postsynaptically on other neurons. (A) $5HT_{1A}$ receptors are located on descending glutamatergic pyramidal neurons that indirectly innervate nigrostriatal dopamine neurons via a GABAergic interneuron in the substantia nigra (SN). Partial agonism of these $5HT_{1A}$ receptors reduces glutamatergic output in the substantia nigra, leading to reduced activity of the GABA interneuron and therefore disinhibition of the nigrostriatal dopamine pathway. The increased dopamine release in the motor striatum can reduce motor side effects caused by D_2 antagonism/partial agonism because there is more dopamine to compete with the D_2 binding agents. (B) $5HT_{1A}$ receptors are located on descending glutamatergic pyramidal neurons that indirectly innervate mesocortical dopamine neurons via a GABAergic interneuron in the ventral tegmental area (VTA). $5HT_{1A}$ partial agonism reduces glutamatergic output in the VTA, leading to reduced activity of the GABA interneuron and therefore disinhibition of the mesocortical dopamine pathway. Increased dopamine release in the prefrontal cortex (PFC) can potentially reduce cognitive, negative, and affective symptoms of psychosis.

has many of the same effects on dopamine release as $5HT_{2A}$ antagonism. As will be discussed later, some drugs used to treat psychosis and mood have both $5HT_{2A}$ antagonist and $5HT_{1A}$ partial agonist properties, which should theoretically enhance the actions on downstream dopamine even further compared to either of these mechanisms alone. So, just as explained above for $5HT_{2A}$ antagonism, $5HT_{1A}$ partial agonism *opposes* D_2 antagonism/partial agonism in some pathways by causing more dopamine release in these sites and thus reversing some of the unwanted D_2 antagonism/partial agonism that causes motor side effects. There is less evidence that $5HT_{1A}$ partial agonism can enhance the efficacy of D_2 antagonism/partial agonism to improve positive symptoms of psychosis. Let's now explain how $5HT_{1A}$ partial agonism could potentially reduce motor side effects and improve mood, affective, negative, and cognitive symptoms by enhancing downstream release of dopamine.

$5HT_{1A}$ partial agonist has actions at glutamatergic neurons indirectly *innervating nigrostriatal dopamine neurons projecting to the* motor striatum *(Figure 5-22A).*

Recall that blocking $5HT_{2A}$ receptors on these same glutamate neurons disinhibits dopamine release to reduce motor side effects (Figure 5-17B). That is exactly what happens with $5HT_{1A}$ partial agonism at these same neurons, namely disinhibition of dopamine release and improvement in motor side effects (Figure 5-22A). As explained above, more dopamine release competes with D_2 blocking agents for the receptors in the motor striatum

to reverse motor side effects. Since D_2 partial agonists are also $5HT_{1A}$ partial agonists, these two properties can combine to reduce many motor side effects, although akathisia can still commonly occur.

$5HT_{1A}$ partial agonist also has actions at glutamatergic neurons* indirectly *innervating mesocortical dopamine neurons projecting to the* prefrontal cortex *(Figure 5-22B).

Recall that blocking $5HT_{2A}$ receptors on these specific glutamate neurons disinhibits dopamine release in the prefrontal cortex (Figure 5-17C). This is just what you need to improve negative, cognitive, and affective/depressive symptoms. That is also what happens with $5HT_{1A}$ partial agonism at these same neurons (Figure 5-22B). These clinical actions may be particularly robust in bipolar and unipolar depression where these serotonin/dopamine partial agonists are frequently used.

LINKS BETWEEN RECEPTOR BINDING PROPERTIES OF DRUGS USED TO TREAT PSYCHOSIS AND OTHER THERAPEUTIC ACTIONS AND SIDE EFFECTS

So far in this chapter we have discussed the antipsychotic mechanisms and side effects of drugs for psychosis that are hypothetically linked to interactions at dopamine D_2, serotonin $5HT_{2A}$, and serotonin $5HT_{1A}$ receptors. The reality is that these same drugs bind to many other neurotransmitter receptors, and are used for many other therapeutic applications. In fact, many more prescriptions for D_2 blockers are written for indications other than psychosis than are written for psychosis, a key reason why they are not called "antipsychotics" here and in international nomenclature. These additional receptor actions are likely relevant to other therapeutic actions and side effects (Figures 5-23 through 5-26). The entire known panoply of receptors that are bound by drugs in this class are discussed in the sections below.

Mania

Essentially all drugs with D_2 antagonist/partial agonist properties are effective in the treatment of acute bipolar mania and in preventing recurrences of mania. Some agents are better studied than others, and the therapeutic effects in acute bipolar mania are present whether the mania is psychotic or nonpsychotic. There is an old saying about drugs that treat psychosis in schizophrenia: "you get mania treatment for free." That is, essentially any drug that can treat the positive symptoms of psychosis can probably also treat the symptoms of mania. That could be because mania is thought to be due to excessive dopamine release from mesolimbic/mesostriatal neurons, just as for the positive symptoms of schizophrenia (Figures 4-15 and 4-16). Thus, it is not surprising that agents that reduce dopamine overactivity in this pathway are effective when the patient is in a manic state as well as in a psychotic state. Further discussion of mania will follow in Chapter 6 and of treatments for mania in Chapter 7.

Antidepressant Actions in Bipolar and Unipolar Depression

The most common use for $5HT_{2A}/D_2$ antagonists and $D_2/5HT_{1A}$ partial agonists is not the treatment of psychosis in schizophrenia or mania in bipolar disorder. Rather, the treatment of unipolar major depressive disorder and bipolar depression is where these agents are most commonly prescribed and at lower doses, especially the newer agents with fewer side effects but higher costs.

Almost all drugs treating psychosis have to be dosed so that 80% or so of D_2 receptors are blocked in the emotional striatum, whereas the doses of these same drugs for depression are lower and likely insufficient to robustly block D_2 receptors. So, how do they work in depression? $5HT_{2A}$ antagonism and $5HT_{1A}$ partial agonism, and the resultant increase in dopamine release in the prefrontal cortex, are thought to be potentially key antidepressant mechanisms. Looking over the vast panoply of receptor actions of the individual drugs in this class (see discussion below and Figures 5-27 through 5-62), one can readily see many additional potential antidepressant mechanisms. These will be discussed and illustrated in detail in Chapters 6 and 7 on mood disorders and their treatments; here we will just mention several of those key mechanisms. Binding properties accompanying D_2 blockade that are candidates for explaining antidepressant actions are shown for all the individual D_2 blockers in the many figures in the sections that follow in this chapter and include:

- monoamine reuptake blocking properties
- α_2 antagonism
- D_3 partial agonism
- $5HT_{2C}$ antagonism
- $5HT_3$ antagonism
- $5HT_7$ antagonism
- others including possibly $5HT_{1B/D}$ antagonism

No two agents in this group have exactly the same binding characteristics and maybe that explains in part

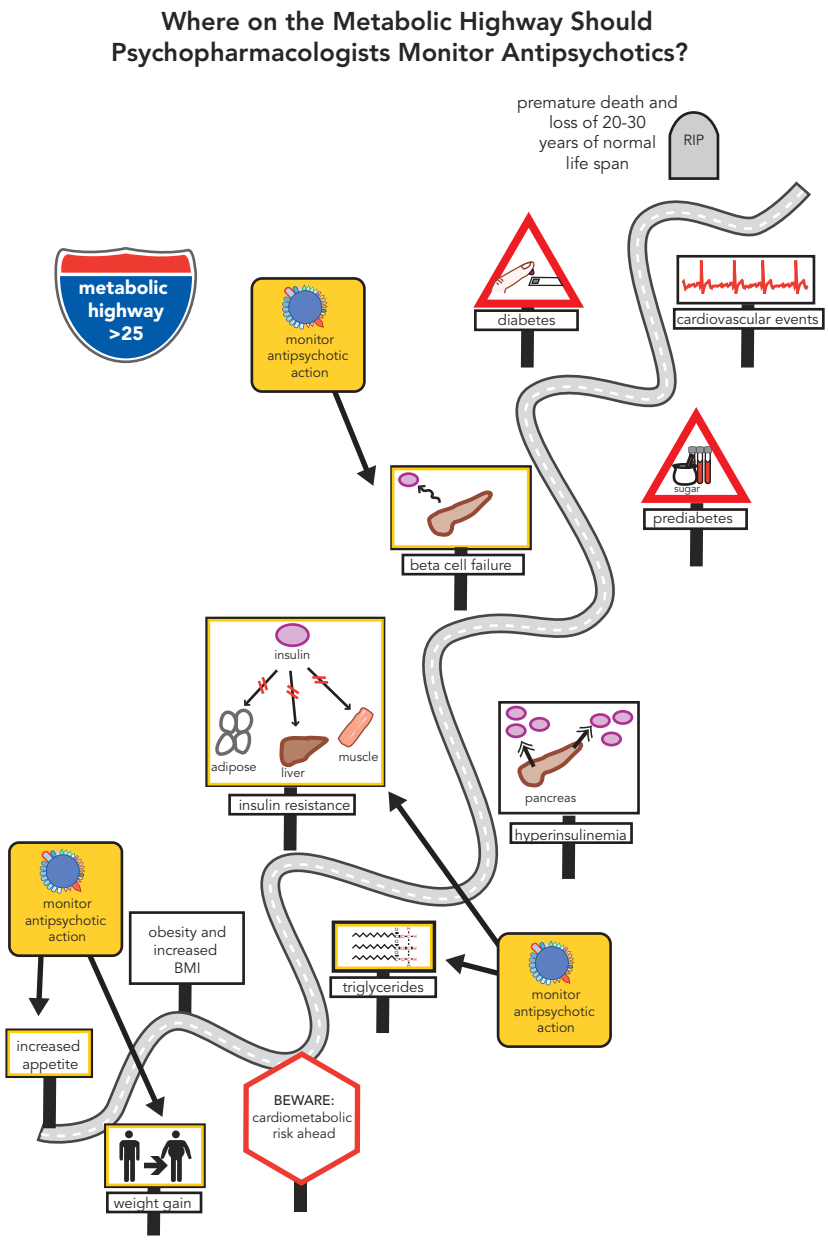


Figure 5-23 Monitoring on the metabolic highway. Monitoring for cardiometabolic side effects is necessary for any patient taking a medication to treat psychosis, although risk can vary by individual agent. First, increased appetite and weight gain can lead to elevated body mass index (BMI) and ultimately obesity. Thus, weight and BMI should be monitored here. Second, some agents can cause insulin resistance by an unknown mechanism; this can be detected by measuring fasting plasma triglyceride levels. Finally, hyperinsulinemia may advance to pancreatic β-cell failure, prediabetes, and then diabetes. Diabetes increases the risk for cardiovascular events and premature death.

why some patients can have an antidepressant response to one agent in this group and not another. Please see the discussion of individual drugs below for which of these actions are part of the mechanisms of those specific drugs.

Anxiolytic Actions

A somewhat controversial use of drugs normally used to treat psychosis is for the treatment of various anxiety disorders. Some studies suggest efficacy of these agents as monotherapy for generalized anxiety disorder and to augment other agents for other anxiety disorders. Another controversial use of these agents is for posttraumatic stress disorder (PTSD). It is possible that the antihistamine and anticholinergic sedative properties of some of these agents are calming in some patients and responsible for anxiolytic/anti-PTSD action in them. If so, why are these uses controversial? There are both

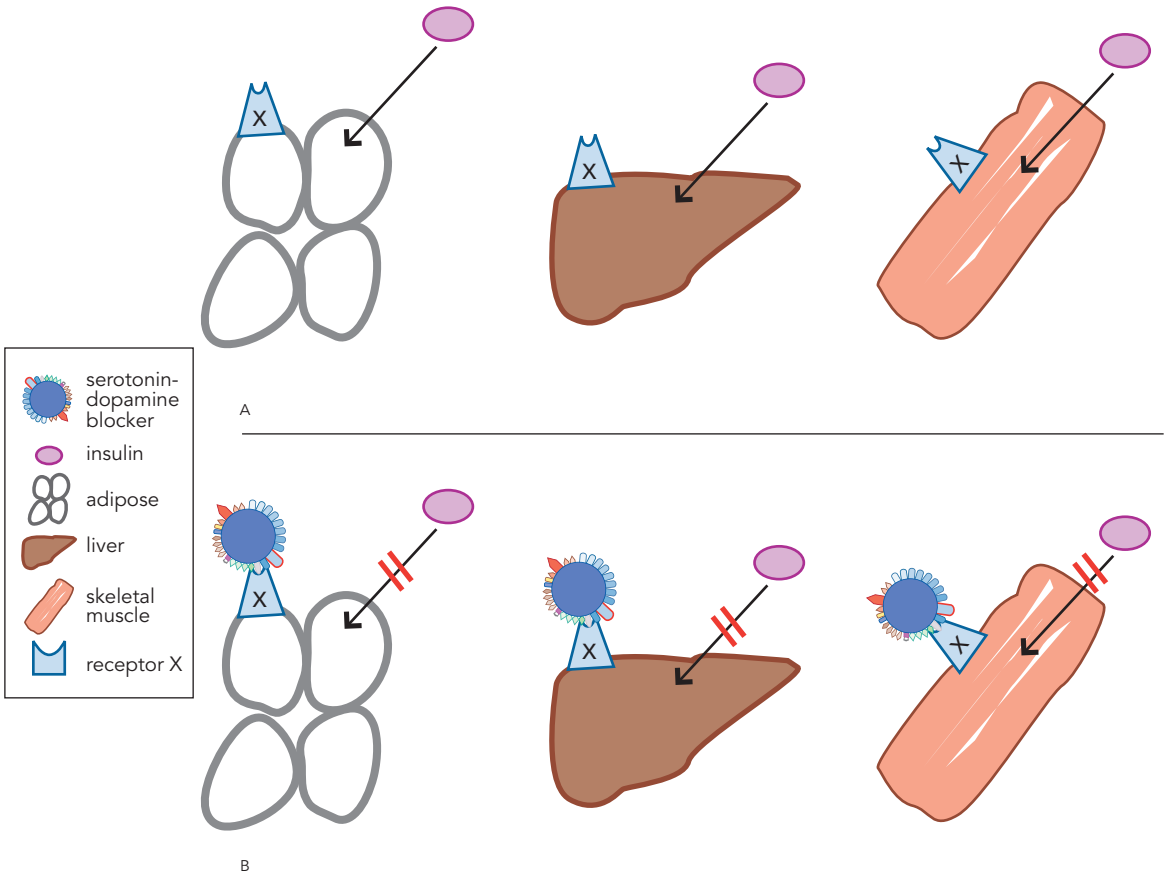


Figure 5-24 **Insulin resistance and elevated triglycerides: caused by tissue actions at an unknown receptor?** Some drugs used to treat psychosis may lead to insulin resistance and elevated triglycerides, independently of weight gain, although the mechanism is not yet established. This figure depicts a hypothesized mechanism in which an agent binds to receptor X at adipose tissue, liver, and skeletal muscle to cause insulin resistance.

positive and negative studies of efficacy for anxiety and PTSD indications; also, given the side effects of many agents used to treat psychosis, the risk:benefit ratio is not necessarily favorable compared to alternative treatments for anxiety and PTSD. A promising exception may be a positive study of one of these agents (brexpiprazole) in combination with a selective serotonin reuptake inhibitor (SSRI), specifically sertraline. This is also mentioned in Chapter 8 on anxiety and traumatic disorders.

Agitation in Dementia

Treating a problematic condition known as agitation in patients with dementia is another controversial use of drugs for psychosis because there is no clear efficacy signal in most studies, and also because there is a safety warning for cardiovascular complications and deaths in elderly dementia patients taking these drugs. Although there is promise for drugs acting by different mechanisms and currently in testing (see Chapter 12 on dementia), there are also positive results for agitation in dementia for one agent that is in the class of drugs for psychosis, namely brexpiprazole, and it may be that it has a satisfactory risk:benefit profile. This is discussed in further detail in Chapter 12 on dementia.

Sedative Hypnotic and Sedating Actions

A long debate exists as to whether sedation is a good or a bad property for antipsychotic action. The answer seems

to be that sedation is both good and bad in the treatment of psychosis. In some cases, particularly for short-term treatment, sedation is a desired therapeutic effect, especially early in treatment, during hospitalization, and when patients are aggressive, agitated, or needing sleep induction. In other cases, particularly for long-term treatment, sedation is generally a side effect to be avoided because diminished arousal, sedation, and somnolence can lead to cognitive impairment. When cognition is impaired, functional outcomes are compromised. The pharmacology of sedation is discussed above and illustrated in Figures 5-8, 5-13, and 5-14 for anticholinergic, antihistamine, and α_1 antagonist actions. Sedative hypnotics are discussed in Chapter 10 on sleep, and aggression and violence are discussed in Chapter 13 on impulsivity.

Cardiometabolic Actions

Although all $D_2/5HT_{2A}/5HT_{1A}$ drugs for treating psychosis share a class warning for causing weight gain and risks for obesity, dyslipidemia, and hyperglycemia/diabetes mellitus, there is actually a spectrum of risk among the various agents:

high metabolic risk: clozapine, olanzapine
moderate metabolic risk: risperidone, paliperidone, quetiapine, asenapine, iloperidone
low metabolic risk: lurasidone, cariprazine, lumateperone, ziprasidone, pimavanserin, aripiprazole, brexpiprazole

The "metabolic highway" shown schematically in Figure 5-23 passes by weight gain, dyslipidemia, and hyperglycemia/diabetes mellitus and ends with the sad destination of premature death. The point of discussing the metabolic highway is to monitor the patient along their journey of taking one of the moderate- or high-risk agents, and to intervene when possible to prevent predictable adverse outcomes. The onramp to the metabolic highway is increased appetite and weight gain, with progression to obesity, insulin resistance, and dyslipidemia with increases in fasting triglyceride levels (Figure 5-23). Ultimately, hyperinsulinemia advances to pancreatic β-cell failure, prediabetes, and then diabetes. Once diabetes is established, risk for cardiovascular events is further increased, as is the risk of premature death (Figure 5-23).

The pharmacological mechanisms for what propels a patient taking a drug with antipsychotic properties along the metabolic highway to these risks and beyond are only beginning to be understood. Increased weight gain associated with some agents may be due to actions at the H_1 histamine receptor and the $5HT_{2C}$ serotonin receptor. When these receptors are blocked, particularly at the same time, patients can experience weight gain. Since weight gain can lead to obesity, and obesity to diabetes, and diabetes to cardiac disease along the metabolic highway (Figure 5-23), it seemed feasible at first that weight gain might explain all the other cardiometabolic complications associated with treatment with those drugs used for psychosis that cause moderate or high amounts of weight gain. This may be true, but only in part, and perhaps mostly for those agents that have both potent antihistamine properties as well as potent $5HT_{2C}$ antagonist properties; notably, clozapine, olanzapine, and quetiapine, as well as the antidepressant mirtazapine (discussed in Chapter 7).

However, it now appears that the cardiometabolic risk cannot simply be explained by increased appetite and weight gain, nor by antagonist actions at these two receptors, even though they certainly do represent the first steps down the slippery slope towards cardiometabolic complications for some of the higher-risk agents. However, many drugs that block one or another of these two receptors do not have a great deal of appetite or weight gain associated with use, and many other drugs that cause weight gain lack actions at these two receptors.

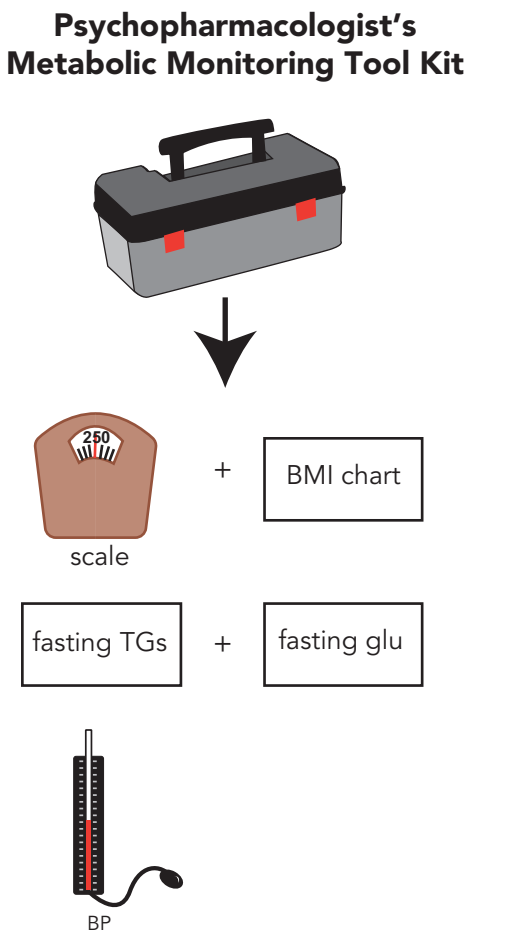
It appears that there may be a second mechanism acting to cause weight gain, dyslipidemia, and diabetes; namely, immediate increase in insulin resistance. This can be measured in part by elevation of fasting triglyceride levels and cannot be explained by weight gain alone, because this occurs prior to gaining significant weight; it is as if there is an acute receptor-mediated action of these drugs on insulin regulation. We still do not know what that receptor might be, but it is hypothesized as receptor "X" on the drug icon in Figure 5-24.

So, there appears to be a second mechanism of metabolic dysfunction other than that which causes increased appetite and weight gain of the $H_1/5HT_{2C}$-mediated mechanism. This outcome was unexpected when these drugs were all developed, and some drugs seem to have this second mechanism (high- and moderate-risk agents) while others seem to lack it (low-risk agents). To date, the mechanism of this increased insulin resistance and elevation of fasting triglycerides has been vigorously pursued but has not yet been identified. The rapid elevation of fasting triglycerides upon initiation of some $D_2/5HT_{2A}$ antagonists, and the rapid fall of fasting triglycerides upon discontinuation of such drugs, is highly suggestive that an unknown

pharmacological mechanism causes these changes, although this remains speculative. The hypothetical actions of agents with this postulated receptor action are shown in Figure 5-24, where adipose tissue, liver, and skeletal muscle all develop insulin resistance in response to administration of certain drugs (e.g., high-risk drugs but not "metabolically friendly" low-risk drugs), at least in certain patients. Whatever the mechanism of this effect, it is clear that fasting plasma triglycerides and insulin resistance can be elevated significantly in some patients taking certain $D_2/5HT_{2A}$ antagonists, that this enhances cardiometabolic risk and moves such patients along the metabolic highway (Figure 5–23), and that this functions as another step down the slippery slope towards the diabolical destination of cardiovascular events and premature death. This does not happen in all patients taking any $D_2/5HT_{2A}$ antagonist, but the development of this problem can be detected by monitoring (Figure 5-25) and it can be managed when it does occur (Figure 5-26).

Another rare but life-threatening cardiometabolic problem is known to be associated with serotonin/dopamine agents that treat psychosis: namely, an association with the sudden occurrence of diabetic ketoacidosis (DKA) or the related condition hyperglycemic hyperosmolar syndrome (HHS). The mechanism of this complication is under intense investigation, and is probably complex and multifactorial. In some cases, it may be that patients with undiagnosed insulin resistance, prediabetes, or diabetes, who are in a state of compensated hyperinsulinemia on the metabolic highway (Figure 5-23), when given certain serotonin/dopamine antagonists, become decompensated because of some unknown pharmacological action. Because of the risk of DKA/HHS, it is important to know the patient's location along the metabolic highway prior to prescribing drugs for psychosis, particularly if the patient has hyperinsulinemia, prediabetes, or diabetes. It is thus important to monitor (Figures 5-23 and 5-25) and manage (Figure 5-26) these risk factors.

Specifically, there are at least three stops along the metabolic highway where a psychopharmacologist should monitor a patient taking a drug for psychosis (or using these same drugs for other indications, particularly depression) and manage their cardiometabolic risks (Figure 5-23). This starts with monitoring weight, body mass index, and fasting glucose to detect the development of diabetes (Figures 5-23 and 5-25). It also means getting a baseline of fasting triglyceride levels and determining whether there is a family history of



FLOW CHART John Doe			
	baseline	visit 1	visit 2
wt/BMI			
fasting TGs			
fasting glu			
BP			

Figure 5-25 Metabolic monitoring tool kit. The psychopharmacologist's metabolic monitoring tool kit includes items for tracking four major parameters: weight/body mass index (BMI), fasting triglycerides (TGs), fasting glucose (glu), and blood pressure (BP). These items are simply a flowchart that can appear at the beginning of a patient's chart, with entries for each visit.

diabetes. The second action to monitor is whether or not these drugs are causing dyslipidemia and increased insulin resistance by measuring fasting triglyceride levels before and after starting a serotonin/dopamine agent (Figure 5-25). If body mass index or fasting triglycerides

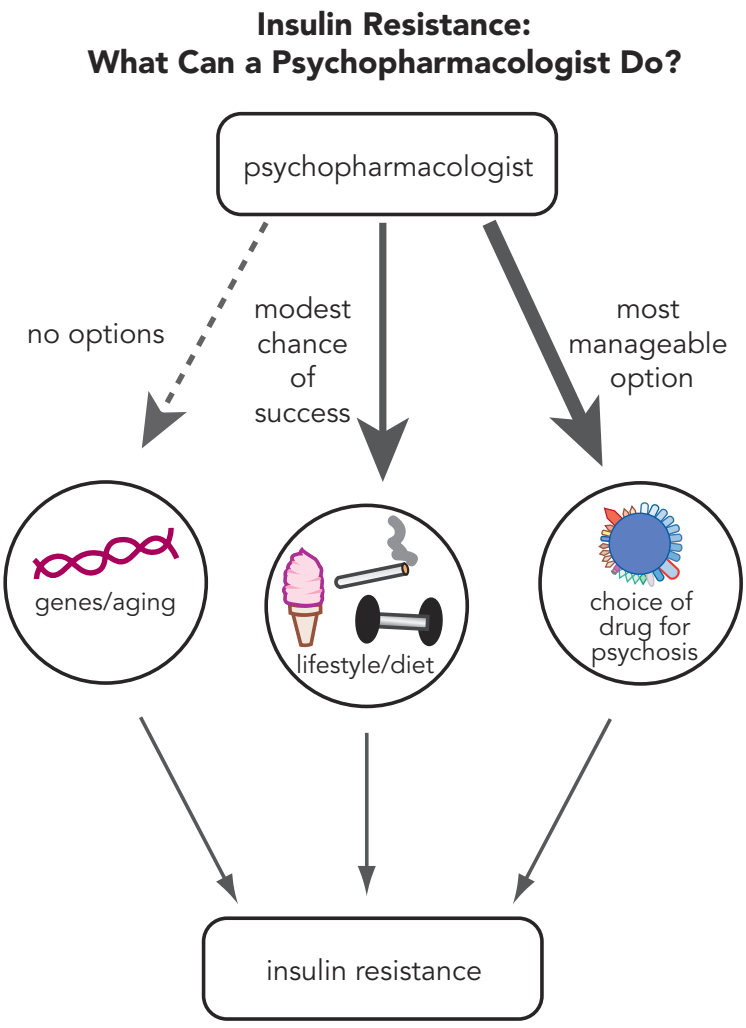


Figure 5-26 Insulin resistance: what can a psychopharmacologist do? Several factors influence whether or not an individual develops insulin resistance, some of which are manageable by a psychopharmacologist and some of which are not. Unmanageable factors include genetic makeup and age, while items that are modestly manageable include lifestyle (e.g., diet, exercise, smoking). Psychopharmacologists exert their greatest influence on managing insulin resistance through the selection of medication treatments that either do or do not cause insulin resistance.

increase significantly, a switch to a different drug in this class, especially a low-metabolic-risk drug, should be considered. In patients who are obese, with dyslipidemia, and either in a prediabetic or diabetic state, it is especially important to monitor blood pressure, fasting glucose, and waist circumference before and after initiating a serotonin/dopamine agent. Best practices are to monitor these parameters in anyone taking any of these drugs, although it is frequently not done, especially not in patients being treated for depression, unfortunately. Too often these same patients are not monitored for other side effects in this class either, such as tardive dyskinesia. If there is one lesson to be learned about knowing the pharmacology of drugs it is that the mechanism dictates not only efficacy but also safety. Too often these drugs are monitored one way when used for psychosis, frequently in inpatient settings, and another way, much less rigorously, when used for depression, often in outpatient settings.

Guess what? These are the same drugs no matter where or in whom they are used.

In high-risk patients, it is especially important to be vigilant for DKA/HHS, and possibly to reduce that risk by maintaining the patient on a drug for psychosis (or mood) with lower cardiometabolic risk. In high-risk patients, especially those with pending or actual pancreatic β-cell failure, as manifested by hyperinsulinemia, prediabetes, or diabetes, fasting glucose and other chemical and clinical parameters can be monitored to detect early signs of rare but potentially fatal DKA/HHS.

The psychopharmacologist's metabolic toolkit is quite simple (Figure 5-25). It involves a flow chart that tracks perhaps as few as four parameters over time, especially before and after switches from one agent to another, or as new risk factors evolve. These four parameters are weight (as body mass index), fasting triglycerides, fasting glucose, and blood pressure.

The management of patients at risk for cardiometabolic disease can be quite simple as well, although patients who already have developed dyslipidemia, hypertension, diabetes, and heart disease will likely require management of these problems by a medical specialist. However, the psychopharmacologist is left with a very simple set of options for managing patients with cardiometabolic risk who are prescribed one of these drugs with any amount of metabolic risk (Figure 5-26). The major factors that determine whether a patient progresses along the metabolic highway to premature death include:

- those that are unmanageable (genetic makeup and age)
- those that are modestly manageable (change in lifestyle such as diet, exercise, and stopping smoking)
- those that are most manageable, namely the selection of medication and perhaps switching from one that is causing increased risk in a particular patient, to one that monitoring demonstrates reduces that risk

Other options for managing the metabolic syndrome and dyslipidemia in patients taking serotonin/dopamine antagonists is the promising possibility that co-therapy with other agents may prevent weight gain and possibly dyslipidemia. That is, the anti-diabetes drug metformin has been shown in several studies to cause weight loss after drug-induced weight gain and, perhaps even more impressively, to reduce weight gain when starting a high- or moderate-metabolic-risk agent. Less consistent results have also been reported for the anticonvulsant topiramate. A new agent on the horizon that can reduce olanzapine-induced weight gain is the combination of the μ-opioid antagonist samidorphan with olanzapine.

PHARMACOLOGICAL PROPERTIES OF SELECTED INDIVIDUAL FIRST-GENERATION D_2 ANTAGONISTS

The original D_2 antagonists launched approximately 70 years ago are still used to treat psychosis and a few of the most commonly prescribed agents are selected for individual discussion here. To characterize all the receptor binding properties of all the various drugs that treat psychosis, we show these properties both by simplified icons and by binding strips that represent all the known receptors that drug binds as one box per receptor, in rank order from most potent on the far left to least potent on the far right (see Figures 5-27 through 5-31 for some of the original D_2 antagonists, and see subsequent figures for the other drugs to treat psychosis). Specifically, the pharmacological binding properties of each drug can be represented as a row of semi-quantitative and rank-order relative binding potencies at numerous neurotransmitter receptors. These figures are conceptual and not precisely quantitative, can differ from one laboratory to another, species to species, method to method, and the consensus values for binding properties evolve over time. More potent binding (higher affinity) is shown to the left of the value for the D_2 receptor, which is indicated by a vertical dotted line; less potent binding (lower affinity) is shown to the right.

Drugs used to treat psychosis are arguably the most complicated medicines in psychopharmacology, if not indeed in all of medicine, and this method should hopefully give the reader a rapid semi-quantitative grasp of the individual pharmacological properties of two dozen different drugs used to treat psychosis, and how these compare to all the other drugs that treat psychosis, and to do it in a glance.

Dopamine 2 antagonists/partial agonists are generally dosed for antipsychotic action so that at least 60–80% of D_2 receptors are occupied. Thus, all receptors to the left of D_2 in the various figures of these drugs are occupied at the level of 60% or *more* at antipsychotic dosing levels. The receptors shown to the right of D_2 in these individual drug figures are occupied at a level of less than 60% at antipsychotic dosing levels. Only those receptors that are bound by a drug within an order of magnitude of potency of D_2 affinity are likely to have clinically relevant actions at antipsychotic doses, and maybe no relevant actions at lower doses such as doses used to treat depression.

Chlorpromazine

One of the very first agents with D_2 antagonist properties used to treat psychosis is chlorpromazine, in the chemical class of phenothiazine. It was originally branded as "Largactil" meaning it had a large number of actions, but none of its actions were known to be linked to any specific receptor at that time. Those "large actions" are shown in Figure 5-27, and in addition to therapeutic D_2 antagonism, chlorpromazine has numerous receptor actions

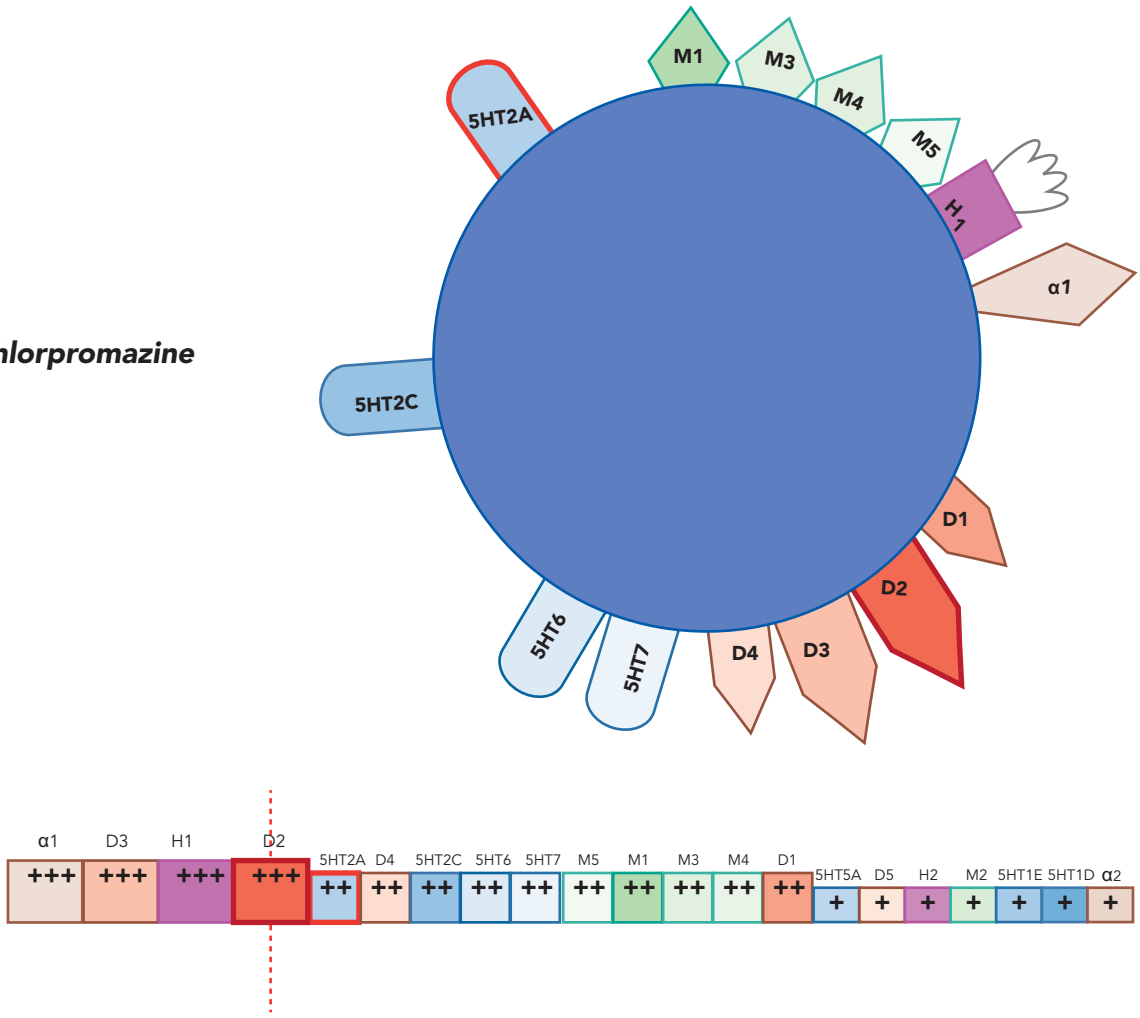


Figure 5-27 Chlorpromazine's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of chlorpromazine. In addition to the D_2 receptor, chlorpromazine binds potently to α_1-adrenergic receptors, D_3 receptors, and H_1 receptors, and also has actions at numerous other receptors as shown. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

associated with sedation (muscarinic, α_1, and histamine antagonism), as well as other side effects (see Figures 5-8 and 5-13). Chlorpromazine is often prescribed to exploit its sedation in patients who do well with sedation, particularly short-term orally or as a short-acting intramuscular injection when needed to treat agitation or a sudden worsening in psychosis, often administered on top of another drug in the same class that is given daily.

Fluphenazine

This agent is another phenothiazine, although more potent than chlorpromazine and less sedating (Figure 5-28). It has both short-acting and long-acting formulations for convenient use, and it is one of the agents for which monitoring plasma drug levels may be useful.

Haloperidol

Haloperidol (Figure 5-29) is one of the most potent D_2 antagonists, and less sedating than some others. It also has both short- and long-acting formulations for convenient use and it, too, is one of the agents for which monitoring plasma drug levels may be useful.

Sulpiride

Sulpiride (Figure 5-30) has D_2 antagonist properties and, as expected, generally causes motor side effects

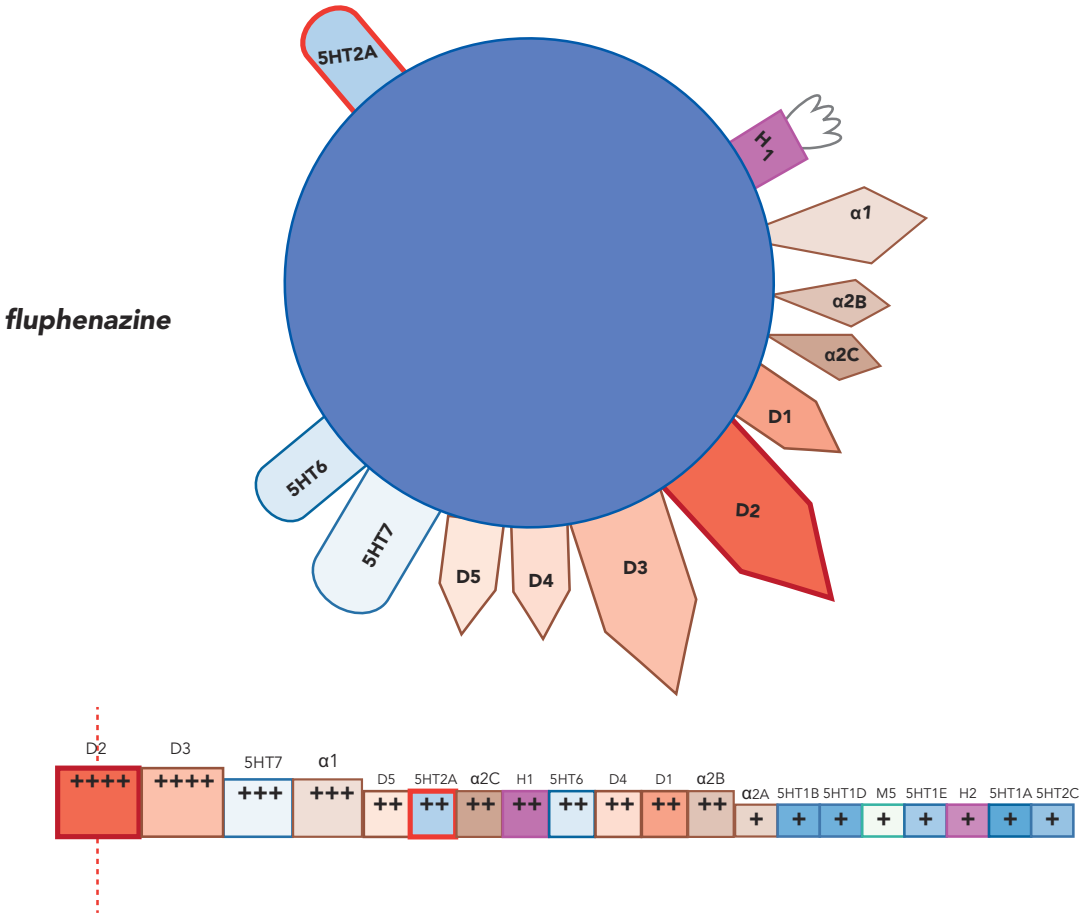


Figure 5-28 **Fluphenazine's pharmacological and binding profile.** This figure portrays a qualitative consensus of current thinking about the binding properties of fluphenazine. Along with D_2 antagonism, fluphenazine has potent actions at D_3, $5HT_7$, and α_1-adrenergic receptors, and binds at numerous other receptors as well. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

and prolactin elevation at usual antipsychotic doses. However, particularly at lower doses, it may be a bit activating, and have efficacy for negative symptoms of schizophrenia and for depression for unclear reasons. Dopamine 3 antagonist/partial agonist actions in depression are discussed in Chapter 7 on treatments for mood disorders, and this is a candidate explanation (see Figure 5-30). Sulpiride remains a popular option for treating psychosis in countries outside the US such as the UK, as it may be better tolerated than some of the other original D_2 agents.

Amisulpride

Amisulpride (Figure 5-31) is structurally related to sulpiride (Figure 5-30) and was developed and marketed outside the US. Some early preclinical data suggest that it might be more selective for mesolimbic/mesostriatal dopamine receptors than for nigrostriatal dopamine receptors, and thus might have a lower propensity for motor side effects at antipsychotic doses. There are reports of amisulpride's efficacy for the negative symptoms of schizophrenia and for depression at doses lower than those used to treat positive symptoms of psychosis. Amisulpride has some D_3 antagonist actions and some weak $5HT_7$ antagonist actions, which may explain some of its negative symptom and antidepressant actions (Figure 5-31). Antidepressant actions of D_3 antagonism/partial agonism and $5HT_7$ antagonism are discussed in Chapter 7. The active isomer of amisulpride is in early clinical testing for possible development in the US.

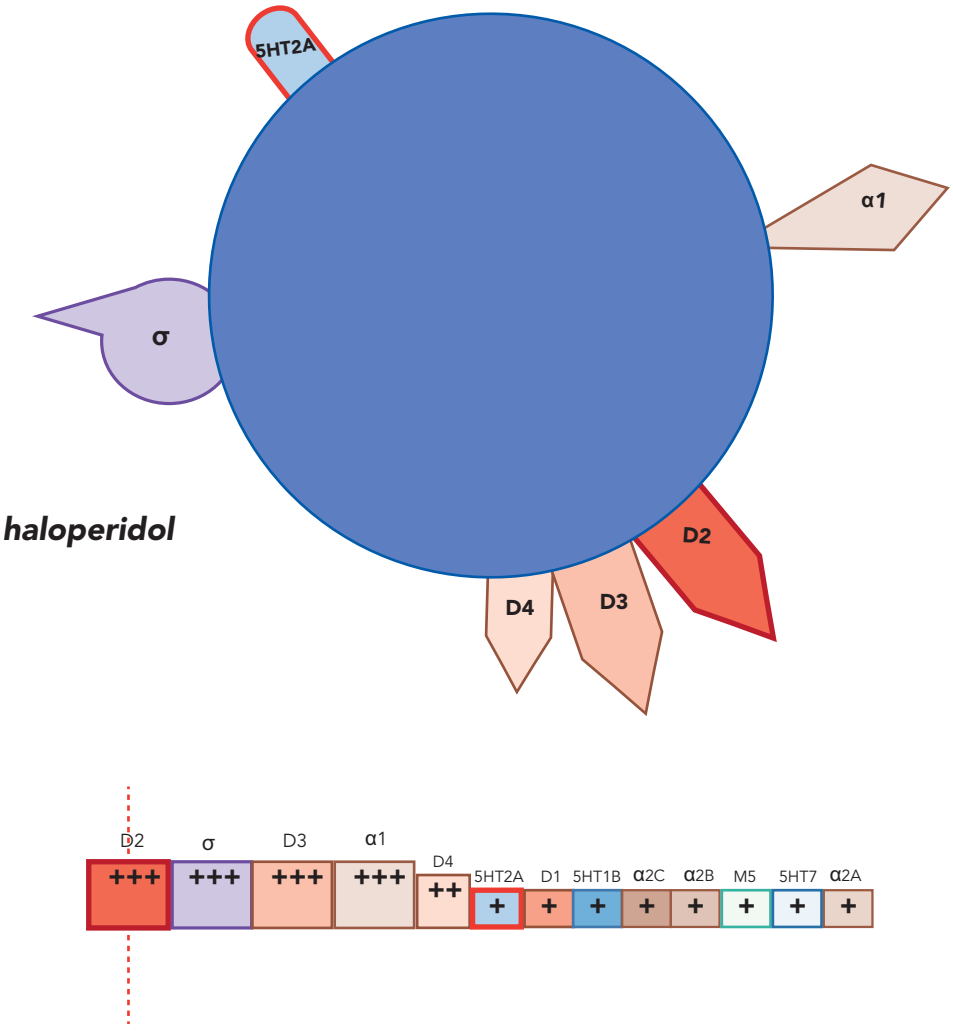


Figure 5-29 Haloperidol's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of haloperidol. Haloperidol binds potently to D_2 receptors as well as to omega, D_3, and α_1-adrenergic receptors. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

AN OVERVIEW OF THE PHARMACOLOGICAL PROPERTIES OF INDIVIDUAL $5HT_{2A}/D_2$ ANTAGONISTS AND $D_2/5HT_{1A}$ PARTIAL AGONISTS: THE PINES (PEENS), MANY DONES AND A RONE, TWO PIPS AND A RIP

We have established that D_2 antagonist/partial agonist properties can explain the antipsychotic efficacy for positive symptoms as well as many side effects of drugs used to treat psychosis. The $5HT_{2A}$ antagonist and/or $5HT_{1A}$ partial agonist properties can help to explain the reduced propensity for motor side effects and prolactin elevation and potential therapeutic enhancement of positive, negative, depressive, and cognitive symptoms. However, the contributions of these properties to each individual agent used to treat psychosis are quite variable. As mentioned above for the original D_2 antagonists, we also characterize all the receptor binding properties of the $D_2/5HT_{2A}/5HT_{1A}$ drugs by binding strips that represent all the known receptors that each drug binds to as one box per receptor, in rank order from most potent on the far left to least potent on the far right (see Figures 5-32

sulpiride

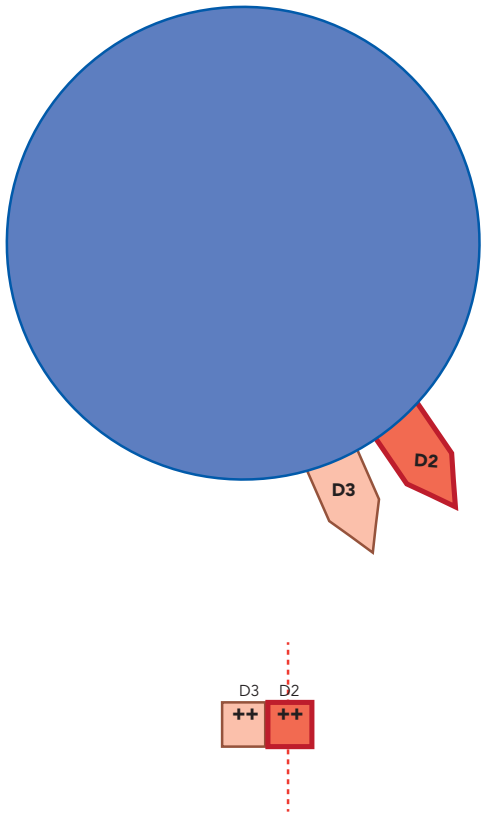


Figure 5-30 Sulpiride's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of sulpiride. At usual antipsychotic doses, sulpiride is a D_2 antagonist and also has D_3 antagonist/partial agonist actions. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

amisulpride

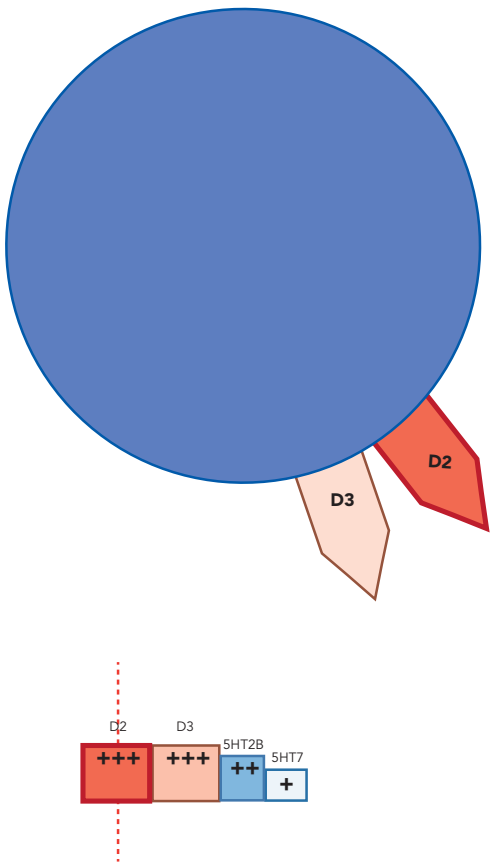


Figure 5-31 Amisulpride's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of amisulpride. In addition to its actions at D_2 receptors, amisulpride has some D_3 antagonist actions and some weak $5HT_7$ antagonist actions. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

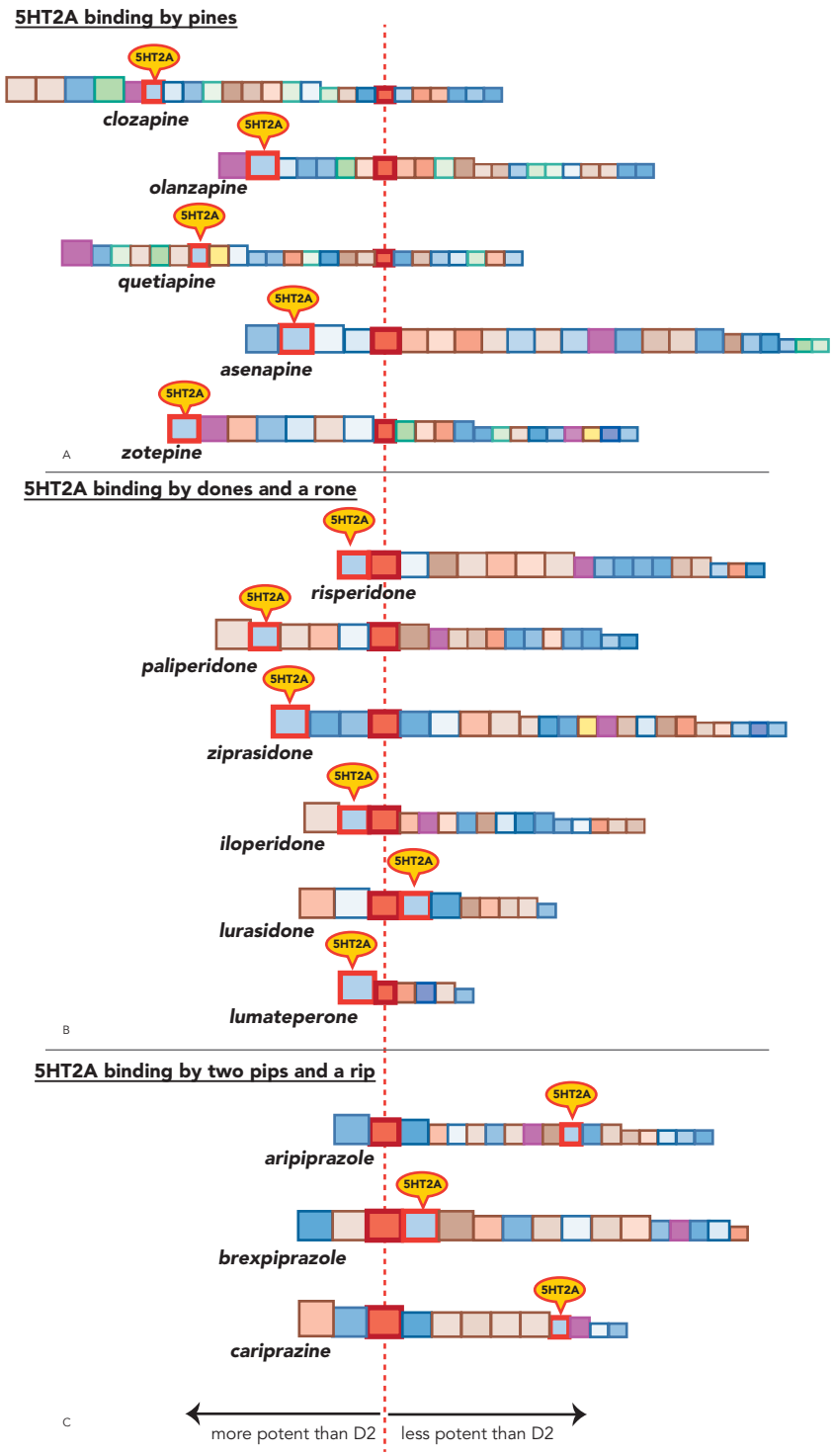


Figure 5-32 $5HT_{2A}$ **binding by drugs used to treat psychosis.** Shown here is a visual depiction of the binding profiles of drugs used to treat psychosis. Each colored box represents a different binding property, with the size and positioning of the box reflecting the binding potency of the property (i.e., size indicates potency relative to a standard K_i scale, while position reflects potency relative to the other binding properties of that drug). The vertical dotted line cuts through the D_2 receptor binding box, with binding properties that are more potent than D_2 on the left and those that are less potent than D_2 on the right. Interestingly, D_2 binding is not the most potent property for any of the agents shown here. (A) The "pines" (i.e., clozapine, olanzapine, quetiapine, asenapine, and zotepine) all bind much more potently to the $5HT_{2A}$ receptor than they do to the D_2 receptor. (B) The "dones" and "rone" (i.e., risperidone, paliperidone, ziprasidone, iloperidone, lurasidone, and lumateperone) also bind more or as potently to the $5HT_{2A}$ receptor as they do to the D_2 receptor. (C) Aripiprazole and cariprazine both bind more potently to the D_2 receptor than to the $5HT_{2A}$ receptor, while brexpiprazole has similar potency at both receptors.

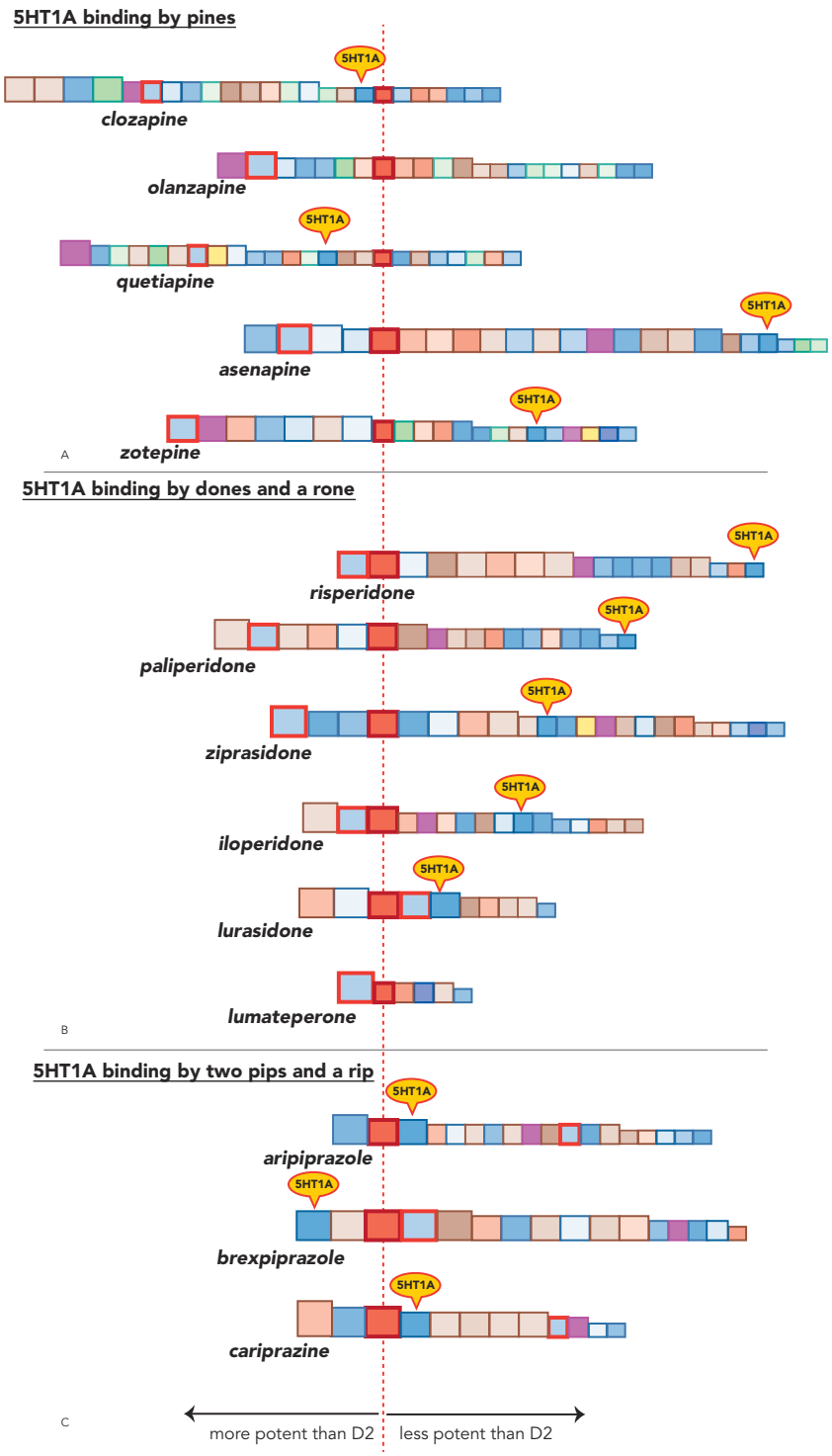


Figure 5-33 $5HT_{1A}$ **binding by drugs used to treat psychosis.** Shown here is a visual depiction of the binding profiles of drugs used to treat psychosis. (A) Clozapine and quetiapine both bind more potently to the $5HT_{1A}$ receptor than they do to the D_2 receptor, while asenapine and zotepine bind less potently to the $5HT_{1A}$ receptor and olanzapine does not bind to it at all. (B) All of the "dones" (i.e., risperidone, paliperidone, ziprasidone, iloperidone, and lurasidone) bind to the $5HT_{1A}$ receptor with less potency than they do to the D_2 receptor; lumateperone does not bind the $5HT_{1A}$ receptor. (C) Aripiprazole, brexpiprazole, and cariprazine each have similar relative potency for the D_2 and $5HT_{1A}$ receptors. $5HT_{1A}$ binding is actually the most potent property of brexpiprazole. Description of graphic: Each colored box represents a different binding property, with the size and positioning of the box reflecting the binding potency of the property (i.e., size indicates potency relative to a standard K_i scale, while position reflects potency relative to the other binding properties of that drug). The vertical dotted line cuts through the D_2 receptor binding box, with binding properties that are more potent than D_2 on the left and those that are less potent than D_2 on the right. Binding at $5HT_{2A}$ (see Figure 5-32) is indicated by an orange outline around the box.

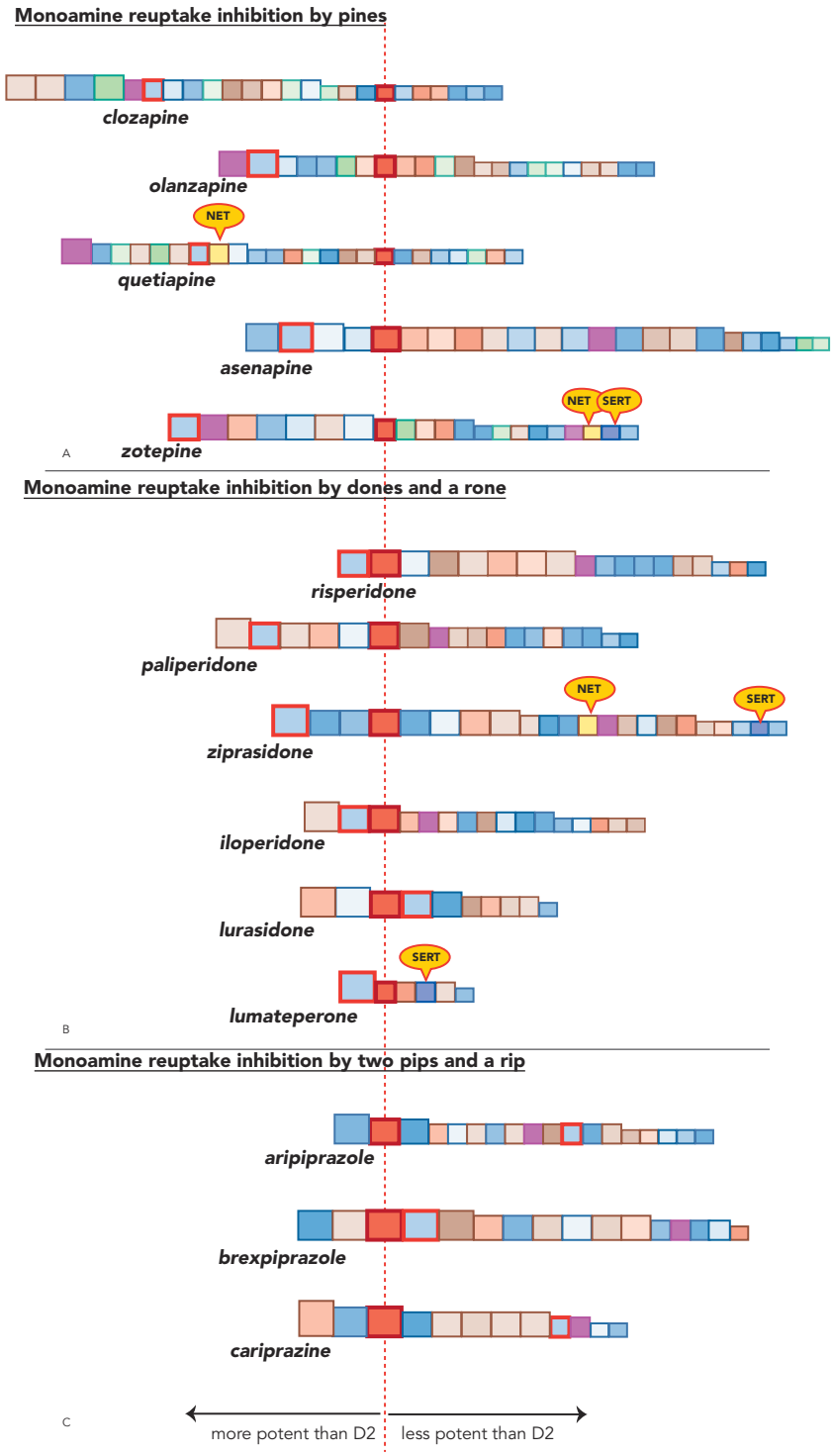


Figure 5-34 Monoamine transporter binding by drugs used to treat psychosis. Shown here is a visual depiction of the binding profiles of drugs used to treat psychosis. (A) Of the "pines," quetiapine is the only one with any relevant monoamine reuptake inhibition. Specifically, it binds to the norepinephrine transporter (NET) with similar potency as it does to the $5HT_{2A}$ receptor, and greater potency than to the D_2 receptor. (B) Ziprasidone binds to NET and the serotonin transporter (SERT), though with less potency than to the D_2 receptor. Lumateperone binds to SERT with similar potency as to the D_2 receptor. (C) Aripiprazole, brexpiprazole, and cariprazine do not bind to any of the monoamine transporters. Description of graphic: Each colored box represents a different binding property, with the size and positioning of the box reflecting the binding potency of the property (i.e., size indicates potency relative to a standard Ki scale, while position reflects potency relative to the other binding properties of that drug). The vertical dotted line cuts through the dopamine 2 (D_2) receptor binding box, with binding properties that are more potent than D_2 on the left and those that are less potent than D_2 on the right. Binding at $5HT_{2A}$ (see Figure 5-32) is indicated by an orange outline around the box.

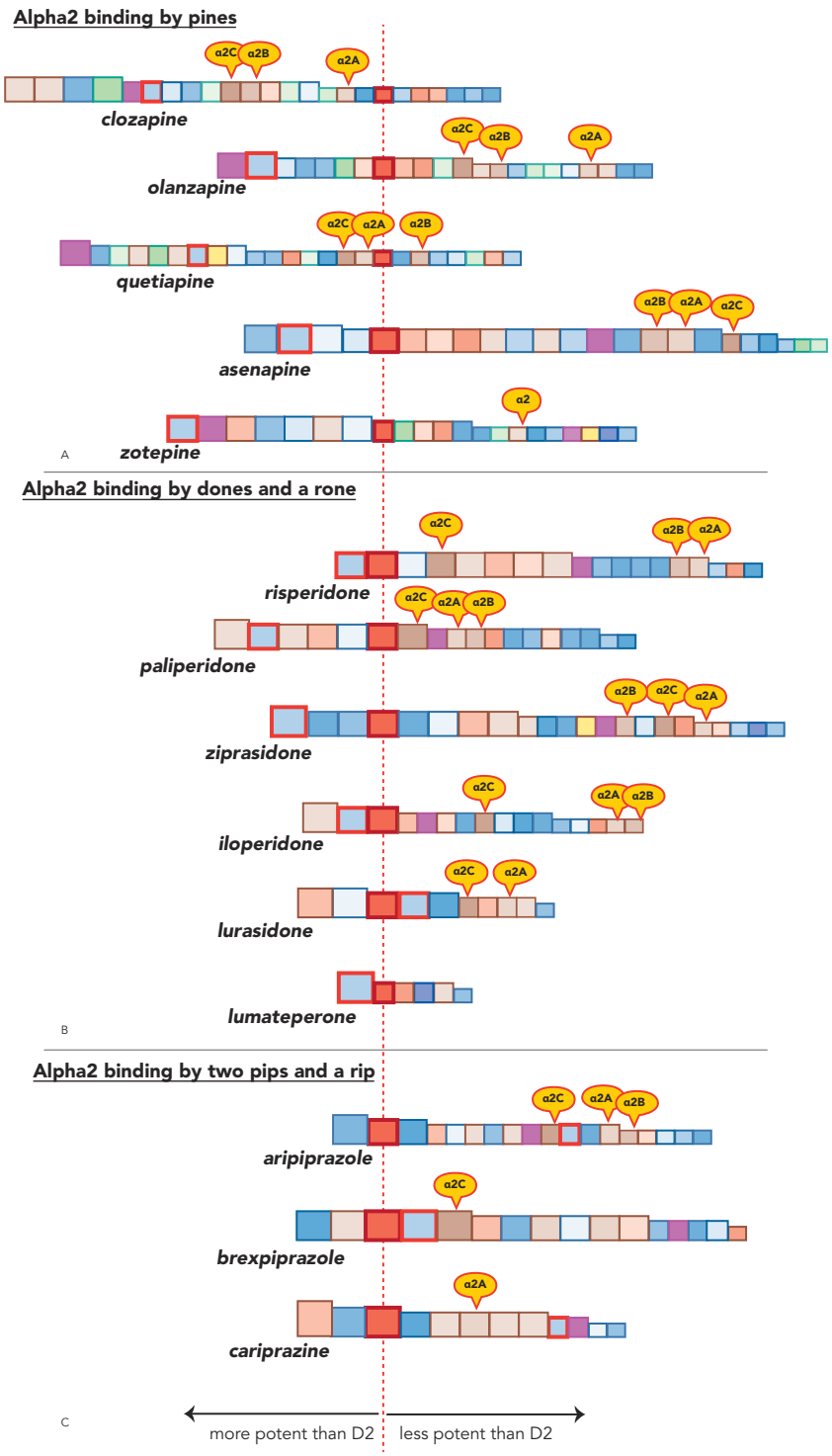


Figure 5-35 **Alpha-2 binding by drugs used to treat psychosis.** Shown here is a visual depiction of the binding profiles of drugs used to treat psychosis. (A) All of the "pines" (i.e., clozapine, olanzapine, quetiapine, asenapine, zotepine) bind to α_2 receptors to varying degrees. Clozapine and quetiapine in particular bind to some α_2 receptor subtypes with greater potency than they do to the D_2 receptor. (B) All of the "dones" (i.e., risperidone, paliperidone, ziprasidone, iloperidone, lurasidone) bind to α_2 receptors to varying degrees. Risperidone and paliperidone bind to the α_{2C} receptor with similar potency as to the D_2 receptor. Lumateperone does not bind to any α_2 receptors. (C) Aripiprazole binds to α_2 receptors with less potency than it does to the D_2 receptor. Brexpiprazole binds to α_{2C} receptors, and cariprazine has some affinity for α_{2A} receptors. Description of graphic: Each colored box represents a different binding property, with the size and positioning of the box reflecting the binding potency of the property (i.e., size indicates potency relative to a standard Ki scale, while position reflects potency relative to the other binding properties of that drug). The vertical dotted line cuts through the dopamine 2 (D_2) receptor binding box, with binding properties that are more potent than D_2 on the left and those that are less potent than D_2 on the right. Binding at $5HT_{2A}$ (see Figure 5-32) is indicated by an orange outline around the box.

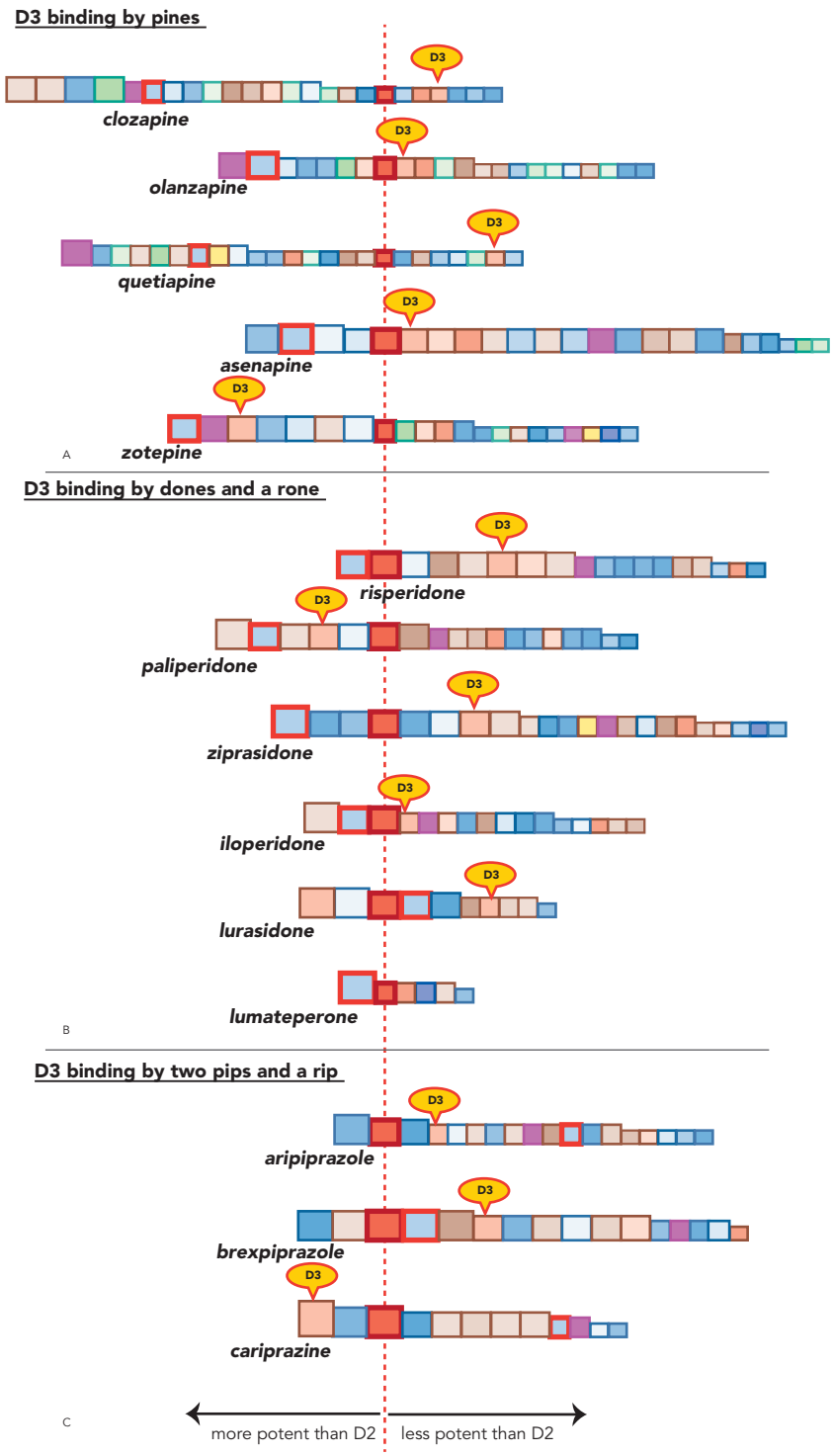


Figure 5-36 D_3 **binding by drugs used to treat psychosis.** Shown here is a visual depiction of the binding profiles of drugs used to treat psychosis. (A) All of the "pines" bind to D_3 receptors, but with varying degrees of potency. (B) Likewise, all of the "dones" bind to D_3 receptors, again with varying degrees of potency. Lumateperone, however, does not bind to D_3 receptors at all. (C) D_3 receptor partial agonism is actually the most potent binding property of cariprazine. Aripiprazole and brexpiprazole also bind to D_3 receptors, less potently than they do to D_2 receptors. Description of graphic: Each colored box represents a different binding property, with the size and positioning of the box reflecting the binding potency of the property (i.e., size indicates potency relative to a standard Ki scale, while position reflects potency relative to the other binding properties of that drug). The vertical dotted line cuts through the dopamine 2 (D_2) receptor binding box, with binding properties that are more potent than D_2 on the left and those that are less potent than D_2 on the right. Binding at $5HT_{2A}$ (see Figure 5-32) is indicated by an orange outline around the box.

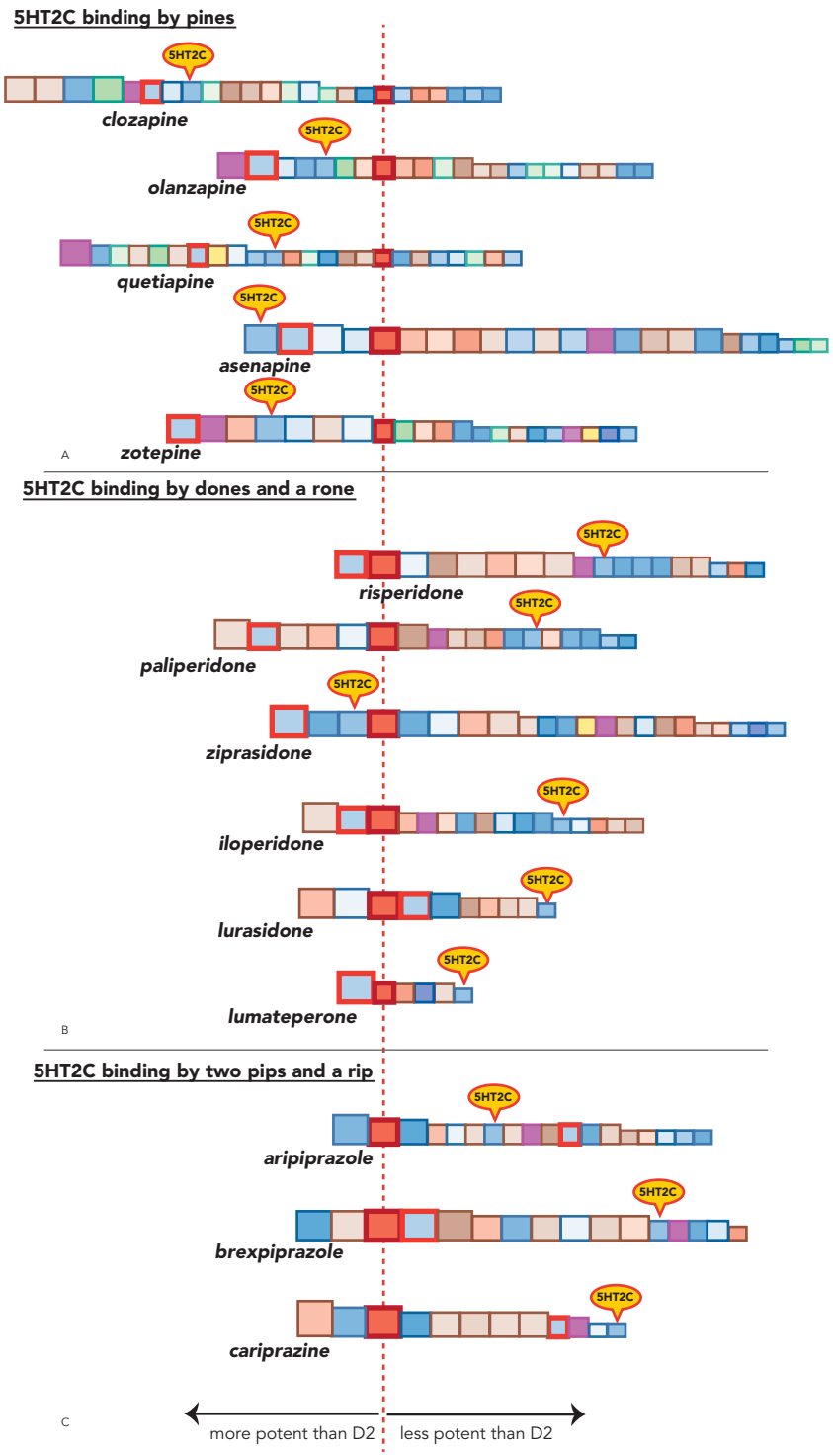


Figure 5-37 $5HT_{2C}$ **binding by drugs used to treat psychosis.** Shown here is a visual depiction of the binding profiles of drugs used to treat psychosis. (A) All of the "pines" (i.e., clozapine, olanzapine, quetiapine, asenapine, zotepine) bind more potently to the $5HT_{2C}$ receptor than they do to the D_2 receptor. (B) All of the "dones" (i.e., risperidone, paliperidone, ziprasidone, iloperidone, lurasidone) as well as lumateperone have some affinity for the $5HT_{2C}$ receptor, although only ziprasidone binds with comparable potency as at the D_2 receptor. (C) Aripiprazole, brexpiprazole, and cariprazine all have relatively weak affinity for the $5HT_{2C}$ receptor. Description of graphic: Each colored box represents a different binding property, with the size and positioning of the box reflecting the binding potency of the property (i.e., size indicates potency relative to a standard Ki scale, while position reflects potency relative to the other binding properties of that drug). The vertical dotted line cuts through the dopamine 2 (D_2) receptor binding box, with binding properties that are more potent than D_2 on the left and those that are less potent than D_2 on the right. Binding at $5HT_{2A}$ (see Figure 5-32) is indicated by an orange outline around the box.

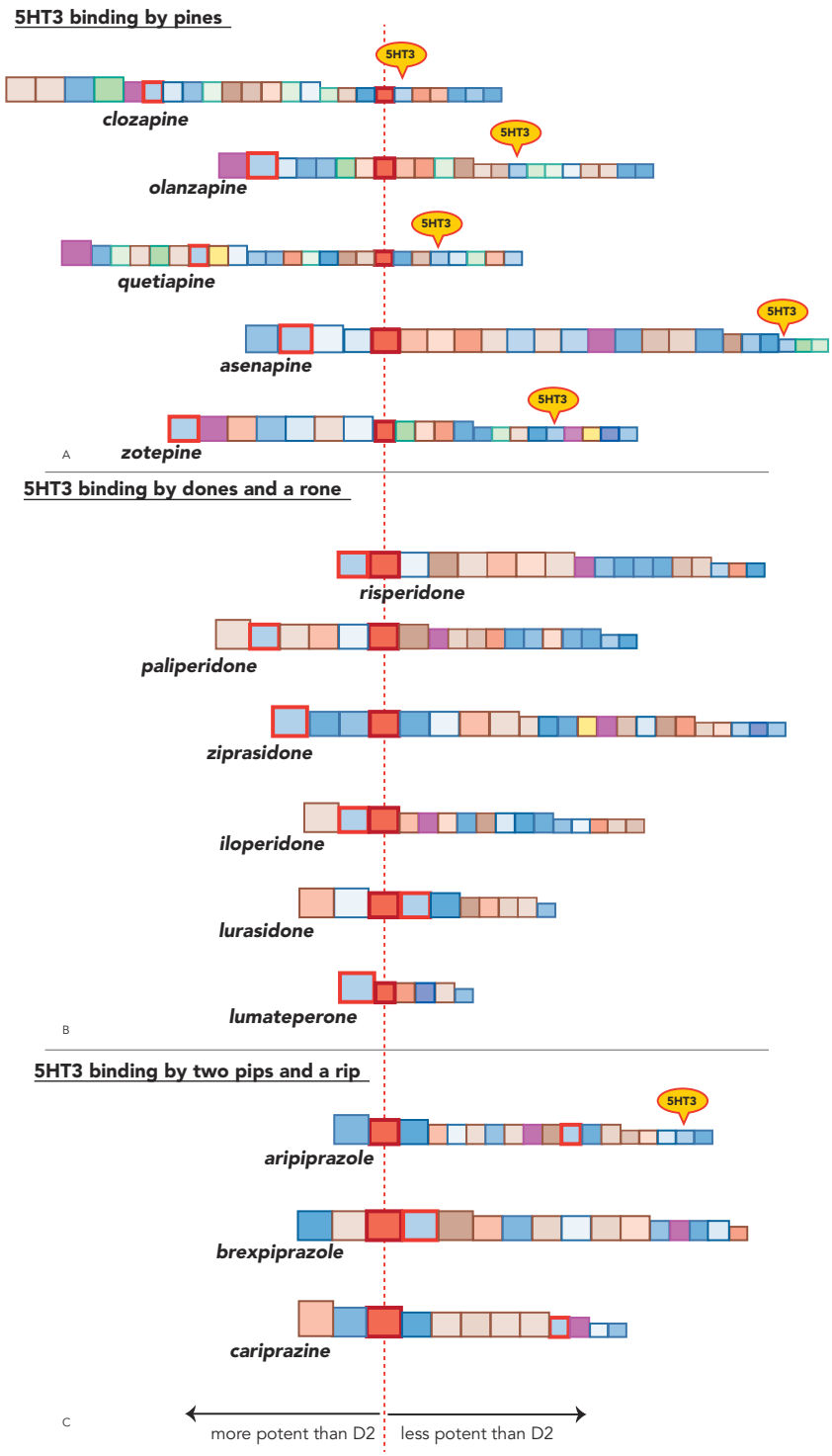


Figure 5-38 **$5HT_3$ binding by drugs used to treat psychosis.** Shown here is a visual depiction of the binding profiles of drugs used to treat psychosis. (A) All of the "pines" bind to $5HT_3$ with less affinity than they have for the D_2 receptor. (B) None of the "dones" or "rone" have any binding activity at $5HT_3$ receptors. (C) Aripiprazole binds weakly to $5HT_3$ receptors. Description of graphic: Each colored box represents a different binding property, with the size and positioning of the box reflecting the binding potency of the property (i.e., size indicates potency relative to a standard Ki scale, while position reflects potency relative to the other binding properties of that drug). The vertical dotted line cuts through the dopamine 2 (D_2) receptor binding box, with binding properties that are more potent than D_2 on the left and those that are less potent than D_2 on the right. Binding at $5HT_{2A}$ (see Figure 5-32) is indicated by an orange outline around the box.

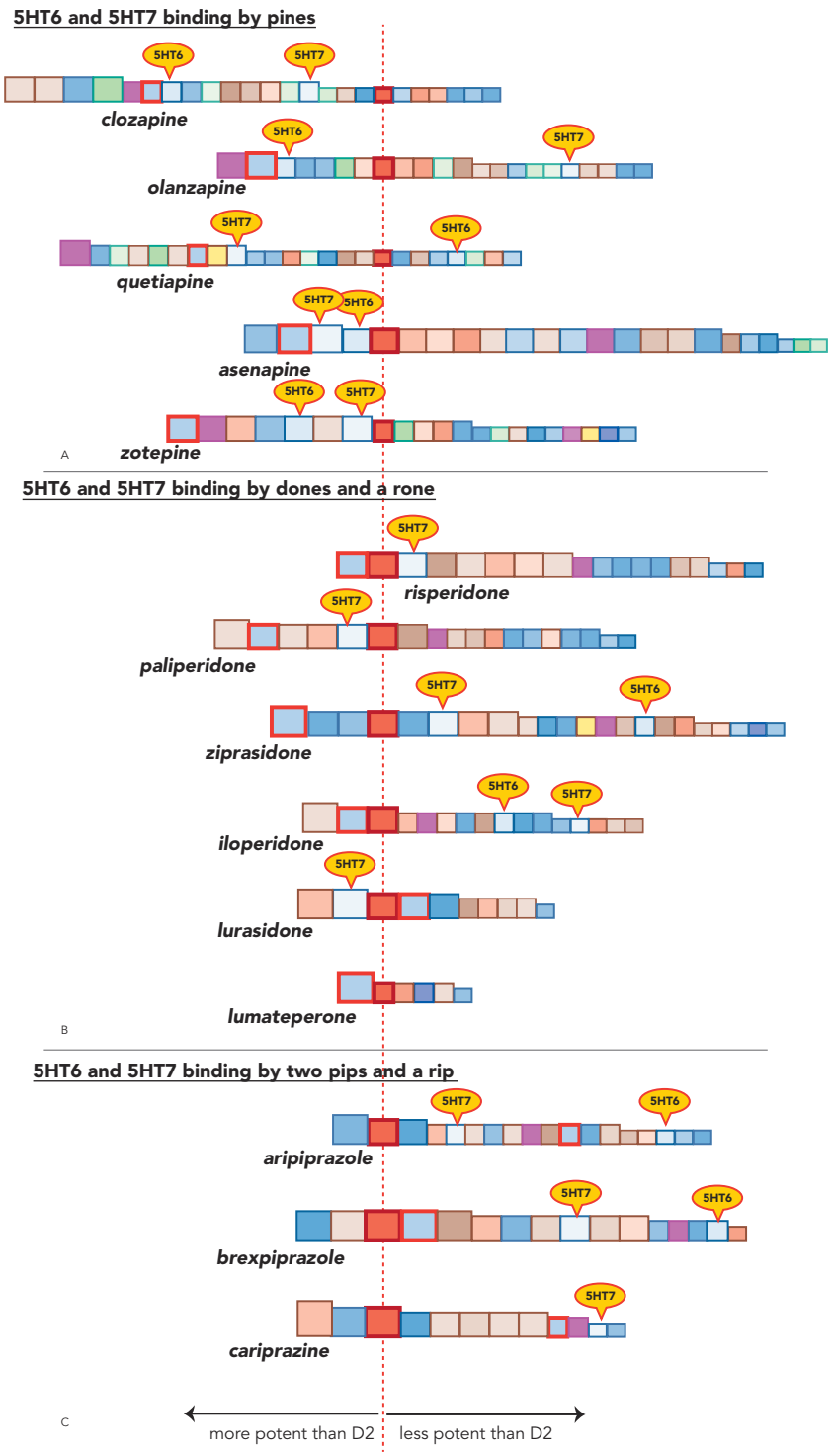


Figure 5-39 $5HT_6$ and $5HT_7$ **binding by drugs used to treat psychosis.** Shown here is a visual depiction of the binding profiles of drugs used to treat psychosis. (A) Clozapine, quetiapine, asenapine, and zotepine each have greater or similar potency for the $5HT_7$ receptor compared to the D_2 receptor, while clozapine, olanzapine, asenapine, and zotepine each have greater or similar potency for the $5HT_6$ receptor compared to the D_2 receptor. (B) Risperidone, paliperidone, ziprasidone, and lurasidone all bind potently to the $5HT_7$ receptor. In fact, lurasidone has greater affinity for the $5HT_7$ receptor than for the D_2 receptor. Ziprasidone and iloperidone also bind to the $5HT_6$ receptor. (C) Aripiprazole, brexpiprazole, and cariprazine all bind to the $5HT_7$ receptor, though none with more potency than for the D_2 receptor. Description of graphic: Each colored box represents a different binding property, with the size and positioning of the box reflecting the binding potency of the property (i.e., size indicates potency relative to a standard Ki scale, while position reflects potency relative to the other binding properties of that drug). The vertical dotted line cuts through the dopamine 2 (D_2) receptor binding box, with binding properties that are more potent than D_2 on the left and those that are less potent than D_2 on the right. Binding at $5HT_{2A}$ (see Figure 5-32) is indicated by an orange outline around the box.

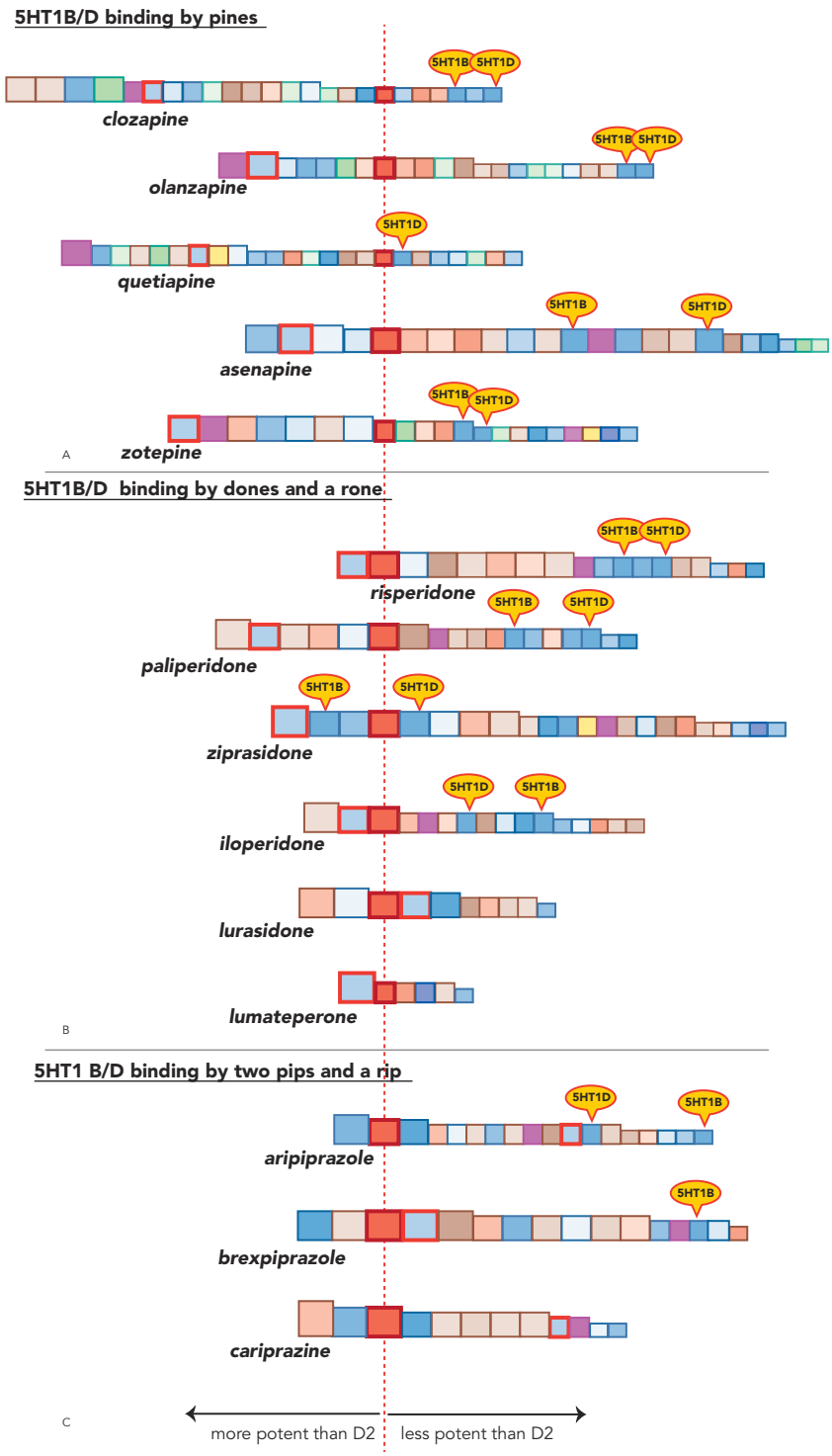


Figure 5-40 $5HT_{1B/D}$ **binding by drugs used to treat psychosis.** Shown here is a visual depiction of the binding profiles of drugs used to treat psychosis. (A) Clozapine, olanzapine, asenapine, and zotepine all bind relatively weakly to the $5HT_{1B}$ and $5HT_{1D}$ receptors, while quetiapine binds relatively weakly only to the $5HT_{1D}$ receptor. (B) Risperidone, paliperidone, ziprasidone, and iloperidone all have some affinity for the $5HT_{1B}$ and $5HT_{1D}$ receptors. In particular, ziprasidone binds with similar potency to these two receptors as it does to the D_2 receptor. Lurasidone and lumateperone do not bind to $5HT_{1B/D}$ receptors. (C) Aripiprazole and brexpiprazole each bind weakly to the $5HT_{1B}$ receptor; aripiprazole also binds to the $5HT_{1D}$ receptor. Cariprazine does not bind to $5HT_{1B/D}$ receptors. Description of graphic: Each colored box represents a different binding property, with the size and positioning of the box reflecting the binding potency of the property (i.e., size indicates potency relative to a standard Ki scale, while position reflects potency relative to the other binding properties of that drug). The vertical dotted line cuts through the dopamine 2 (D_2) receptor binding box, with binding properties that are more potent than D_2 on the left and those that are less potent than D_2 on the right. Binding at $5HT_{2A}$ (see Figure 5-32) is indicated by an orange outline around the box.

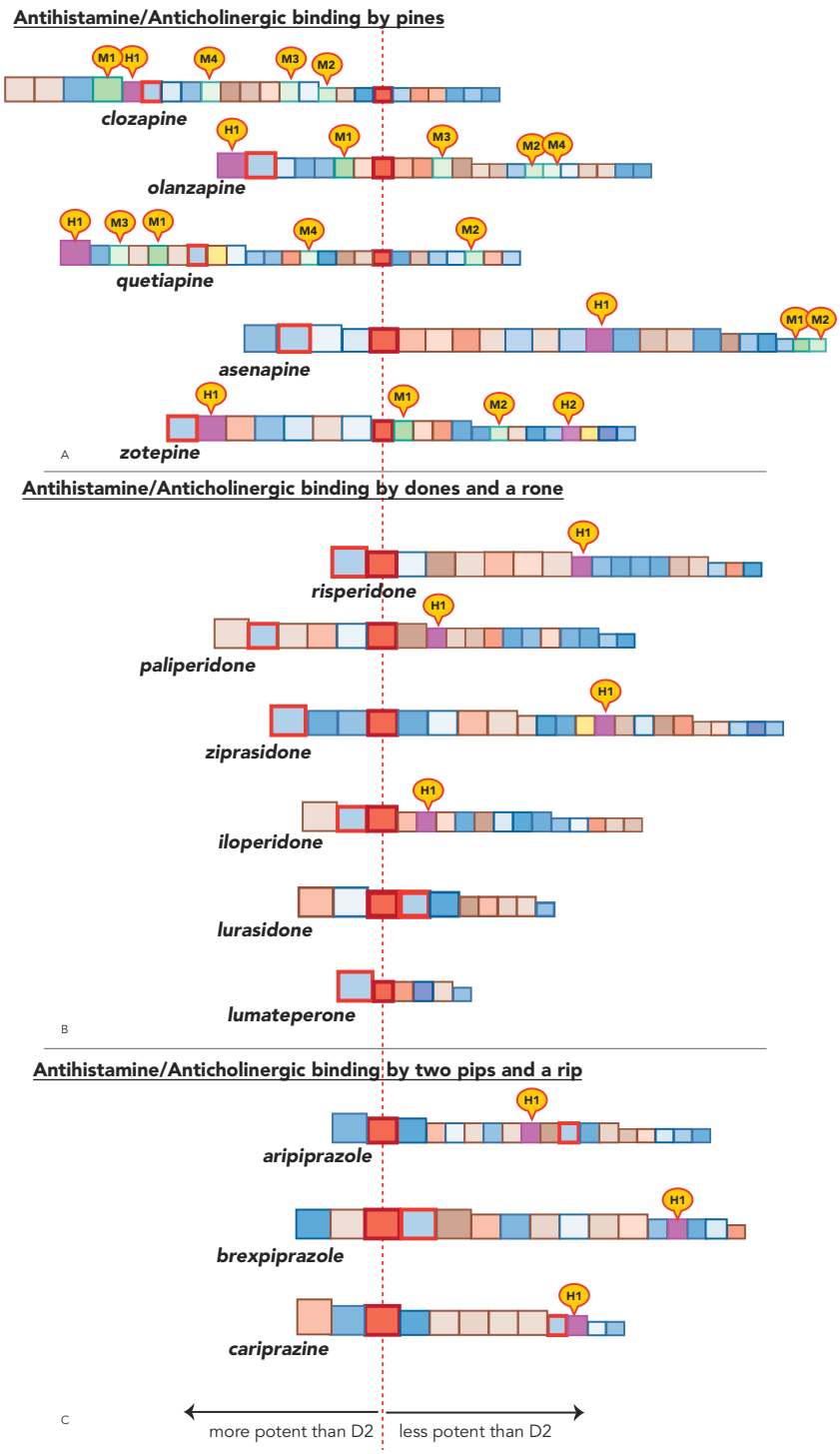


Figure 5-41 Antihistamine/anticholinergic binding by drugs used to treat psychosis. Shown here is a visual depiction of the binding profiles of drugs used to treat psychosis. (A) Clozapine, olanzapine, quetiapine, and zotepine all have strong potency for histamine 1 receptors; clozapine, olanzapine, and quetiapine also have strong potency for muscarinic receptors. Asenapine has some affinity for histamine H_1 receptors and weak affinity for muscarinic receptors. (B) None of the "dones" or "rones" have anticholinergic properties. Risperidone, paliperidone, ziprasidone, and iloperidone all have some potency for H_1 receptors. (C) Aripiprazole, brexpiprazole, and cariprazine all bind at the H_1 receptor with less potency than they do to the D_2 receptor, and do not bind to muscarinic receptors. Description of graphic: Each colored box represents a different binding property, with the size and positioning of the box reflecting the binding potency of the property (i.e., size indicates potency relative to a standard Ki scale, while position reflects potency relative to the other binding properties of that drug). The vertical dotted line cuts through the dopamine 2 (D_2) receptor binding box, with binding properties that are more potent than D_2 on the left and those that are less potent than D_2 on the right. Binding at $5HT_{2A}$ (see Figure 5-32) is indicated by an orange outline around the box.

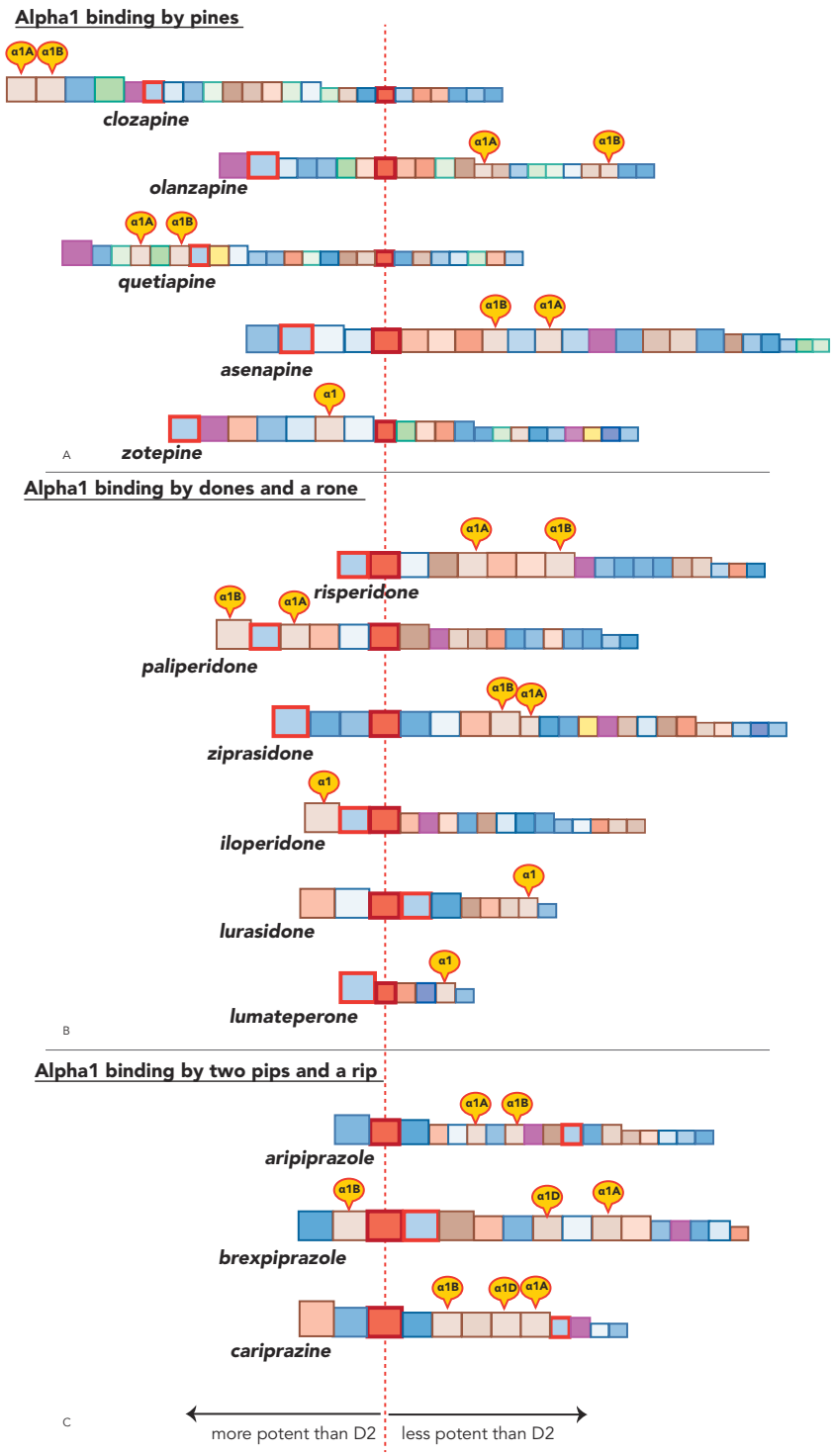


Figure 5-42 Alpha-1 binding by drugs used to treat psychosis. Shown here is a visual depiction of the binding profiles of drugs used to treat psychosis. (A) Clozapine, quetiapine, and zotepine each have greater potency for α_1 receptors than for the D_2 receptor, while asenapine binds with similar potency to the α_2 and the D_2 receptors. (B) All of the "dones" (i.e., risperidone, paliperidone, ziprasidone, iloperidone, lurasidone) as well as lumateperone bind to the α_1 receptor. In particular, paliperidone and iloperidone bind with greater potency than they do to the D_2 receptor. (C) Aripiprazole, brexpiprazole, and cariprazine each have some binding potency at α_1 receptors. Description of graphic: Each colored box represents a different binding property, with the size and positioning of the box reflecting the binding potency of the property (i.e., size indicates potency relative to a standard Ki scale, while position reflects potency relative to the other binding properties of that drug). The vertical dotted line cuts through the dopamine 2 (D_2) receptor binding box, with binding properties that are more potent than D_2 on the left and those that are less potent than D_2 on the right. Binding at $5HT_{2A}$ (see Figure 5-32) is indicated by an orange outline around the box.

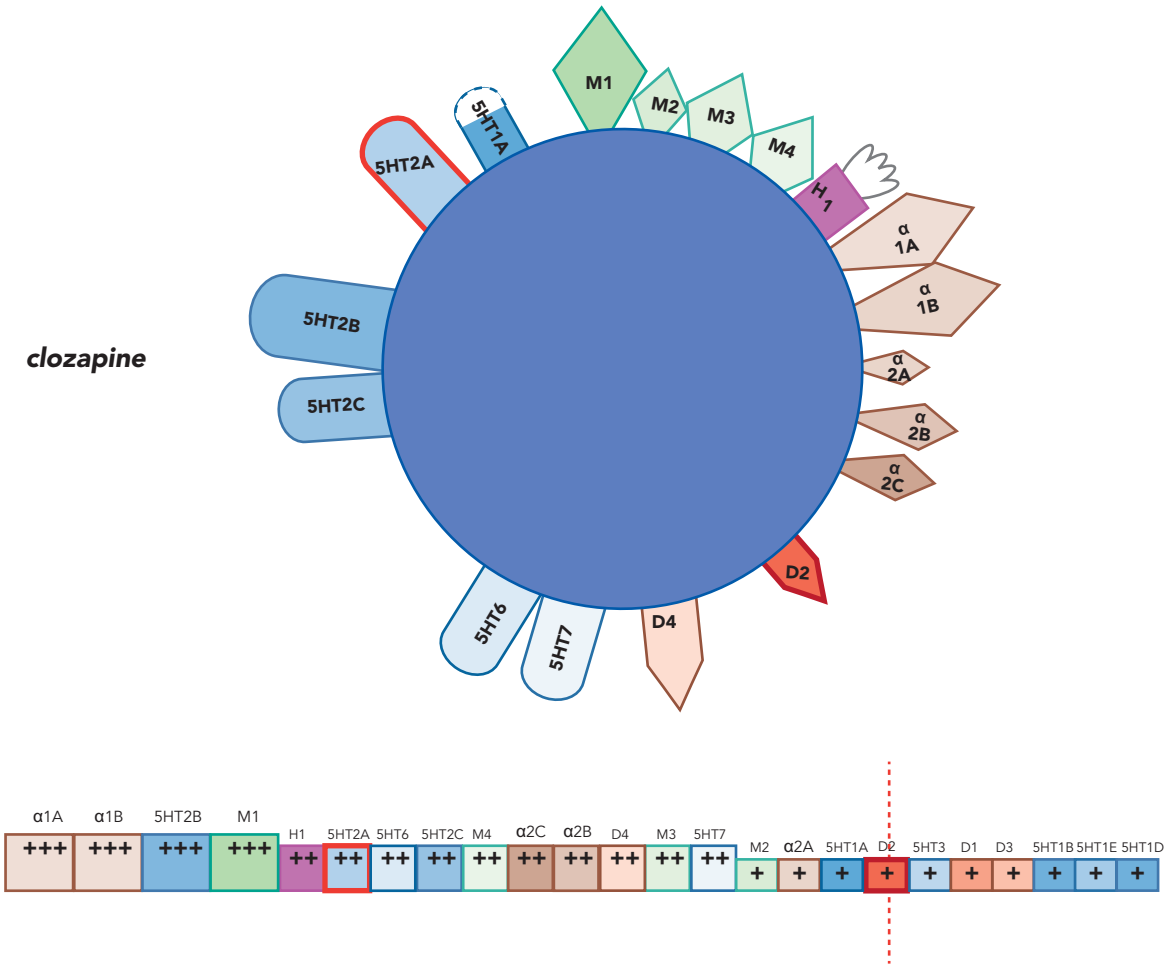


Figure 5-43 Clozapine's pharmacological icon and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of clozapine. In addition to $5HT_{2A}/D_2$ antagonism, numerous other binding properties have been identified for clozapine, most of which are more potent than its binding at the D_2 receptor. It is unknown which of these contribute to clozapine's special efficacy or to its unique side effects. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

through 5-63). These pharmacological binding properties are again represented as a row of semi-quantitative and rank-order relative binding potencies at numerous neurotransmitter receptors, with each figure highlighting a specific receptor so the relative binding potencies of all these drugs can be compared at a glance. More potent binding (higher affinity) is shown to the left of the value for the D_2 receptor, which itself is indicated by a vertical dotted line; less potent binding (lower affinity) is shown to the right.

Determining whether all drugs for psychosis should be in a single class, or a small number of classes, or whether each drug should be treated uniquely, is a bit like the famous quote of baseball great Yogi Berra, when he was once asked if he and his son were a lot the same. He paused, pondered for a bit, then answered, "Yes, but our similarities are different." The same could be said for all these drugs used to treat psychosis (and mood, see Chapter 7). In some ways they are a lot the same, but in many ways their similarities are different!

So, how are they similar? Beginning with the relative potencies of each of these agents for $5HT_{2A}$ receptors compared to D_2 receptors, the reader can see at a glance in Figure 5-32 that almost all agents show $5HT_{2A}$ binding to the left of D_2 binding, meaning these drugs with $5HT_{2A}$ to the left all have higher affinity for $5HT_{2A}$ receptors than for D_2 receptors and would be expected to bind even more to $5HT_{2A}$ receptors than to D_2 receptors. The

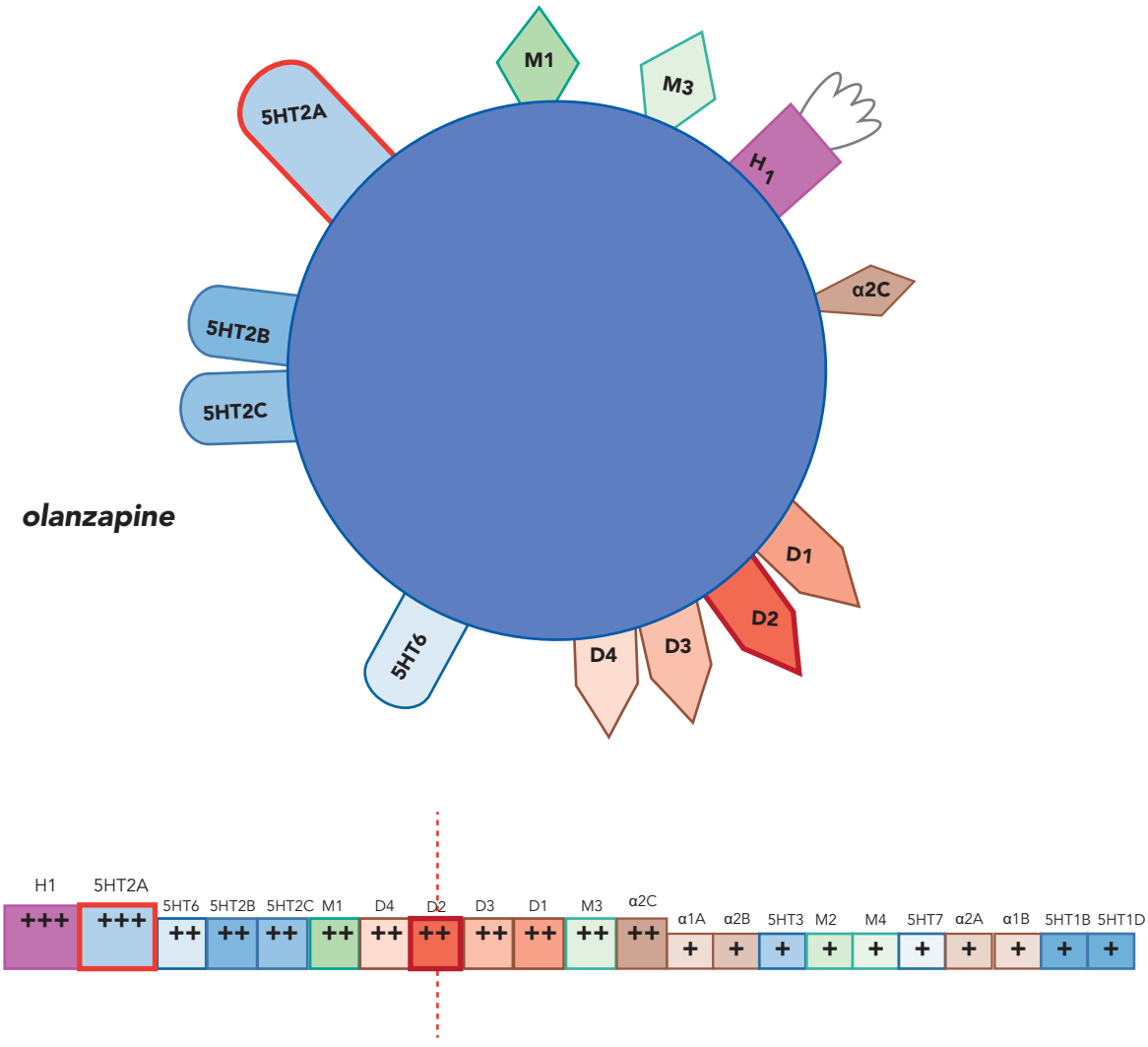


Figure 5-44 Olanzapine's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of olanzapine. Olanzapine binds at several receptors more potently than it does at the D_2 receptor; in fact, it has strongest potency for the H_1 and $5HT_{2A}$ receptors. Olanzapine's $5HT_{2C}$ antagonist properties may contribute to its efficacy for mood and cognitive symptoms, although together with its H_1 antihistamine properties they could also contribute to its propensity to cause weight gain. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

exceptions are the D_2 partial agonists, but these drugs all show comparable potency for $5HT_{1A}$ receptors and D_2 receptors (Figure 5-33). However, D_2 antagonists with potent $5HT_{2A}$ properties generally do not have high affinity for $5HT_{1A}$ receptors (compare drugs in Figure 5-32 with the same drugs in Figure 5-33 for their $5HT_{2A}$ versus their $5HT_{1A}$ properties). Maybe that does not really matter. Recall that many of the same downstream actions of $5HT_{2A}$ antagonism are also caused by $5HT_{1A}$ partial agonism (see discussion above and Figures 5-17 and 5-22). Yet, no two drugs are exactly the same and it can be expected that their clinical properties linked to $5HT_{2A}$ and $5HT_{1A}$ receptors may also differ, even though essentially all drugs listed have $5HT_{2A}$ antagonism, $5HT_{1A}$ partial agonism, or both, at least to some degree. One example of how drugs that all have potent $5HT_{2A}$ antagonist properties nevertheless differ from each other is the observation that the greater the separation of $5HT_{2A}$ binding from D_2 binding (i.e., the further $5HT_{2A}$ is to the left of D_2), the less D_2 receptor occupancy may be

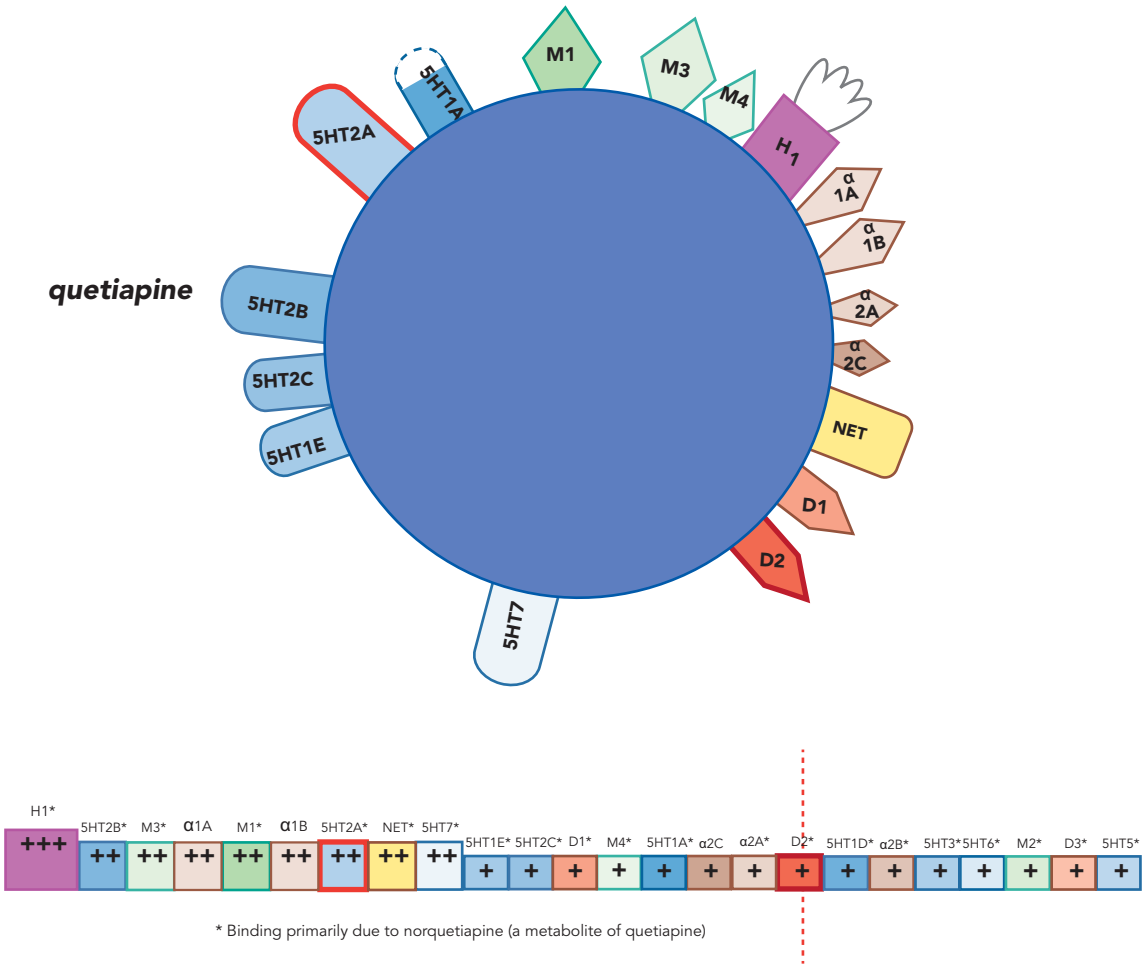


Figure 5-45 Quetiapine's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of quetiapine. Quetiapine does not actually have particularly potent binding at D_2 receptors. Quetiapine's prominent H_1 antagonist properties probably contribute to its ability to enhance sleep, and this may contribute as well to its ability to improve sleep disturbances in bipolar and unipolar depression as well as in anxiety disorders. However, this property can also contribute to daytime sedation, especially combined with M_1 antimuscarinic and α_1-adrenergic antagonist properties. A potentially important active metabolite of quetiapine, norquetiapine, may contribute additional actions at receptors, as noted in the binding profile with an asterisk. $5HT_{1A}$ partial agonist actions, norepinephrine transporter (NET) inhibition, and $5HT_{2C}$, α_2, and $5HT_7$ antagonist actions may all contribute to mood-improving properties of quetiapine. However, $5HT_{2C}$ antagonist actions combined with H_1 antagonist actions may contribute to weight gain. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

needed for an antipsychotic effect, explaining why studies show that those with the widest separation (namely, lumateperone, quetiapine, and clozapine) also have the lowest D_2 occupancy at antipsychotic doses, in fact lower than 60%. Perhaps all this discussion is just a fancy way of saying that the drugs to treat psychosis are all the same but their similarities are different.

If what is the same about these drugs is D_2 binding and some degree of binding to either $5HT_{2A}$ or $5HT_{1A}$ receptors, that is where the similarities stop. These various agents have many, many pharmacological properties other than just dopamine and serotonin receptor binding, and these additional pharmacological properties are shown in the next nine figures (Figures 5-34 through 5-42). The first seven of these allow visual comparisons of putative antidepressant mechanisms mentioned above and that will be discussed in detail in Chapter 7. For example, the various receptor properties linked to postulated antidepressant actions are shown in the following figures:

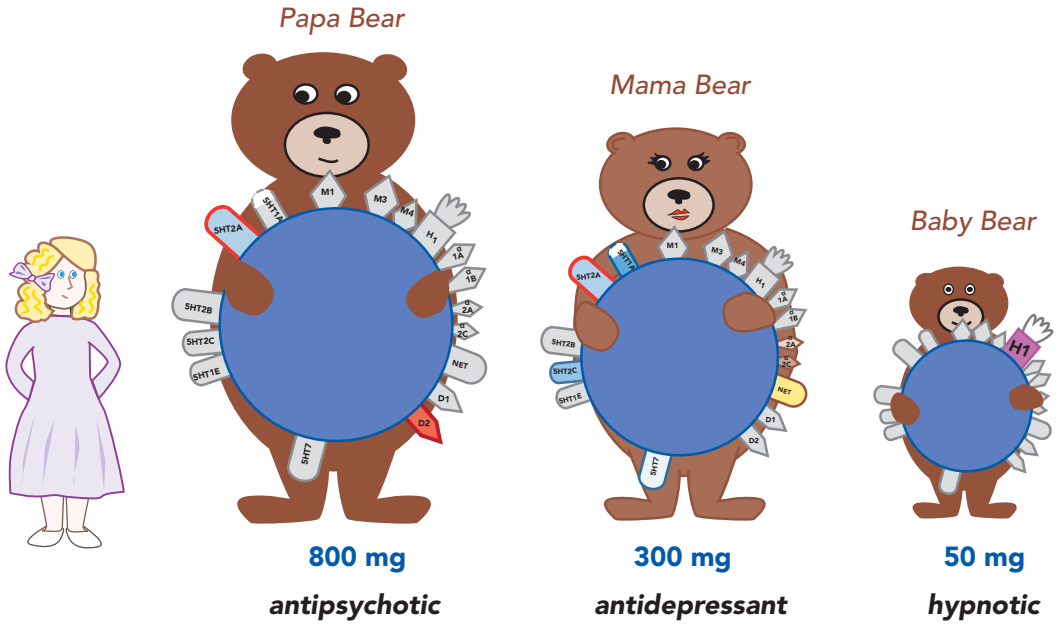


Figure 5-46 **Binding profile of quetiapine at different doses.** The binding properties of quetiapine vary depending on the dose used. At antipsychotic doses (i.e., up to 800 mg/day), quetiapine has a relatively wide binding profile, with actions at multiple serotonergic, muscarinic, and α-adrenergic receptors. Histamine 1 receptor blockade is also present. At antidepressant doses (i.e., approximately 300 mg/day), the binding profile of quetiapine is more selective and includes norepinephrine reuptake inhibition, $5HT_{1A}$ partial agonism, and $5HT_{2A}$, α_2, $5HT_{2C}$, and $5HT_7$ antagonism. At sedative hypnotic doses (i.e., 50 mg/day), the most prominent pharmacological property of quetiapine is H_1 antagonism.

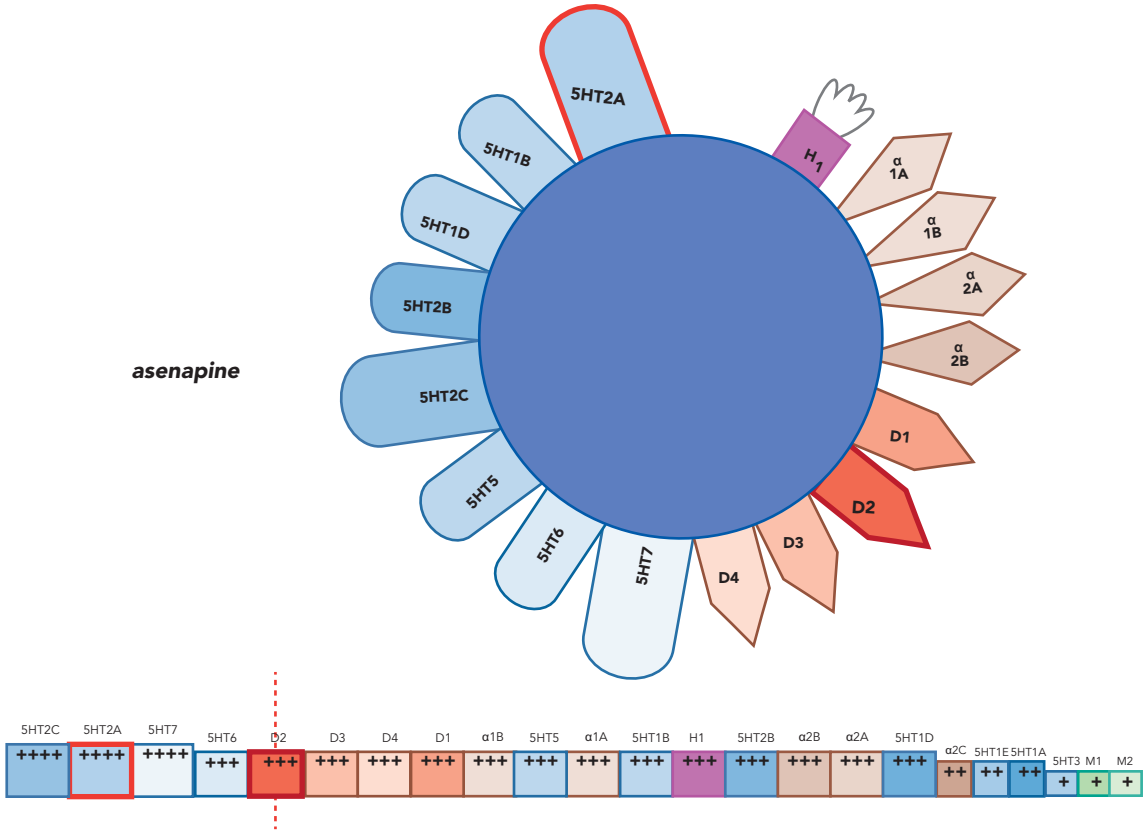


Figure 5-47 **Asenapine's pharmacological and binding profile.** This figure portrays a qualitative consensus of current thinking about the binding properties of asenapine. Asenapine has a complex binding profile, with potent binding at multiple serotonergic and dopaminergic receptors, α_1 and α_2 receptors, and H_1 histamine receptors. In particular, $5HT_{2C}$ antagonist properties may contribute to its efficacy for mood and cognitive symptoms, while $5HT_7$ antagonist properties may contribute to its efficacy for mood, cognitive, and sleep symptoms. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

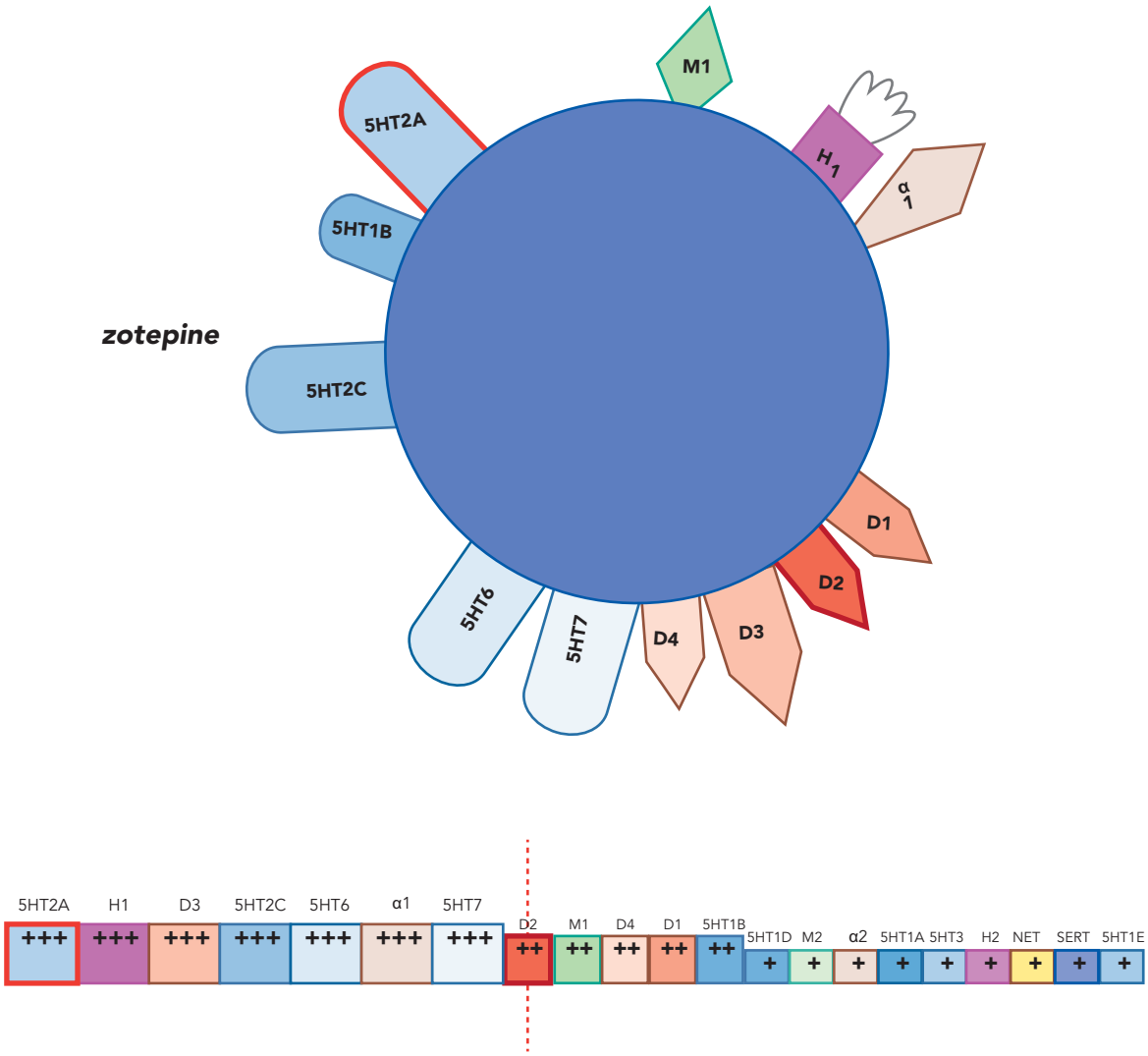


Figure 5-48 Zotepine's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of zotepine. Zotepine is a $5HT_{2C}$ antagonist, an α_2 antagonist, and a $5HT_7$ antagonist, suggesting potential antidepressant effects. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

monoamine reuptake blocking properties (Figure 5-34)
α_2 antagonism (Figure 5-35)
D_3 partial antagonism/partial agonism (Figure 5-36)
$5HT_{2C}$ antagonism (Figure 5-37)
$5HT_3$ antagonism (Figure 5-38)
$5HT_6$ and $5HT_7$ antagonism (Figure 5-39)
$5HT_{1B/D}$ antagonism (Figure 5-40)

Also, the various receptor binding properties theoretically linked to side effects are shown in these figures:

antihistamine and anticholinergic (Figure 5-41),
α_1 antagonism (Figure 5-42).

The point of these figures showing all these binding properties is to be able to see the differences amongst these drugs as well as the similarities. Individual agents have quite different mechanisms theoretically linked to antidepressant actions that may help explain why some are indicated for unipolar or bipolar depression and others are not, and also why one patient's depression may respond to one drug in this group but not to another. Another way to help the reader take this tour de force through two dozen complicated drugs a bit more easily,

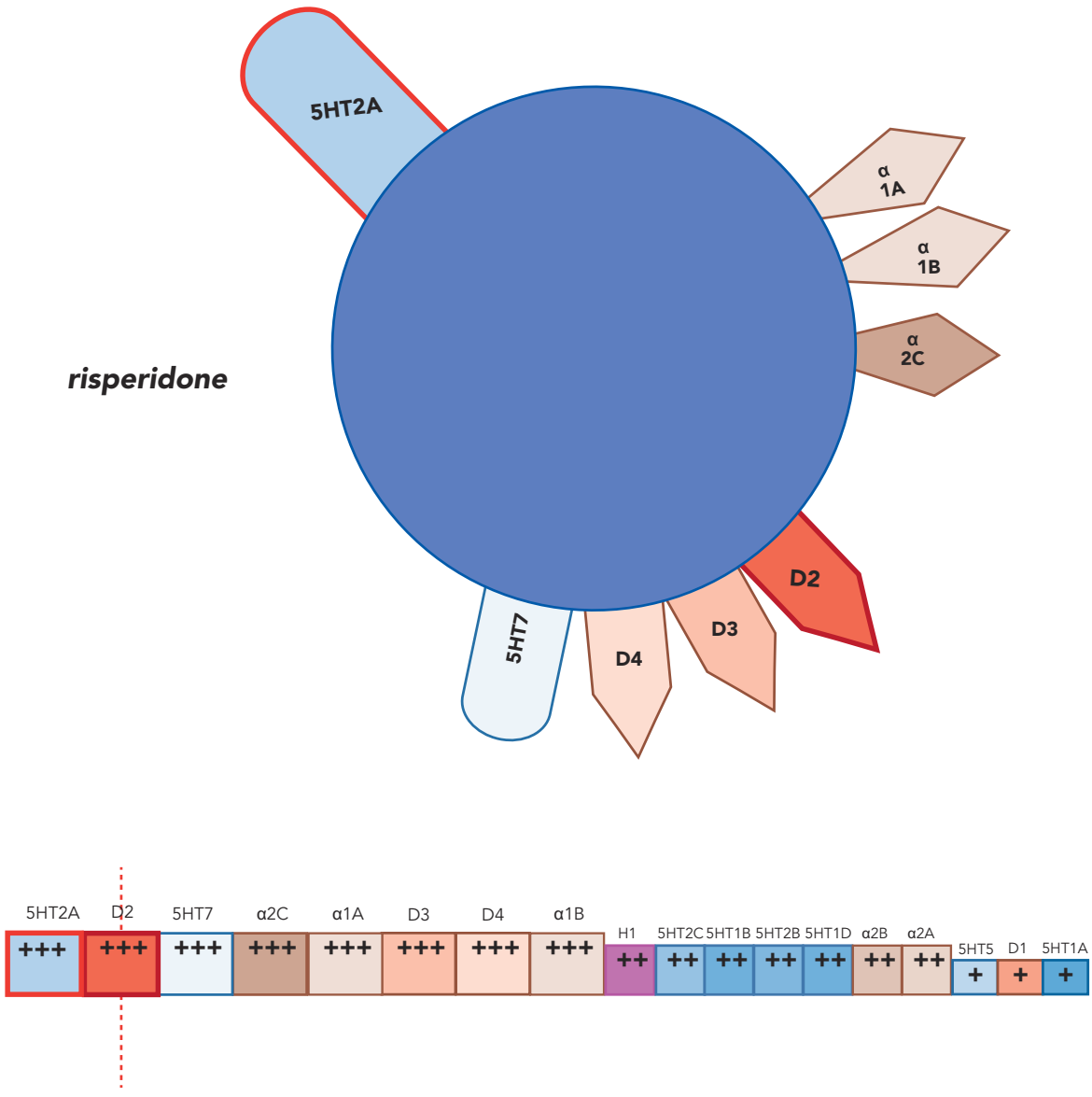


Figure 5-49 Risperidone's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of risperidone. Alpha-2 antagonist properties may contribute to efficacy for depression, but this can be diminished by simultaneous α_1 antagonist properties, which can also contribute to orthostatic hypotension and sedation. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

and for a bit of fun, is to organize all of them into three whimsical groups:

the pines (peens)
many dones and a rone
two pips and a rip

The members of each of the three groups have already been organized this way in Figures 5-32 through 5-42 and now we provide a brief description of each individual agent clustered into each of these three groups to try to make learning their distinctions easier and memorable.

The Pines (Peens)

Clozapine

Clozapine (Figure 5-43) is widely recognized as being particularly effective when other drugs for psychosis fail, and is thus the "gold standard" for efficacy in

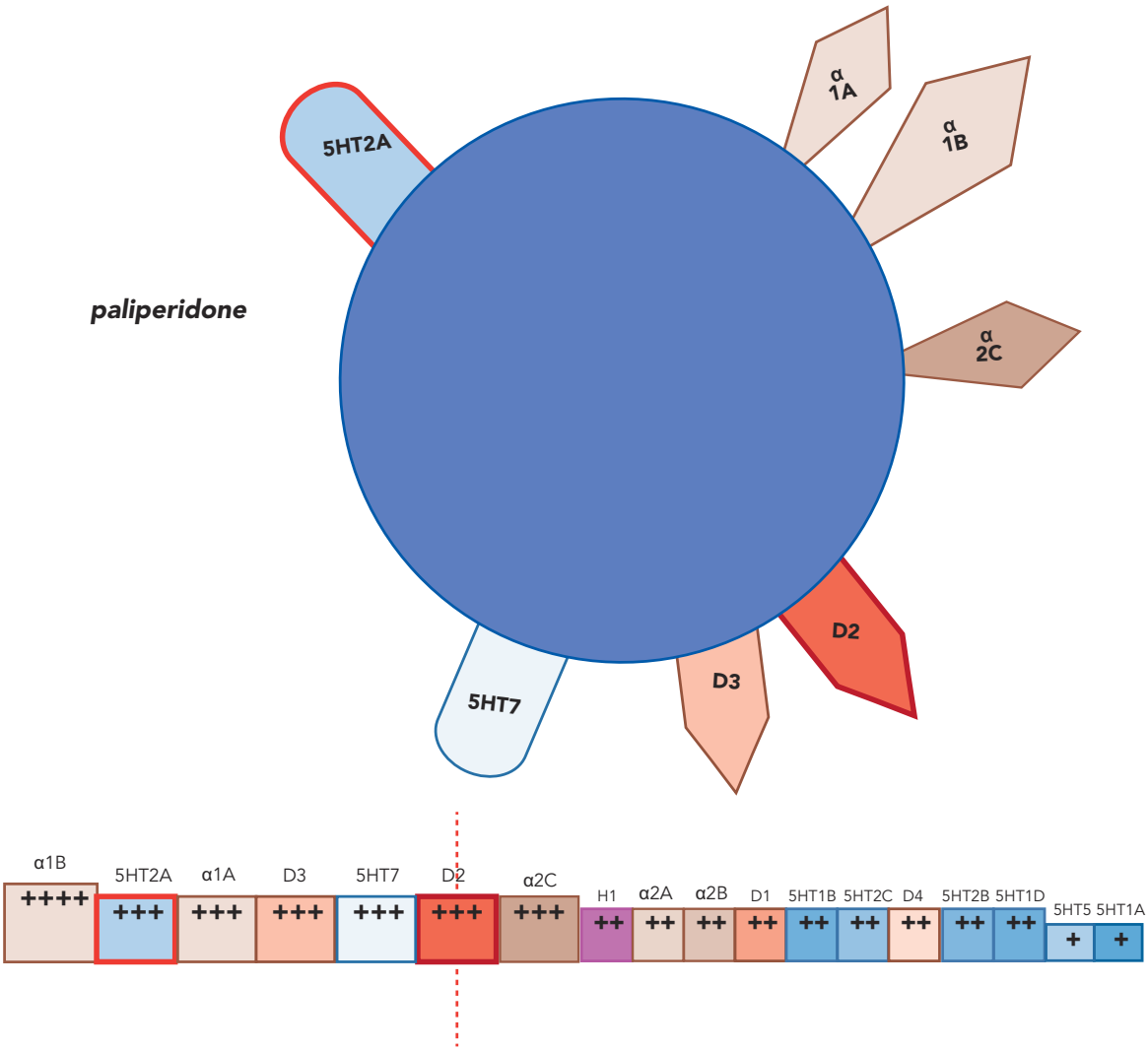


Figure 5-50 Paliperidone's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of paliperidone, the active metabolite of risperidone. Paliperidone shares many pharmacological properties with risperidone. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

schizophrenia. Clozapine is also the only antipsychotic that has been documented to reduce the risk of suicide in schizophrenia and may have a particular niche in treating aggression and violence in psychotic patients. It is unknown what pharmacological property accounts for this gold standard enhanced efficacy of clozapine, but it is unlikely to be D_2 antagonism since at therapeutic doses, clozapine occupies fewer D_2 receptors than the other drugs that treat psychosis. Likely, it works by an unknown but non-D_2 mechanism. Patients treated with clozapine may occasionally experience an "awakening" (in the Oliver Sachs sense), characterized by a return to a near-normal level of cognitive, interpersonal, and vocational functioning, and not just significant improvement in positive symptoms of psychosis, but this is unfortunately rare. The fact that awakenings can be observed at all, however, gives hope to the possibility that a state of wellness might some day be achieved in schizophrenia by the right mix of pharmacological mechanisms.

In terms of side effects, clozapine causes little in the way of motor symptoms, does not seem to cause tardive dyskinesia and may even be effective in treating tardive dyskinesia, and also does not elevate prolactin. That's the good news. The bad news is that clozapine has some unique side effects (Table 5-2), and prescribing clozapine effectively means the ability to manage these side effects

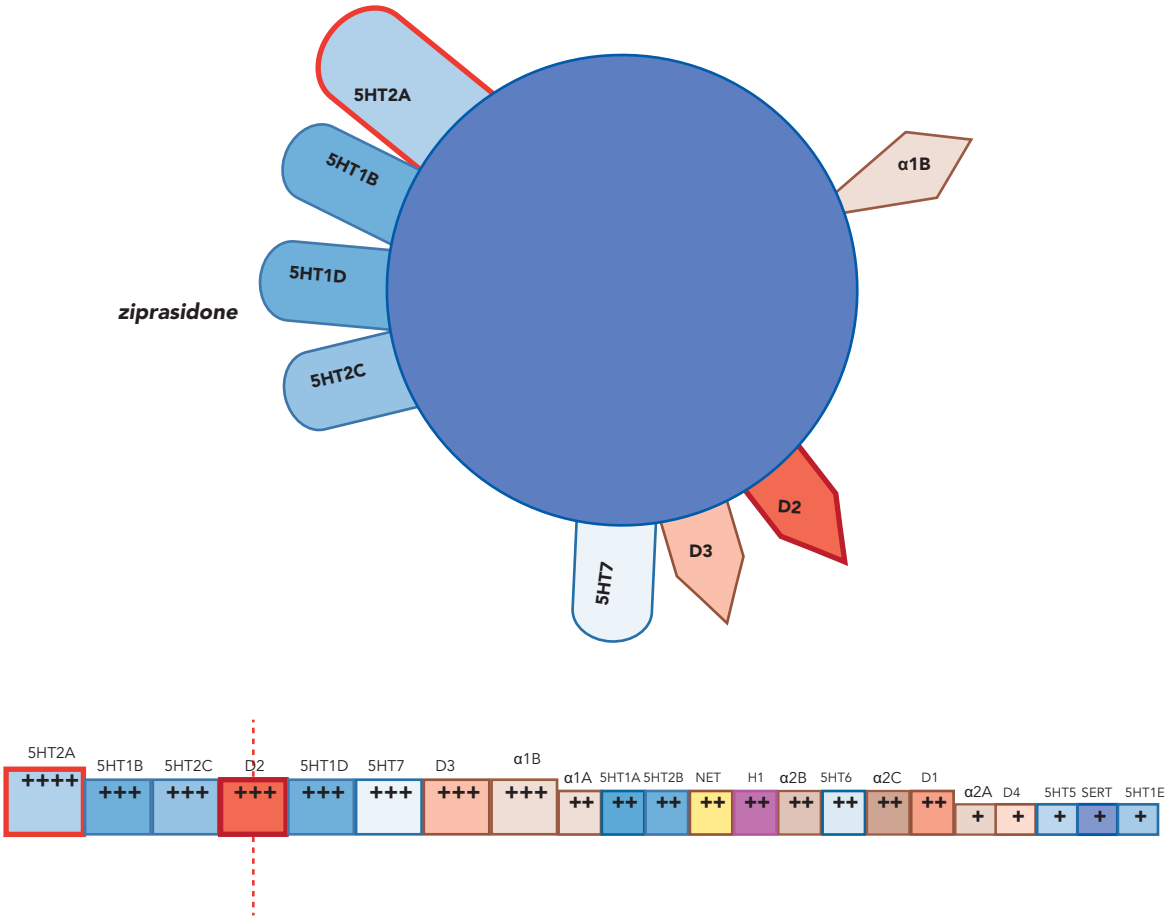


Figure 5-51 Ziprasidone's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of ziprasidone. This compound seems to lack the pharmacological actions associated with weight gain and increased cardiometabolic risk such as increasing fasting plasma triglyceride levels or increasing insulin resistance. Ziprasidone also lacks many of the pharmacological properties associated with significant sedation. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

if they arise. One life-threatening and occasionally fatal complication of clozapine treatment is neutropenia, requiring patients to have their blood counts monitored for as long as they are treated.

Clozapine also has an increased risk of seizures, especially at high doses (Table 5-2). It can be very sedating, has an increased risk of myocarditis, and is associated with the greatest degree of weight gain and possibly the greatest cardiometabolic risk among the drugs for psychosis. Clozapine can also cause excessive salivation, which can be mitigated by pro-cholinergic treatment or even by localized botulinum toxin injections for severe cases. Thus, clozapine may have the greatest efficacy but also the most side effects among the atypical antipsychotics.

Table 5-2 Side effects of clozapine requiring expert management

Neutropenia
Constipation/paralytic ileus
Sedation, orthostasis, tachycardia
Sialorrhea
Seizures
Weight gain, dyslipidemia, hyperglycemia
Myocarditis, cardiomyopathy, interstitial nephritis
DRESS (drug reaction with eosinophilia and systemic symptoms), serositis

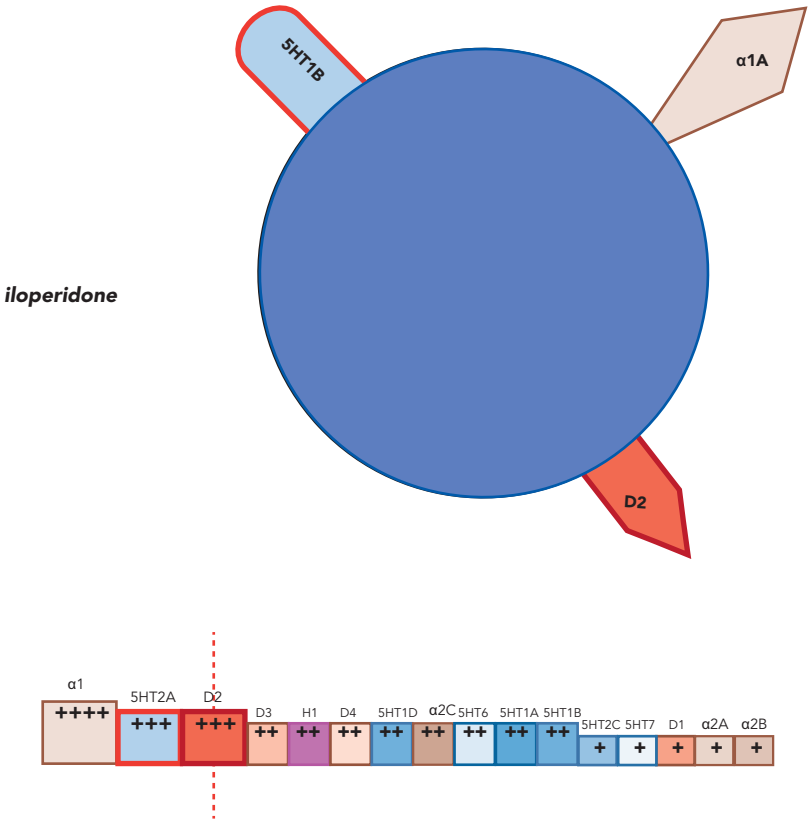


Figure 5-52 Iloperidone's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of iloperidone. Among the medications discussed here, iloperidone has one of the simplest pharmacological profiles and comes closest to a serotonin dopamine antagonist (SDA). Its other prominent pharmacological property is potent α_1 antagonism, which may be responsible for the risk of orthostatic hypotension but also may contribute to its low risk of drug-induced parkinsonism (DIP). As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

Because of these side-effect risks, clozapine is not considered to be a first-line treatment, but is used when other antipsychotics fail. The mechanisms of clozapine's ability to cause neutropenia and myocarditis are entirely unknown; its weight gain may be partially associated with its potent blockade of both H_1 histamine and $5HT_{2C}$ receptors (Figure 5-43). Sedation is probably linked to clozapine's potent antagonism of muscarinic M_1, H_1, and α_1-adrenergic receptors (Figures 5-8, 5-14, and 5-43). Profound muscarinic blockade can also cause excessive salivation, especially at higher doses, as well as severe constipation that can lead to bowel obstruction, especially if administered concomitantly with other anticholinergic agents, such as benztropine, or other drugs for psychosis with potent anticholinergic properties, such as chlorpromazine.

Because of these side effects and the hassle of arranging for blood counts, the use of clozapine is low in clinical practice, and probably too low given the great number of patients with inadequate responses to the other drugs for psychosis. To reduce one logistical and pragmatic barrier to clozapine use, a point-of-care blood-count-monitoring system is now available with a finger stick rather than a blood draw and local assay rather than sending away to a distant laboratory. It is important not to lose the art of how to prescribe clozapine and for whom, and how to mitigate and manage side effects, as clozapine remains a powerful and unfortunately underutilized therapeutic intervention for many patients. Therapeutic drug monitoring of plasma drug levels can be of great assistance in finding the right dose of clozapine. This specific drug is a subject all to itself and for this reason the author has co-written a handbook on how to use clozapine that the reader may wish to consult for details (Meyer and Stahl, *The Clozapine Handbook*).

Olanzapine

Olanzapine (Figure 5-44) is an antagonist at both $5HT_{2A}$ and D_2 receptors, and although not proven as effective as clozapine for psychosis, it is widely considered (by clinical experience rather than by definitive clinical trials) to be the next most effective agent, with at least a bit more efficacy than the others in this class except

lurasidone

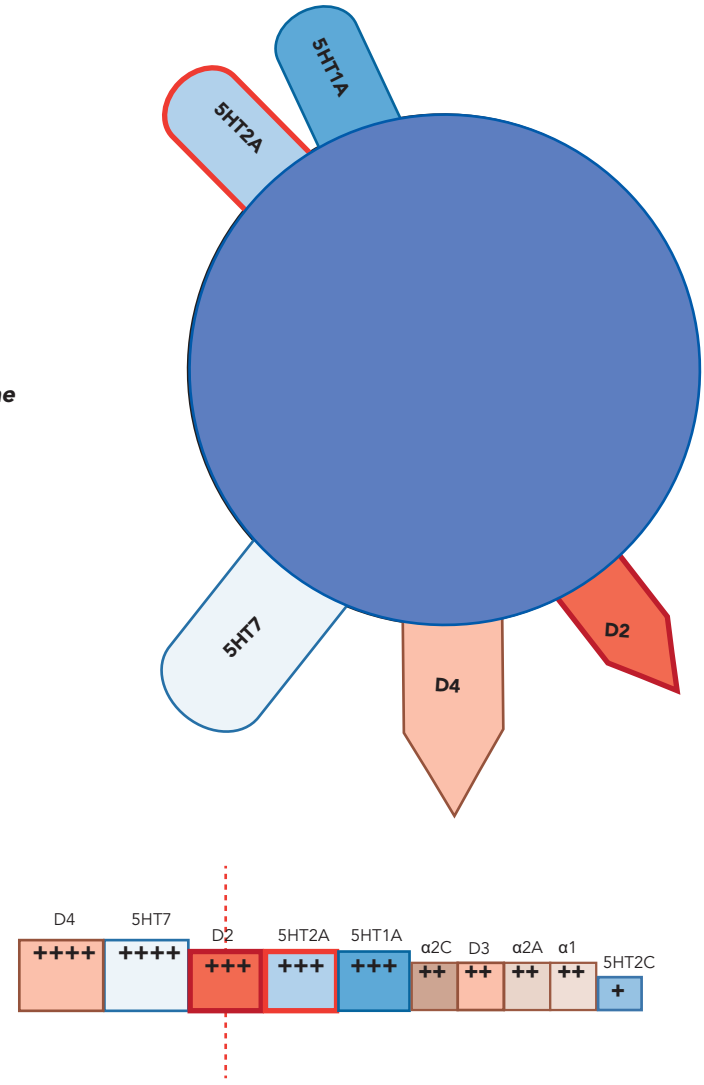


Figure 5-53 Lurasidone's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of lurasidone. Lurasidone has a relatively simple pharmacological profile. It binds most potently to the D_4 receptor, the effects of which are not well understood, and to the $5HT_7$ receptor, which may contribute to efficacy for mood, cognitive, and sleep symptoms. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

clozapine. It also has a higher risk for metabolic side effects. Olanzapine tends to be used in higher doses than originally studied and approved for marketing, especially when guided by plasma drug levels, since clinical use suggests that higher doses may have greater efficacy, especially in patients who have not responded to other drugs for psychosis or to olanzapine at lower doses.

Olanzapine is approved for schizophrenia and for maintaining response in schizophrenia (age 13 or older), for agitation associated with schizophrenia or with bipolar mania (intramuscular), acute bipolar mania/mixed mania and maintenance (age 13 or older), and in combination with fluoxetine for both bipolar depression and treatment-resistant unipolar depression (in the US). Perhaps the $5HT_{2C}$ antagonist properties, with weaker α_2 antagonist properties (see Figures 5-35 and 5-37 and also Figure 5-44), especially when combined with the $5HT_{2C}$ antagonist properties of the antidepressant fluoxetine (see Chapter 7 on treatments for mood disorders), may explain some aspects of olanzapine's apparent efficacy in unipolar and bipolar depression. Olanzapine is available as an oral disintegrating tablet, as an acute intramuscular injection, and as a long acting 4-week intramuscular depot. An inhaled formulation for rapid onset use is in late clinical development. As mentioned earlier, olanzapine is also in late-stage clinical testing with the μ-opioid antagonist samidorphan to mitigate weight gain and metabolic disturbances.

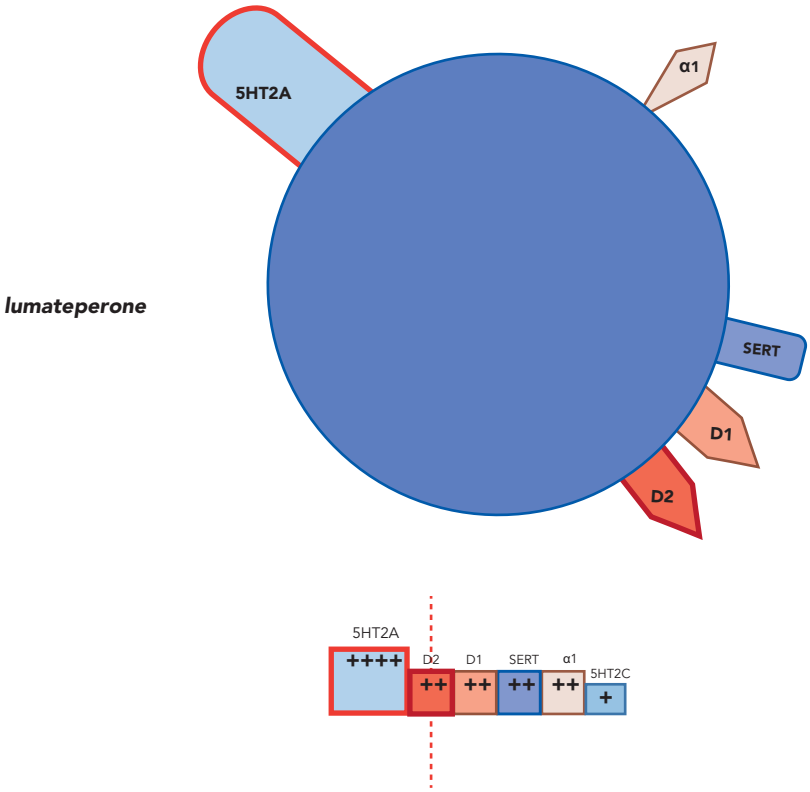


Figure 5-54 Lumateperone's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of lumateperone. Lumateperone has very high affinity for the $5HT_{2A}$ receptor and moderate affinity for the D_2, D_1, and α_1 receptor. It also has moderate affinity for the serotonin transporter. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

Quetiapine

Quetiapine (Figure 5-45) is an antagonist at both serotonin $5HT_{2A}$ and dopamine D_2 receptors, but has several differentiating pharmacological properties, especially at different doses. The net pharmacological actions of quetiapine are actually due to the combined pharmacological actions not only of quetiapine itself, but also of its active metabolite, norquetiapine (Figure 5-45 adds together the net actions of quetiapine and norquetiapine). Norquetiapine has unique pharmacological properties compared to quetiapine, especially norepinephrine transporter (NET) inhibition (i.e., norepinephrine reuptake inhibition) (Figure 5-34), but also, combined with the parent drug quetiapine, it has $5HT_7$ (Figure 5-39), $5HT_{2C}$ (Figure 5-37), and α_2 antagonism (Figure 5-35), and $5HT_{1A}$ partial agonist actions (Figure 5-33), all of which may contribute to quetiapine's overall clinical profile, especially its robust antidepressant effects. Thus, quetiapine has an overall very complex set of binding properties to many neurotransmitter receptors, many of which have higher potency than to the D_2 receptor, and this may account for why this drug appears to be far more than simply a drug for psychosis. In fact, like the others in this class, quetiapine is far more often prescribed for indications other than psychosis, including frequently as a hypnotic for insomnia, a drug for depression, for anxiety, for Parkinson's disease psychosis, or as an adjunct for psychosis with other $5HT_{2A}/5HT_{1A}/D_2$ drugs.

Different Drug at Different Doses?

The story of quetiapine dosing can be told as Goldilocks and the three bears (Figure 5-46). For psychosis, quetiapine is an 800 mg Papa Bear. For depression, quetiapine is a 300 mg Mama Bear. For insomnia, quetiapine is a 50 mg Baby Bear. Starting with Baby Bear, only the most potent binding properties of quetiapine to the far left in the strip at the bottom of Figure 5-45 are relevant, especially H_1 antihistamine properties (see also Figure 5-41). Baby Bear doses are not approved for use as a hypnotic, and this can be an option with metabolic risks, so is not considered a first-line option for sleep. At this dose, hypothetically there are insufficient numbers of $5HT_{2C}$ receptors or NETs blocked for antidepressant efficacy; also, there is insufficient occupancy of D_2 receptors for antipsychotic efficacy.

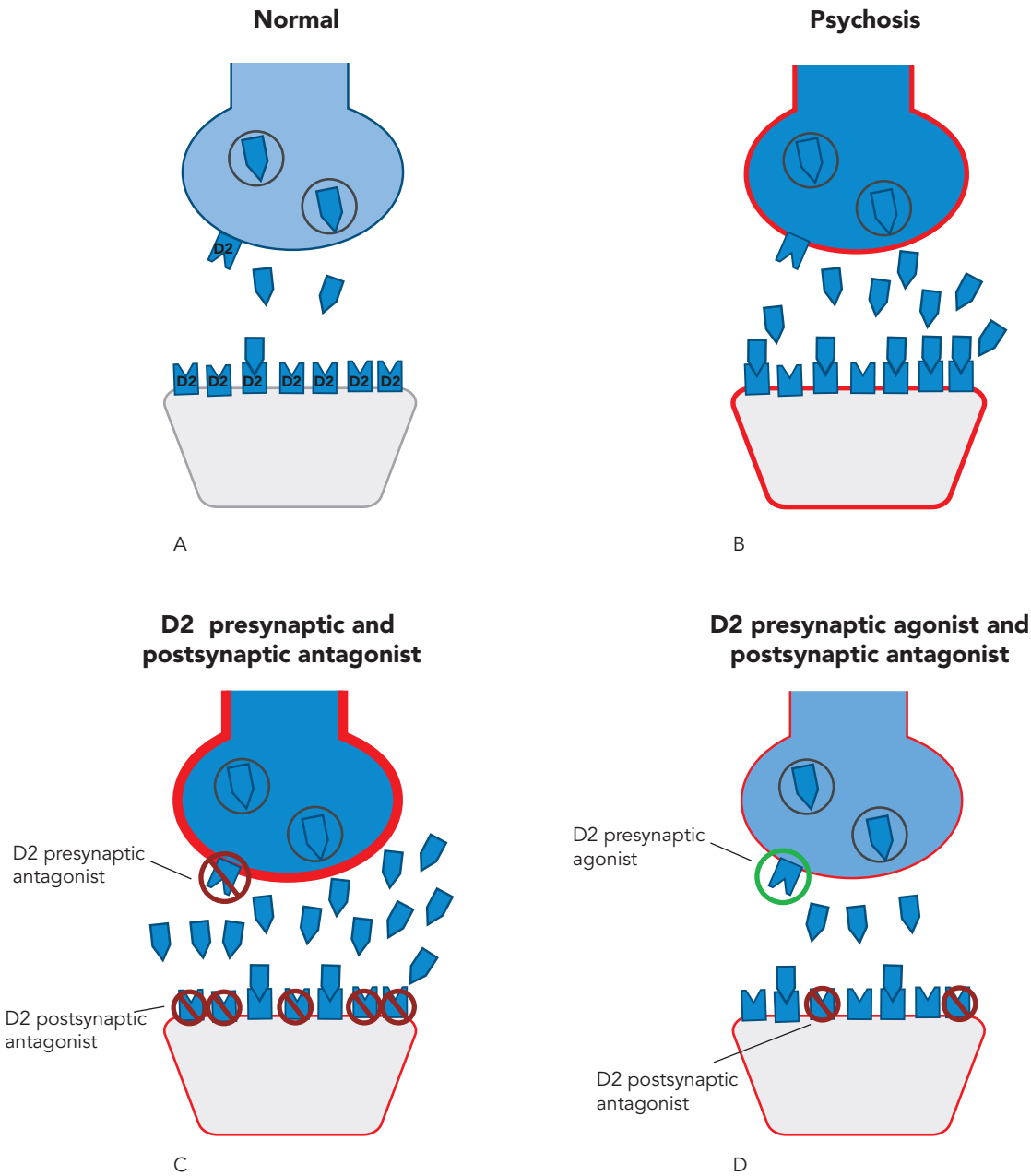


Figure 5-55 Pre- and postsynaptic dopamine 2 receptor binding. (A) D_2 receptors are present both pre- and postsynaptically; dopamine binding at these receptors is inhibitory. (B) In psychosis, dopamine synthesis and release are enhanced, leading to excessive stimulation of postsynaptic D_2 receptors. (C) Most D_2 antagonists block both pre- and postsynaptic D_2 receptors. Blockade of presynaptic D_2 receptors disinhibits presynaptic dopamine release, thus further enhancing dopamine release. Full blockade of postsynaptic D_2 receptors, however, can counter the effect of presynaptic D_2 blockade. (D) Lumateperone is unusual among D_2 antagonists in that it seems to be an antagonist at postsynaptic D_2 receptors but a partial agonist at presynaptic D_2 receptors. This would mean that less postsynaptic D_2 antagonism would be necessary to achieve an antipsychotic effect, because dopamine release would already be diminished.

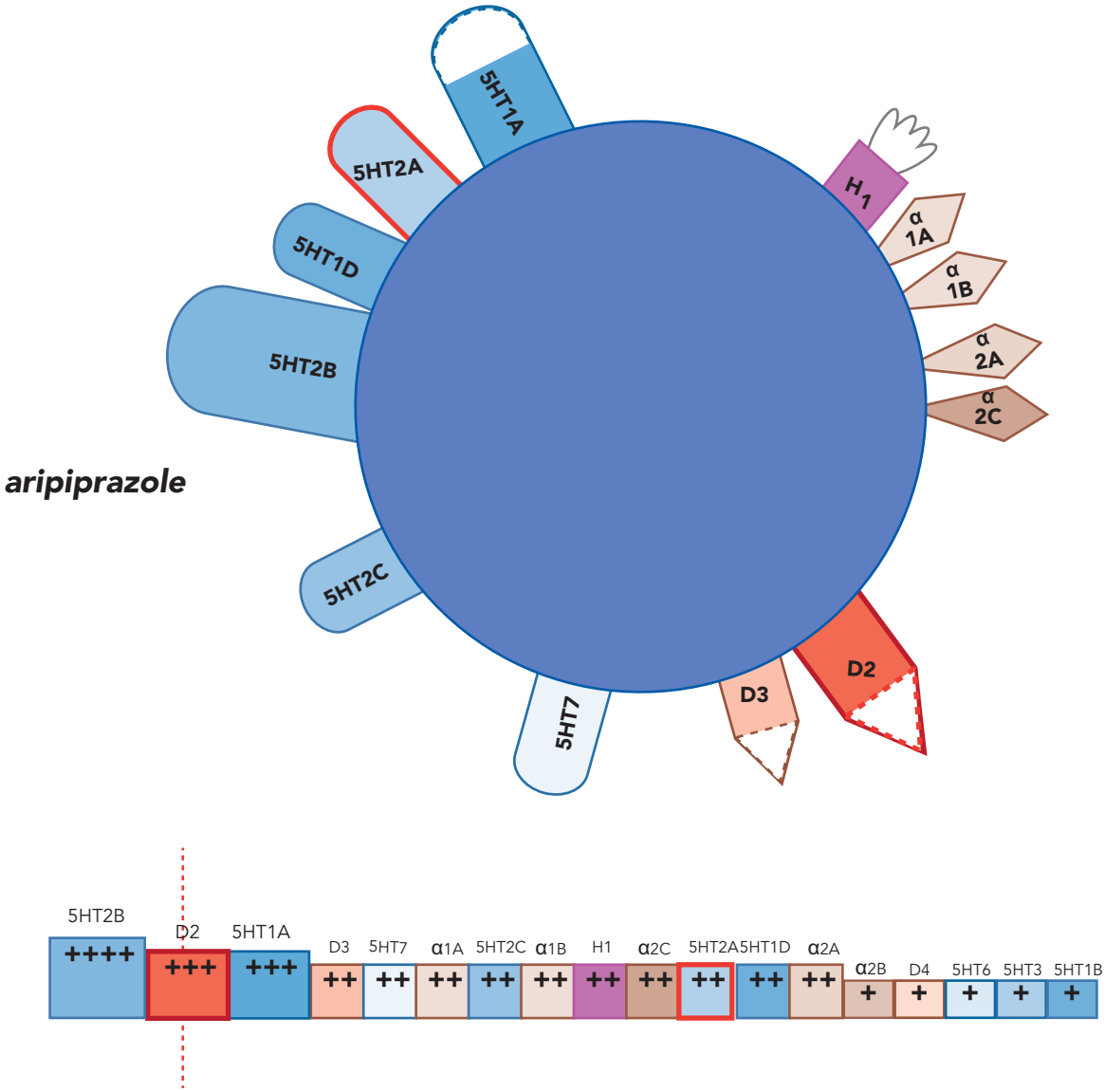


Figure 5-56 **Aripiprazole's pharmacological and binding profile.** This figure portrays a qualitative consensus of current thinking about the binding properties of aripiprazole. Aripiprazole is a partial agonist at D_2 receptors rather than an antagonist. Additional important pharmacological properties that may contribute to its clinical profile include $5HT_{2A}$ antagonist actions, $5HT_{1A}$ partial agonist actions, $5HT_7$ antagonist actions, and $5HT_{2C}$ antagonist actions. Aripiprazole lacks or has weak binding potency at receptors usually associated with significant sedation. Aripiprazole also seems to lack the pharmacological actions associated with weight gain and increased cardiometabolic risk, such as increasing fasting plasma triglyceride levels or increasing insulin resistance. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

Mama Bear at 300 mg range has robust antidepressant effects in depression by combining several simultaneous known antidepressant mechanisms discussed above. Thus, the combination of these antidepressant mechanisms would enhance dopamine and norepinephrine release (via norepinephrine reuptake inhibition, $5HT_{1A}$ partial agonism, and $5HT_{2A}$, α_2, and $5HT_{2C}$ antagonism) and serotonin release (by $5HT_7$ antagonism) (see Chapter 7 for explanation and illustrations for all these antidepressant mechanisms). Especially when combined with selective serotonin reuptake inhibitors (SSRIs)/serotonin–

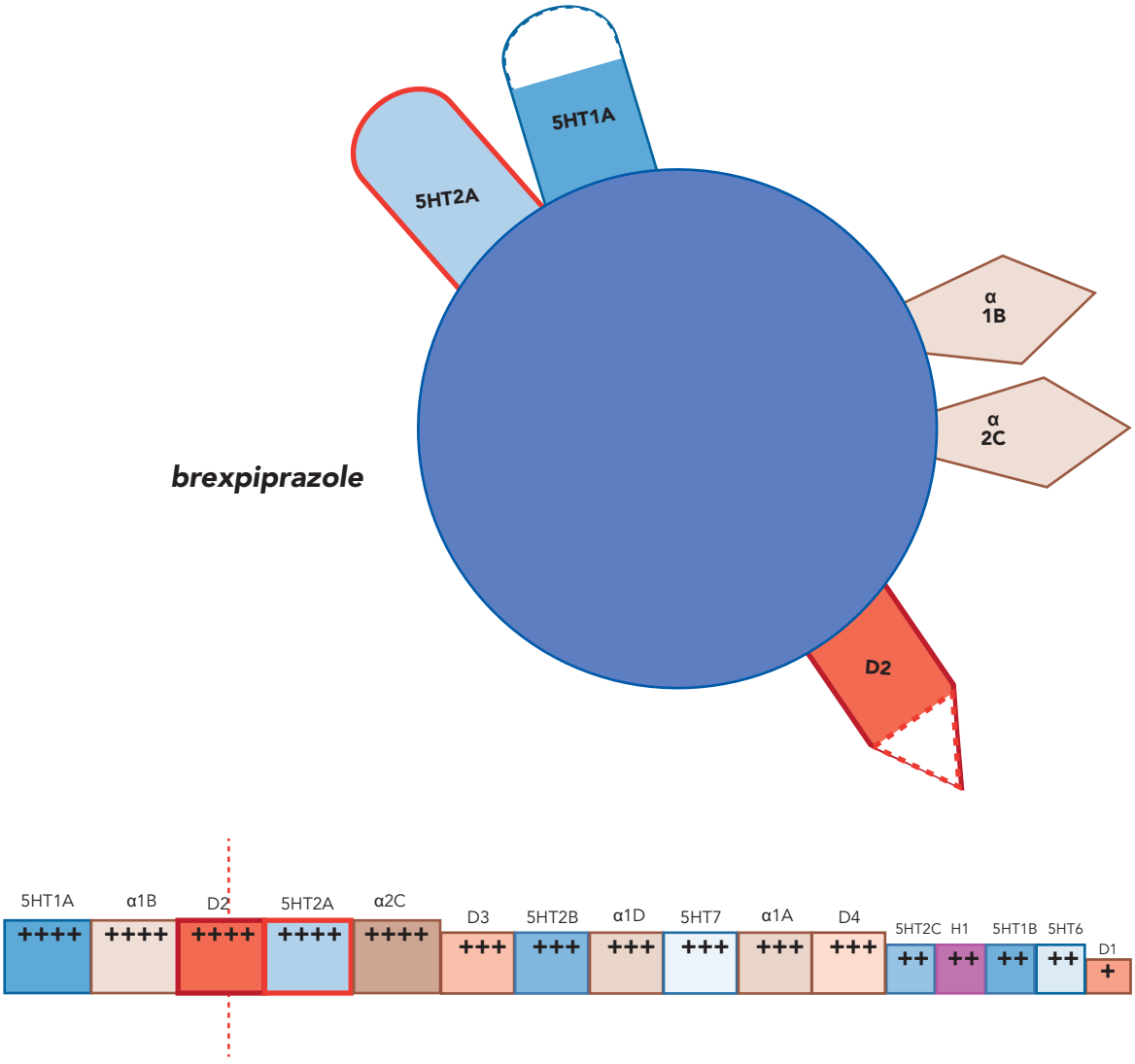


Figure 5-57 Brexpiprazole's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of brexpiprazole. Brexpiprazole is a partial agonist at D_2 receptors rather than an antagonist, and also binds potently to $5HT_{2A}$, $5HT_{1A}$, and α_1 receptors. Brexpiprazole also seems to lack actions at receptors usually associated with significant sedation, weight gain, and increased cardiometabolic risk, although it is too early to evaluate the clinical profile of this medication. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

norepinephrine reuptake inhibitors (SNRIs) there would be triple monoamine actions of increasing serotonin as well as norepinephrine and dopamine while simultaneously treating symptoms of insomnia and anxiety by antihistaminic action (Figure 5-45). Quetiapine is approved both for bipolar depression and as an augmenting agent to SSRIs/SNRIs in unipolar depression that fails to respond sufficiently to those agents (in the US).

Finally, Papa Bear is 800 mg quetiapine, which completely saturates both H_1 histamine and $5HT_{2A}$ receptors continuously in both cases, but has more inconsistent occupancy above 60% for D_2 receptors, especially between doses. Quetiapine is approved both for schizophrenia/schizophrenia maintenance (ages 13 and above) and for mania/mixed mania and maintenance (ages 10 and above). The pharmacology of quetiapine suggests why it is used more often in depression and insomnia than in

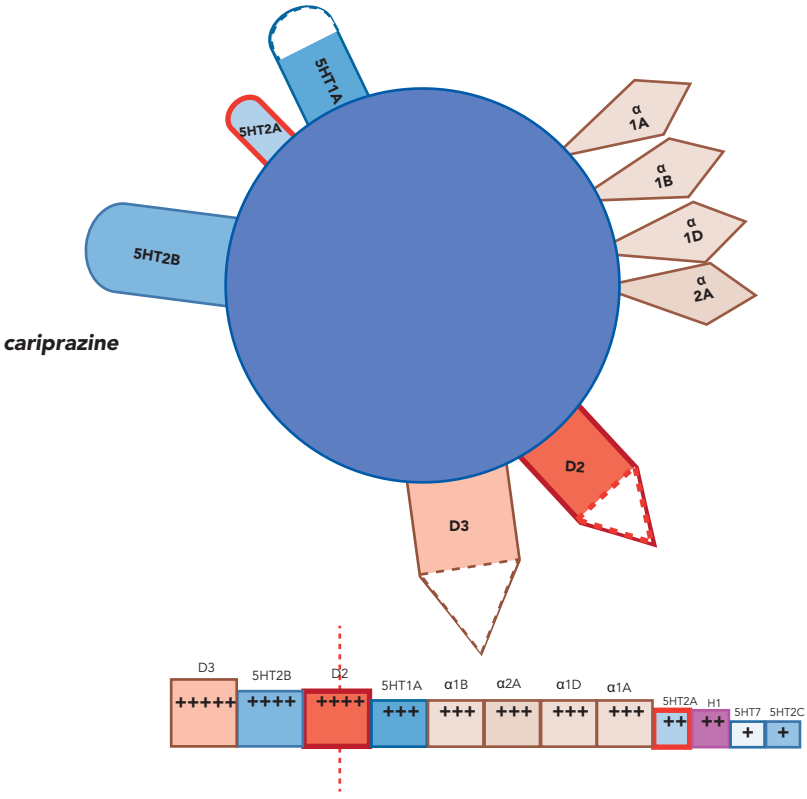


Figure 5-58 Cariprazine's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of cariprazine. Cariprazine has potent actions at D_3, $5HT_{2B}$, D_2, and $5HT_{1A}$ receptors, with relatively weaker affinity for $5HT_{2A}$ and H_1 receptors. Cariprazine actually has higher affinity for the D_3 receptor than dopamine does. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

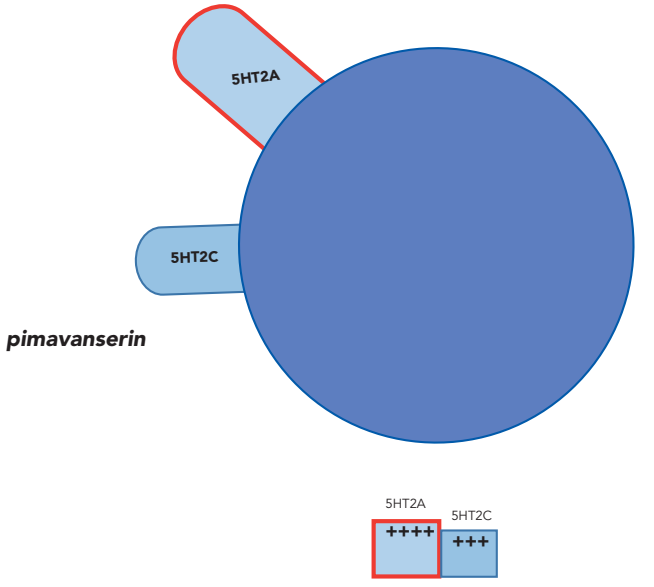


Figure 5-59 Pimavanserin's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of pimavanserin. Pimavanserin is the only known drug with proven antipsychotic efficacy that does not bind to D_2 receptors. Instead, it has potent $5HT_{2A}$ antagonism (sometimes called inverse agonism) with lesser $5HT_{2C}$ antagonist actions. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

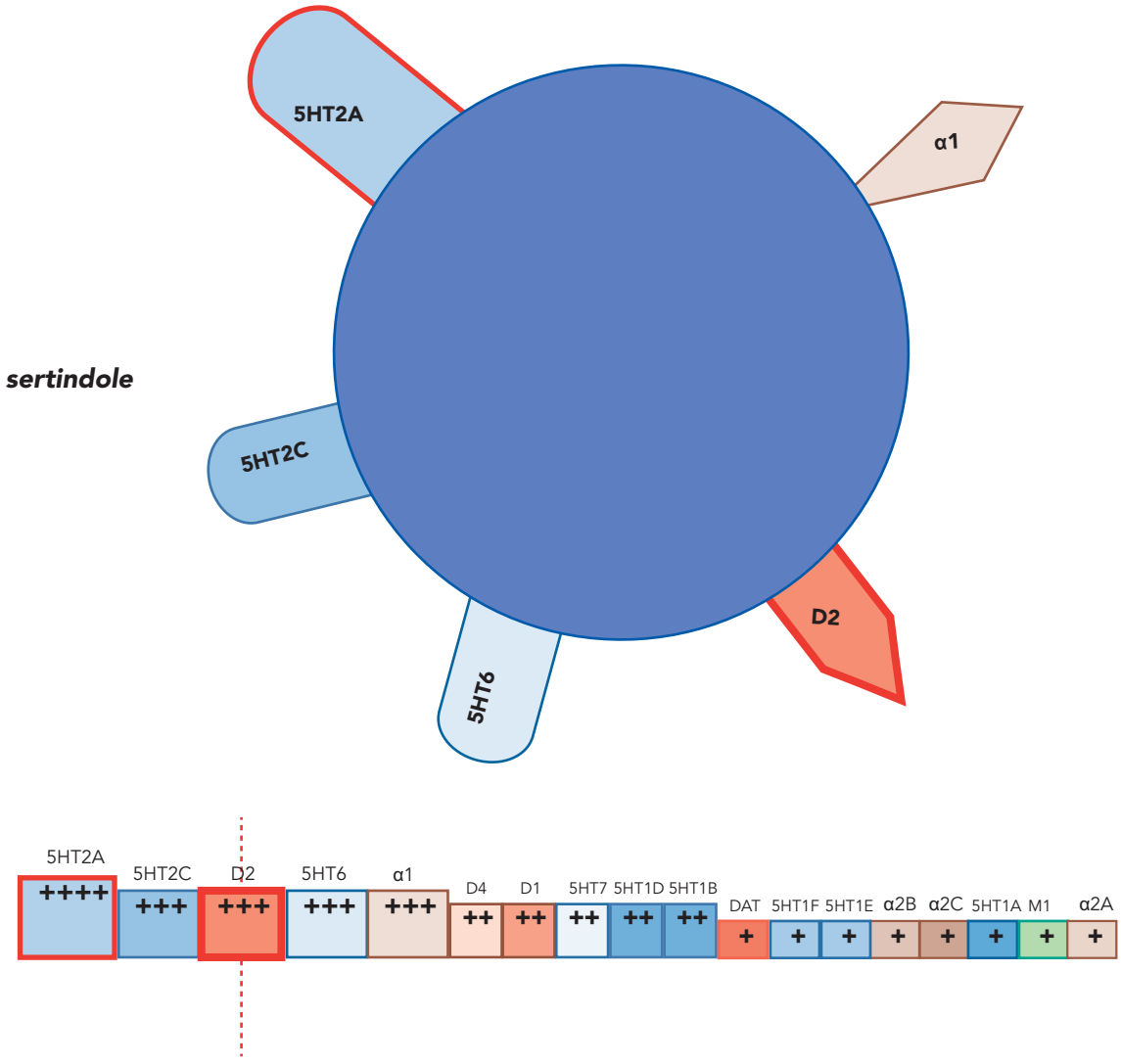


Figure 5-60 Sertindole's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of sertindole. Potent antagonist actions at α_1 receptors may account for some of sertindole's side effects. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

psychosis. Quetiapine causes virtually no motor side effects nor prolactin elevations. However, quetiapine has at least moderate risk for weight gain and metabolic disturbances.

Asenapine

Asenapine (Figure 5-47) has a chemical structure related to the antidepressant mirtazapine and shares several of mirtazapine's pharmacological binding properties, especially $5HT_{2A}$, $5HT_{2C}$, H_1, and α_2 antagonism, plus many other properties that mirtazapine does not have, especially D_2 antagonism, as well as actions upon many additional serotonin receptor subtypes (Figure 5-47). This suggests that asenapine would have antidepressant actions, but only antipsychotic/antimanic actions have been proven. Asenapine is unusual in that it is given as a sublingual formulation, because it is not absorbed if it is swallowed. The surface area of the oral cavity for oral absorption limits the size of the dose, so asenapine is generally taken twice a day despite a long half-life. Since asenapine is rapidly absorbed sublingually with rapid peak drug levels, unlike other formulations that simply dissolve rapidly in the mouth but are followed

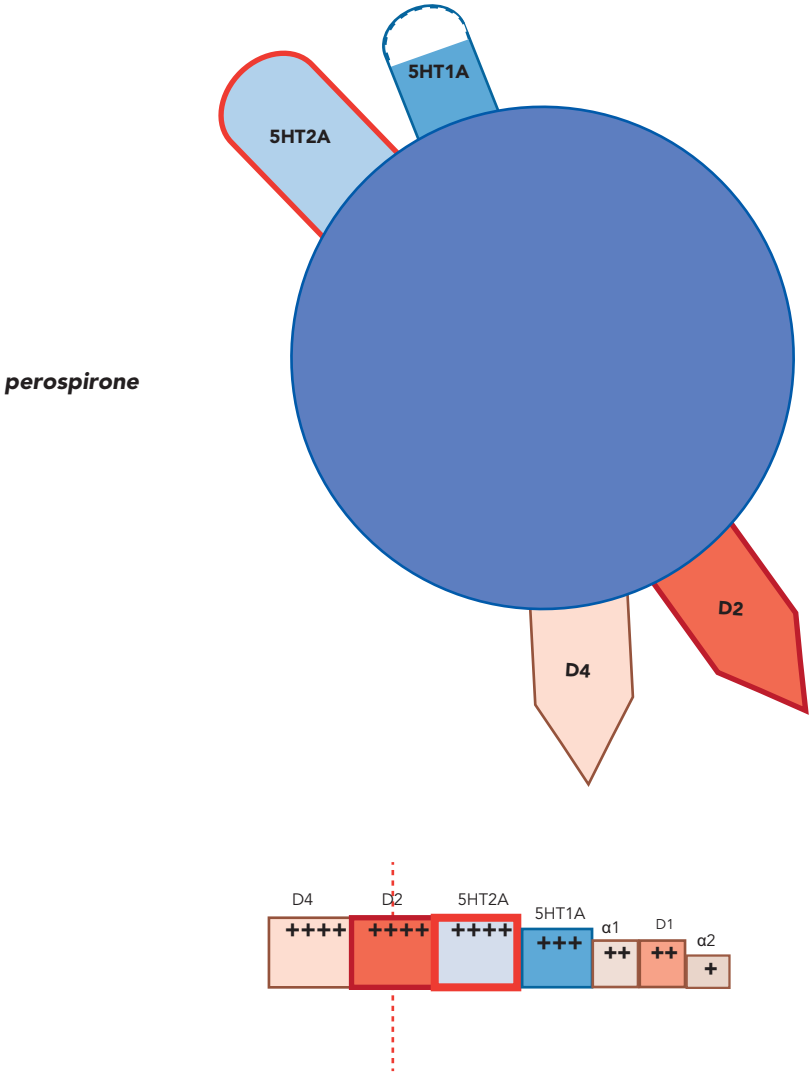


Figure 5-61 Perospirone's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of perospirone. $5HT_{1A}$ partial agonist actions may contribute to efficacy for mood and cognitive symptoms. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

by delayed absorption (e.g., orally dissolving olanzapine preparations), asenapine can be used as rapid-acting oral PRN (as needed) antipsychotic to "top up" patients without resorting to an injection. One side effect of sublingual administration in some patients is oral hypoesthesia; also, patients may not eat or drink for 10 minutes following sublingual administration to avoid the drug being washed into the stomach where it will not be absorbed. Asenapine can be sedating, especially upon first dosing, and has a moderate propensity for weight gain, metabolic disturbances, or motor side effects. It is approved for schizophrenia/maintenance in adults and in the US for bipolar mania (ages 10 or older). It is also available in a transdermal formulation.

Zotepine

Zotepine (Figure 5-48) is available in Japan and Europe, but not the US. Zotepine has $5HT_{2A}$ and D_2 antagonist properties and is not as popular as other drugs for psychosis because it has to be administered three times a day. There may be an elevated risk of seizures. Zotepine is a $5HT_{2C}$ antagonist, an α_1 antagonist, a $5HT_7$ antagonist, and a weak partial agonist of $5HT_{1A}$ receptors as well as a weak inhibitor of norepinephrine reuptake (NET),

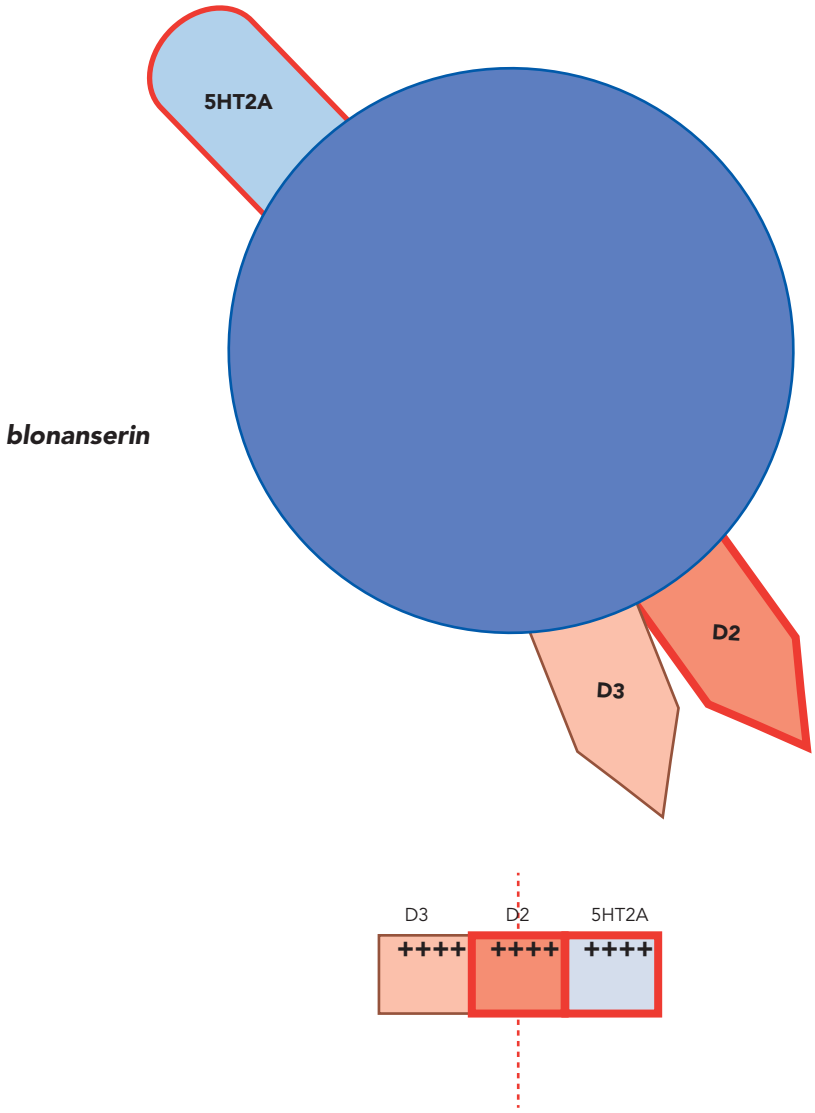


Figure 5-62 Blonanserin's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of blonanserin. Blonanserin has high affinity for D_3 receptors; in fact, it has higher affinity for D_3 receptors than does dopamine itself. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

suggesting potential antidepressant effects that have not been well established yet in clinical trials.

Many Dones and a Rone

Risperidone

Risperidone (Figure 5-49) is the original "done" and has a different chemical structure and a different pharmacological profile than the pines (compare pines and dones in Figure 5-32). Risperidone has favored uses in schizophrenia/maintenance (age 13 and older) and bipolar mania/maintenance (ages 10 and older). Some prefer this agent for children and adolescents in particular where it is also approved for treatment of irritability associated with autistic disorder, including symptoms of aggression towards others, deliberate self-injury, tantrums, and quickly changing moods (ages 5–16). Low-dose risperidone is occasionally used "off-label" for the controversial – due to a "black box" safety warning – treatment of agitation and psychosis associated with dementia. This practice may lessen as other drugs in the pipeline get approved for this indication. Risperidone is available in long-term depot injectable formulations lasting for 2 or 4 weeks and it can be useful to monitor plasma drug levels of risperidone and its active metabolite paliperidone, especially to guide dosing for patients receiving long-term depot

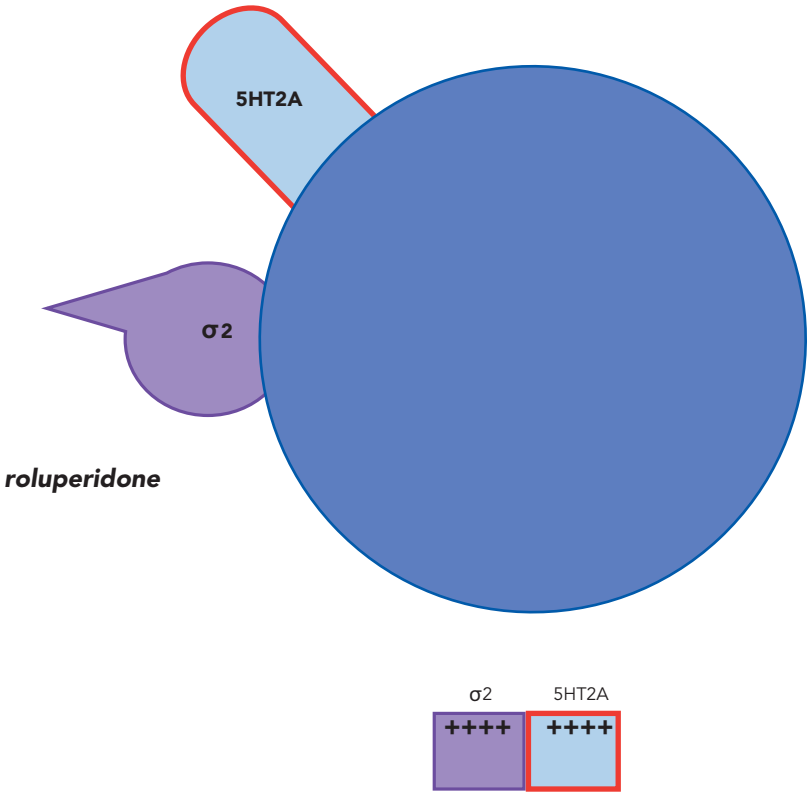


Figure 5-63 Roluperidone's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of roluperidone. Still in clinical testing, roluperidone is a $5HT_{2A}$ antagonist with additional σ_2 antagonism. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

injections and who are treatment-resistant. There is also an orally disintegrating tablet and liquid formulation of risperidone.

Although risperidone does have somewhat reduced motor side effects at lower doses, it raises prolactin levels even at low doses. Risperidone has a moderate amount of risk for weight gain and dyslipidemia. Weight gain can be particularly a problem in children.

Paliperidone

Paliperidone, the active metabolite of risperidone, is also known as 9-hydroxy-risperidone and like risperidone has $5HT_{2A}$ and D_2 receptor antagonism (Figure 5-50). One pharmacokinetic difference, however, between risperidone and paliperidone is that paliperidone, unlike risperidone, is not hepatically metabolized, but its elimination is based upon urinary excretion and thus it has few pharmacokinetic drug interactions. Another pharmacokinetic difference is that the oral form of paliperidone is provided in a sustained-release oral formulation, which risperidone is not, and this actually changes some of the clinical characteristics of paliperidone compared to risperidone, a fact that is not always well recognized and can lead to underdosing of oral paliperidone. Oral sustained release means that paliperidone only needs to be administered once a day, whereas risperidone, especially when treatment is initiated, and especially in children or the elderly, may need to be given twice daily to avoid sedation and orthostasis. Side effects of risperidone may be related in part to the rapid rate of absorption and higher peak doses with greater drug-level fluctuation leading to shorter duration of action, properties that are eliminated by the controlled release formulation of paliperidone.

Despite the similar receptor binding characteristics of paliperidone and risperidone, paliperidone tends to be more tolerable, with less sedation, less orthostasis, and fewer motor side effects, although this is based upon anecdotal clinical experience and not head-to-head clinical studies. Paliperidone has moderate risk for weight gain and metabolic problems. Paliperidone is approved specifically for schizophrenia/maintenance (ages 12 and older).The main advantage of paliperidone over risperidone is that the long-acting injectable for paliperidone is easier to load, easier to dose, and has both a 1-month and a 3-month formulation, with studies in progress for a 6-month

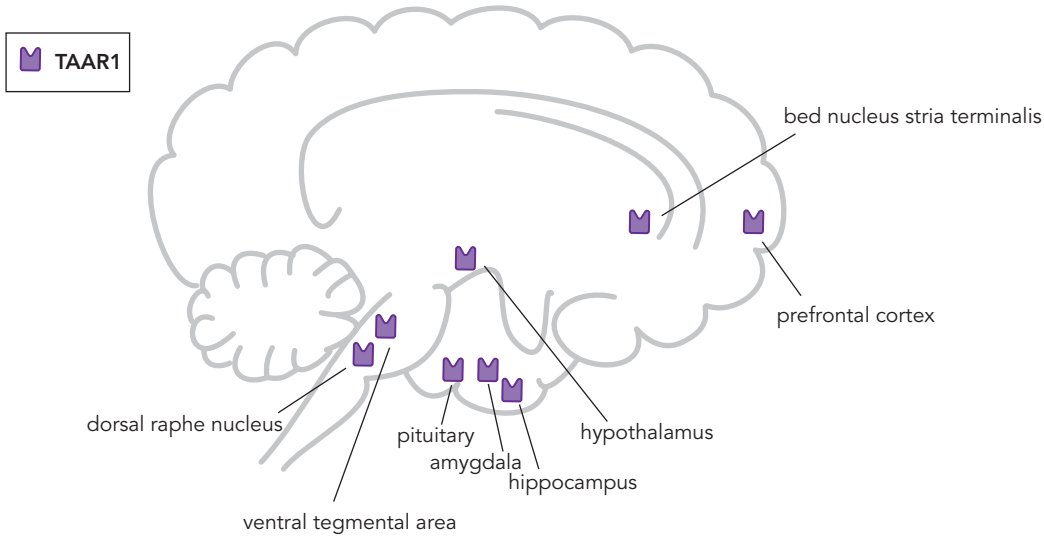


Figure 5-64 Localization of trace amine-associated receptor type 1 (TAAR1). A new potential mechanism of antipsychotic action is agonism of the trace amine-associated receptor type 1 (TAAR1). TAAR1 is widely expressed throughout the brain, including in monoamine brainstem centers (dorsal raphe nucleus, ventral tegmental area) and in monoamine projection areas.

formulation. It can be useful to monitor plasma drug levels to guide dosing, especially for patients receiving long-term depot injections and who are treatment-resistant.

Ziprasidone

Ziprasidone (Figure 5-51) is a $5HT_{2A}/D_2$ antagonist with the major differentiating feature being that it has little or no propensity for weight gain or metabolic disturbances. However, it is short acting, requires more than once a day dosing, and must be taken with food. Earlier concerns about dangerous QTc prolongation by ziprasidone now appear to be exaggerated. Unlike iloperidone, zotepine, sertindole, and amisulpride, ziprasidone does not cause dose-dependent QTc prolongation, and few drugs have the potential to increase ziprasidone's plasma levels. Ziprasidone has an intramuscular dosage formulation for rapid use in urgent circumstances. Ziprasidone is approved in schizophrenia/maintenance and in bipolar mania/maintenance.

Iloperidone

Iloperidone (Figure 5-52) also has $5HT_{2A}/D_2$ antagonist properties. Its most distinguishing clinical properties include a very low level of motor side effects, low level of dyslipidemia, and moderate level of weight gain associated with its use. Its most distinguishing pharmacological property is its potent α_1 antagonism (Figure 5-52). As discussed earlier in this chapter, α_1 antagonism is generally associated with the potential for orthostatic hypotension and sedation, especially if rapidly dosed. Although iloperidone has an 18- to 33-hour half-life that theoretically supports once daily dosing, it is generally dosed twice daily and titrated over several days when initiated in order to avoid both orthostasis and sedation. Slow dosing can delay onset of antipsychotic effects, so iloperidone is often used as a switch agent in non-urgent situations. It is approved in the US for schizophrenia/maintenance.

Lurasidone

Lurasidone is a $5HT_{2A}/D_2$ antagonist (Figure 5-53) approved for use in schizophrenia and much more popular for use in bipolar depression. This compound exhibits high affinity for both $5HT_7$ receptors (Figure 5-39) and $5HT_{2A}$ receptors (Figure 5-32), moderate affinity for $5HT_{1A}$ (Figure 5-33) and α_2 receptors (Figure 5-35), yet minimal affinity for H_1 histamine and M_1 cholinergic receptors (Figure 5-41), properties that may explain some of lurasidone's antidepressant profile, with low risk of weight gain or metabolic dysfunction. Risk of motor side effects or sedation are reduced if lurasidone is dosed at night. Due perhaps to the synergism amongst the several potential antidepressant properties accompanied by good tolerability, especially lack of weight gain, it is a highly effective agent for bipolar depression (ages 10 and older) and one of the preferred agents for this use in the countries where it is approved for this use such as in the US. Lurasidone is approved

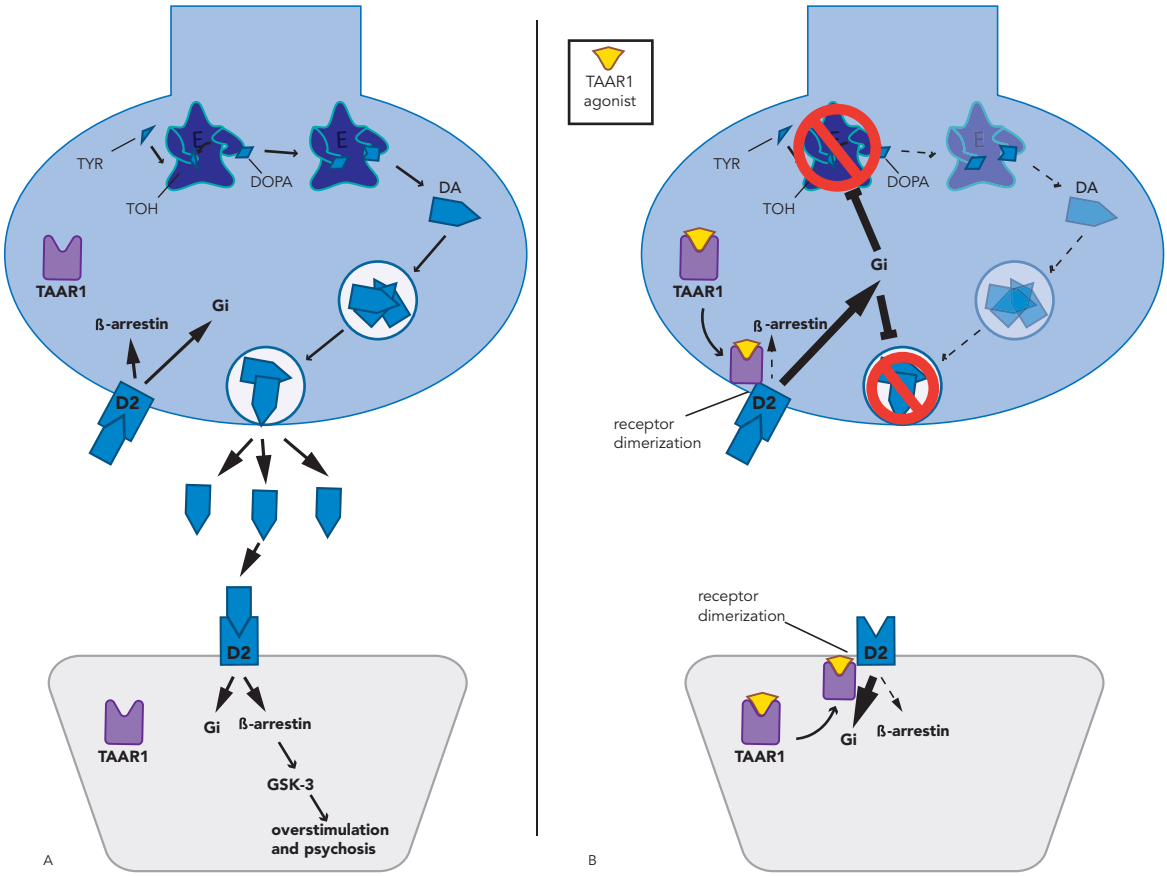


Figure 5-65 Agonism of trace amine-associated receptor type 1 (TAAR1). Trace amines are formed from amino acids when either the tyrosine hydroxylase (TYR) step or the tryptophan hydroxylase (TOH) step is omitted during production of dopamine or serotonin, respectively. (A) Dopamine is produced and packaged into synaptic vesicles, then released into the synapse. Dopamine binding at both pre- and postsynaptic D_2 receptors can either trigger the inhibitory G (Gi) protein signal transduction cascade or the β-arrestin 2 signal transduction cascade. The β-arrestin 2 cascade leads to production of glycogen synthase kinase 3 (GSK-3); too much GSK-3 activation may be associated with mania or psychosis. (B) When TAAR1 receptors are bound by an agonist, they translocate to the synaptic membrane and couple with D_2 receptors (heterodimerization). This biases the D_2 receptor toward activating the Gi signal transduction cascade instead of the β-arrestin cascade. Presynaptically, amplification of the Gi pathway leads to inhibition of the synthesis and release of dopamine, which would be beneficial in cases of psychosis. Postsynaptically, amplification of the Gi pathway can lead to reduced production of GSK-3.

worldwide for schizophrenia/maintenance (ages 10 and higher) and because of its good tolerability it is often preferred for the treatment of children.

A glutamate modulator D-cycloserine combined with lurasidone, called NRX101 (Cyclurad), combines antagonism of the glycine site of the NMDA receptor (see Figures 4-21, 4-22, 4-26, 4-27) with lurasidone, for the potential treatment of acute suicidal ideation and behavior, as well as for bipolar depression, with early positive findings.

Lumateperone

Lumateperone (Figure 5-54) is a more recently approved $5HT_{2A}/D_2$ antagonist for schizophrenia. It has very high affinity for the $5HT_{2A}$ receptor (Figure 5-32) and moderate affinity for D_2, D_1 (Figure 5-54), and α_1 receptors (Figure 5-42), and low affinity for histamine H_1 receptors (Figure 5-41). Unusually, lumateperone also has moderate affinity for the serotonin transporter (Figure 5-34). Early clinical experience suggests efficacy for schizophrenia without dose titration and good tolerability in terms of little or no weight gain or metabolic disturbances. Two key points on its mechanism of action include a wide separation between its $5HT_{2A}$ antagonist and its D_2 antagonist binding, perhaps explaining why it has antipsychotic actions at doses that have relatively low occupancy of D_2 receptors, and maybe also why there are low D_2-type side effects (e.g., little or no drug-induced parkinsonism

SEP-363856

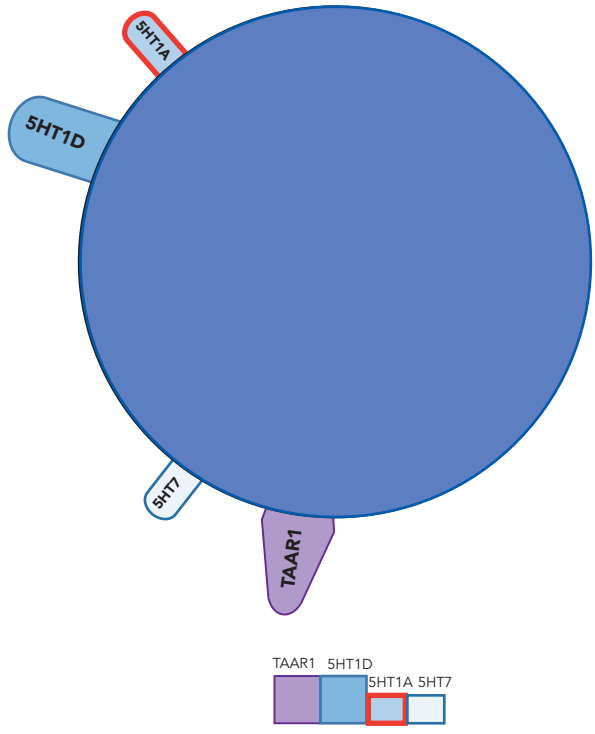


Figure 5-66 SEP-363856's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of SEP-363856. A new potential mechanism of antipsychotic action is agonism of the trace amine-associated receptor type 1 (TAAR1). SEP-363856 is an agonist at TAAR1 receptors; it also has $5HT_{1D}$, $5HT_{1A}$, and $5HT_7$ receptor binding properties. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

xanomeline

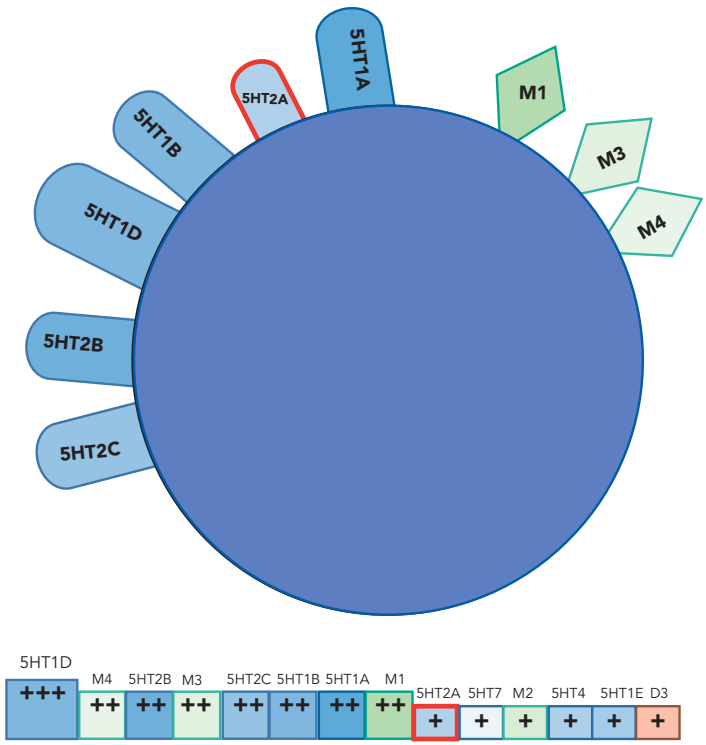


Figure 5-67 Xanomeline's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of xanomeline. Xanomeline is being studied for its potential use in psychosis because of its agonism at central muscarinic cholinergic receptors; specifically, the M_4 and M_1 receptors. Xanomeline also binds to multiple serotonin receptor subtypes. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

or akathisia). The presence of moderate affinity for serotonin reuptake inhibition suggests antidepressant potential and indeed early studies in bipolar depression show promising efficacy.

Although not yet clarified completely, preclinical evidence suggests a novel mechanism of action of lumateperone at D_2 receptors. Recall that PET findings show enhanced presynaptic dopamine synthesis and release (Figures 4-15 and 4-16; also compare Figure 5-55A and B). Dopamine 2 blockers generally do not discriminate between presynaptic D_2 receptors and postsynaptic D_2 receptors (Figure 5-55C). When these D_2 blockers are administered, they block presynaptic D_2 receptors, causing disinhibition of presynaptic dopamine release, making things worse! Although that might be the last thing you want in treating schizophrenia psychosis, the solution is to so fully block the D_2 receptors postsynaptically that this extra dopamine release does not matter (Figure 5-55C). However, in the case of lumateperone, preclinical evidence suggests that it may have presynaptic agonist actions and postsynaptic antagonist actions, a unique combination of mechanisms. How this may occur as an action potentially differentiating it from other D_2 blocking drugs for psychosis is suggested by preclinical data showing potentially unique actions to reduce dopamine synthesis by either presynaptic tyrosine hydroxylase and other presynaptic protein phosphorylation or changes in glutamate-mediated ionic currents (Figure 5-55D). Whatever the mechanism, if presynaptic D_2 agonism is caused by lumateperone rather than presynaptic antagonism characteristic of the other drugs in this class, lumateperone would theoretically turn off dopamine synthesis presynaptically to reduce the oversupply of dopamine present in presynaptic dopamine synapses in psychosis (Figure 5-55D). That would mean less postsynaptic D_2 antagonism would be necessary to have an antipsychotic effect because dopamine release is already diminished. If lumateperone can be proven to have such a mechanism of presynaptic partial agonism of D_2 receptors, combined with its well-established highly potent $5HT_{2A}$ antagonism, this could account for why lumateperone has antipsychotic efficacy in schizophrenia with low amounts of postsynaptic D_2 antagonism compared to most other drugs in this class (and low amounts of motor and metabolic side effects). Further investigations are needed to clarify this possible explanation. Lumateperone is also in clinical trials for bipolar depression.

Two Pips and a Rip

Aripiprazole

Aripiprazole is the original "pip" and is a $D_2/5HT_{1A}$ partial agonist (see Figure 5-56). Because of its D_2 partial agonist actions, aripiprazole has relatively low motor side effects, mostly akathisia, and actually reduces prolactin rather than elevating it. It has only moderate affinity for $5HT_{2A}$ receptors (Figure 5-32), but higher affinity for $5HT_{1A}$ receptors (Figure 5-33). Aripiprazole is effective in treating schizophrenia/maintenance (age 13 and older) and also agitation (intramuscular) and bipolar mania/maintenance (ages 10 and older), and is also approved for use in various other child and adolescent groups, including autism-related irritability (ages 5 to 17) and Tourette syndrome (ages 6 to 18). It is approved for adjunctive treatment to SSRIs/SNRIs for major depressive disorder, and this is by far its major use in clinical practice in the US. It is not approved for bipolar depression but commonly used off-label for that. How aripiprazole works in depression compared to how it works in schizophrenia is of course unknown, but its potent $5HT_{1A}$ partial agonist (Figure 5-33) and $5HT_{2C}$ and $5HT_7$ antagonist properties (Figures 5-37 and 5-39) are theoretical explanations for potential antidepressant actions, as these would be active at the low doses generally used to treat depression. Aripiprazole lacks the pharmacological properties normally associated with sedation, namely, muscarinic cholinergic and H_1 histamine antagonist properties (Figure 5-41), and thus is not generally sedating. A major differentiating feature of aripiprazole is that it has, like ziprasidone and lurasidone, little or no propensity for weight gain, although weight gain can be a problem for some, including some children and adolescents.

An intramuscular dosage formulation of aripiprazole for short-term use is available as an orally disintegrating tablet and a liquid formulation. One long-acting 4-week injectable and another 4- to 6- to 8-week long-acting injectable, the latter with a loading injection on the first day not requiring continuing oral loading, are available. These formulations are commonly used options for assuring compliance, especially in early-onset psychosis where aripiprazole's favorable tolerability profile may be particularly well received.

Brexpiprazole

The second "pip" is brexpiprazole (Figure 5-57). Just as its name suggests, brexpiprazole is chemically and pharmacologically related to aripiprazole. However, it does differ pharmacologically from aripiprazole in that

it has more potent $5HT_{2A}$ antagonism (Figure 5-32), $5HT_{1A}$ partial agonism (Figure 5-33), and α_1 antagonism (Figure 5-42) relative to its D_2 partial agonism (Figure 5-57) than aripiprazole (Figure 5-56), which should theoretically reduce its propensity to cause motor side effects and akathisia. There is some indication that there may be reduced akathisia with brexpiprazole compared to aripiprazole, but this has not been proven in head-to-head trials. Like aripiprazole, brexpiprazole is approved for the treatment of schizophrenia, but unlike aripiprazole, is not indicated for the treatment of acute bipolar mania.

Brexpiprazole (Figure 5-57) has $5HT_{1A}$ partial agonist (Figure 5-33) and relatively higher potency for α_1 (Figure 5-42) and α_2 (Figure 5-35) binding than aripiprazole. These properties could theoretically contribute to antidepressant actions (mechanisms further explained and illustrated in Chapter 7 on treatments for mood disorders). Alpha-1 actions in particular could theoretically help explain the efficacy brexpiprazole has demonstrated in some of its potential novel indications. Specifically, brexpiprazole is in late-stage clinical development with positive studies for the treatment of agitation in dementia (discussed further in Chapter 12 on dementia). There are also promising preliminary data for brexpiprazole when combined with the SSRI sertraline for the treatment of PTSD.

Cariprazine

Cariprazine (Figure 5-58) is the "rip" of this group and is another $D_2/5HT_{1A}$ partial agonist approved for schizophrenia and also for acute bipolar mania. Cariprazine with its potent $5HT_{1A}$ partial agonist actions (Figure 5-33) despite lesser $5HT_{2A}$ antagonism (Figure 5-32) exhibits low incidence of drug-induced parkinsonism, but some akathisia, which can be much reduced by slow-dose titration. Cariprazine has two long- to very long-lasting active metabolites with the novel and interesting potential for development as a weekly or biweekly or even monthly "oral depot," which takes longer to reach steady state but has less reduction in plasma drug levels as a dose is skipped.

Cariprazine has proven to be a highly effective and well-tolerated agent for the treatment of bipolar depression in lower doses. Like lurasidone, which is also approved for bipolar depression, cariprazine has a very low propensity for weight gain or metabolic disturbance. Like other drugs in this class, cariprazine has both $5HT_{1A}$ and α_1 and α_2 actions, suggesting antidepressant efficacy, but it is the very potent D_3 partial agonist actions that are perhaps the most distinguishing and novel pharmacological characteristics. The role of D_3 receptors is just now being clarified in humans since preclinical studies suggest therapeutic potential of D_3 partial agonism for cognition, mood, emotions, and reward/substance abuse, as well as negative symptoms. In fact, cariprazine has been shown to be superior to $D_2/5HT_{2A}$ antagonist treatment for the improvement of negative symptoms in schizophrenia.

The mechanism of action of D_3 partial agonism will be illustrated and explained in further detail in Chapter 7 on treatments for mood disorders. In brief, D_3 antagonist/partial agonist action may block key postsynaptic D_3 receptors in limbic areas to reduce dopamine overactivity in emotional striatum and key somatodendritic presynaptic D_3 receptors in the ventral tegmental area/mesostriatal/integrative hub to increase dopamine release in the prefrontal cortex and improve negative, affective, and cognitive symptoms. For this reason, clinical trials and clinical experience suggest robust efficacy of cariprazine across the mood-disorder spectrum for all mixtures of mania and depression, as will be illustrated and described in Chapter 7.

Selective $5HT_{2A}$ Antagonist

Pimavanserin

Pimavanserin (Figure 5-59) is the only known drug with proven antipsychotic efficacy that does not have D_2 antagonist/partial agonist actions. This agent has potent $5HT_{2A}$ antagonist with lesser $5HT_{2C}$ antagonist actions, sometimes called inverse agonism, as explained earlier in this chapter and as illustrated in Figure 5-15. The role if any of $5HT_{2C}$ antagonism in the treatment of psychosis is not clear but $5HT_{2C}$ antagonist actions would theoretically improve dopamine release in both depression and in the negative symptoms of schizophrenia. Indeed, pimavanserin is in testing as an augmenting agent to SSRIs/SNRIs, with some positive preliminary results in major depressive disorder, and as an augmenting agent to $D_2/5HT_{2A}/5HT_{1A}$ agents in negative symptoms of schizophrenia, also with positive results from early trials. It is approved for the treatment of psychosis in Parkinson's disease and in late-stage testing for psychosis in dementia.

The Others

Sertindole

Sertindole (Figure 5-60) is a $5HT_{2A}/D_2$ receptor antagonist originally approved in some European countries, then withdrawn for further testing of its

cardiac safety and QTc-prolonging potential, and then reintroduced into certain countries as a second-line agent. It may be useful for some patients in whom other antipsychotics have failed, and who can have close monitoring of their cardiac status and drug interactions.

Perospirone

Perospirone (Figure 5-61) is another $5HT_{2A}$ and D_2 antagonist available in Asia to treat schizophrenia. $5HT_{1A}$ partial agonist actions may contribute to its efficacy and/or tolerability. Its ability to cause weight gain, dyslipidemia, insulin resistance, and diabetes is not well investigated. It is generally administered three times a day, with more experience in the treatment of schizophrenia than in the treatment of mania.

Blonanserin

Blonanserin (Figure 5-62) is also a $5HT_{2A}/D_2$ antagonist, available in Asia to treat schizophrenia, and is administered twice a day. Blonanserin has the unique property of higher affinity for the D_3 receptor than dopamine has for the D_3 receptor (like cariprazine), suggesting possible utility for the negative symptoms of schizophrenia and for bipolar depression, but it is not yet well studied in these indications.

FUTURE TREATMENTS FOR SCHIZOPHRENIA

Roluperidone (MIN-101)

Roluperidone (Figure 5-63) is a $5HT_{2A}$ antagonist with additional σ_2 antagonist actions, which is in study for schizophrenia. Early studies suggest possibly efficacy for negative symptoms, and trials are ongoing.

D_3 Antagonists

In addition to cariprazine and blonanserin (both of which are unique in their highly potent D_3 antagonist/partial agonist properties), other D_3 antagonists/partial agonists are in clinical trials. One is F17464, which has higher selectivity for D_3 than for D_2 or $5HT_{1A}$ receptors, and which has shown efficacy in schizophrenia in early studies.

Trace Amine Receptor Agonists and SEP-363856

An exciting new potential mechanism of antipsychotic action is trace amine agonism specifically acting at the trace amine-associated receptor type 1 (TAAR1). What is a trace amine and why would targeting its receptors have antipsychotic action? There are five principal trace amines in humans and six human trace amine-associated receptors, but the most important receptor is TAAR1 (Table 5-3). Trace amines are formed from amino acids when the tyrosine hydroxylase (see Figure 4-2) step is omitted or the tryptophan hydroxylase (see Figure 4-36) step is omitted. Trace amines have long been a mystery as they are only present in trace amounts, are not stored in synaptic vesicles, and are not released upon nerve firing. The fact that TAAR1 receptors are localized in monoamine brainstem centers and in monoamine projection areas (Figure 5-64) has long made psychopharmacologists think that trace amines might be involved in regulating monoamine action even though trace amines are not neurotransmitters in their own right. Instead, trace amines have been called "the rheostat of dopaminergic, glutamatergic, and serotonergic neurotransmission," maintaining central neurotransmission within defined physiological limits.

The current hypothesized mechanism of antipsychotic action for TAAR1 agonists is that they act tonically both presynaptically and postsynaptically to prevent the dopaminergic hyperactivity of psychosis and mania (Figures 4-15 and 4-16). Thus, TAAR1 agonists are potentially a novel way to prevent dopamine overactivity at D_2 receptors.

How do they do this? TAAR1 receptors theoretically prevent dopamine overactivity after occupancy by an agonist through translocation to the synaptic membrane, where they couple with D_2 receptors (called heterodimerization), which makes the second-messenger system decide to go with the inhibitory G (Gi) protein

Table 5-3 Trace amines and their receptors

Five principal trace amines in humans
β-Phenylethylamine (PEA)
p-Tyramine
Tryptamine
p-Octopamine
p-Synephrine
Six human trace amine-associated receptors (TAARs)
TAAR1 (main TAAR in humans)
TAAR2
TAAR5
TAAR6
TAAR8
TAAR9

signal transduction cascade rather than the β-arrestin 2 pathway (Figure 5-65A, B). TAAR1 receptors can be said to "bias" D_2 receptors away from β-arrestin 2 and towards Gi-protein-regulated second messengering (Figure 5-65B).

Why does this matter? When heterodimerization with TAAR1 happens to presynaptic D_2 receptors, the downstream consequences of the Gi pathway are amplified and those include inhibiting the synthesis and release of dopamine (presynaptic area of Figure 5-65B). That would be a good thing if dopamine is in excess presynaptically, as it seems to be in psychosis and in mania. When D_2 receptor signaling postsynaptically is also shunted away from the β-arrestin 2 pathway to the Gi pathway by "biased" and heterodimerized postsynaptic D_2 receptors, this theoretically mitigates the consequences of excessive signals through β-arrestin to excessive GSK-3 (glycogen synthase kinase 3) activation that results from postsynaptic D_2 receptor overstimulation (postsynaptic area of Figure 5-65B).

The bottom line of all this is that TAAR1 agonists may enhance presynaptic D_2 autoreceptors (thus turning off dopamine synthesis and release) while simultaneously reducing some of the unwanted downstream functions of overly active postsynaptic D_2 receptors (thus mitigating the effects of excessive dopamine release in psychosis and mania). Furthermore, TAAR1 agonism does both pre- and postsynaptic actions without actually directly pharmacologically blocking the D_2 receptor! (Figure 5-65B).

SEP-363856 (Figure 5-66) is an example of a TAAR1 agonist with weak affinity for the TAAR1 receptor as well as weaker affinities for the $5HT_{1D}$ and $5HT_7$ receptors as antagonist and for the $5HT_{1A}$ receptor as agonist. This drug surprisingly showed preclinical behavioral evidence of efficacy serendipitously for psychosis, and only then did its pharmacological and molecular mechanism of action on TAAR1 receptors get discovered. Already, an early study in patients with schizophrenia has confirmed antipsychotic action with few side effects, and the drug has been given breakthrough status by regulators. Further trials are ongoing.

Cholinergic Agonists

Activation of central muscarinic cholinergic receptors, either directly or by allosteric modulation, is under investigation as a novel antipsychotic mechanism. Preclinical and postmortem studies in patients with schizophrenia suggest that central cholinergic receptor alterations may be key to the pathophysiology of schizophrenia. M_4 receptor agonism may reduce psychotic symptoms whereas M_1 receptor agonism may be most relevant to improving the cognitive deficits of schizophrenia. Xanomeline (Figure 5-67), as an M_4/M_1 central agonist, decreases dopamine cell firing in the ventral tegmental area. This would theoretically reduce positive psychotic symptoms. Xanomeline also increases extracellular levels of dopamine in the prefrontal cortex, which theoretically would improve cognitive, negative, and affective symptoms. Xanomeline combined with tropsium, an anticholinergic that does not penetrate into the brain and that blocks M_2 and M_3 activated side effects in the periphery, has shown promising efficacy and tolerability for the psychotic symptoms of schizophrenia with improved side effects and is progressing as a potential breakthrough into advanced clinical trials. The known binding profile of xanomeline at muscarinic cholinergic receptors as well as serotonin receptors is shown in Figure 5-67.

A Few Other Ideas

Although several agents targeting glutamate neurotransmission have been studied in schizophrenia, most have not had consistently positive or robust efficacy findings. A novel idea still being pursued is to inhibit the enzyme DAO (D-amino acid oxidase) as a way to boost glutamate function (see Figure 4-22).

Another novel approach to blocking the effects of hyperactive dopamine is to block the action of the enzyme phosphodiesterase type 9/10; several potential drugs are in clinical development. This mechanism alters the second-messenger signal transduction cascade of dopamine at D_1 and D_2 receptors and may have downstream effects similar to blocking D_2 receptors, and do it more selectively in the dopamine neurons thought to be hyperactive in schizophrenia.

SUMMARY

This chapter reviews drugs used to treat psychosis, but has avoided the term "antipsychotics," since these same agents are used more frequently for other indications such as unipolar and bipolar depression. Instead, the hypothetical mechanism of "antipsychotic action" is explored in detail. Specifically, this chapter reviews the pharmacology of drugs that treat psychosis, including those with predominantly D_2 antagonist properties, those

with $5HT_{2A}$ antagonist/D_2 antagonist properties, those with $D_2/5HT_{1A}$ partial agonist properties, and those with $5HT_{2A}$ selective antagonist properties. These agents are compared and contrasted across these various dopamine and serotonin receptor subtypes and their receptor actions linked to hypothetical therapeutic actions as well as side effects. Multiple additional receptor binding properties at other neurotransmitter receptor sites that are hypothesized to be linked to additional clinical actions of these agents, especially to their antidepressant actions, are presented and discussed. Still other receptor actions hypothetically linked to additional side effects are also presented. The pharmacological and clinical properties of two dozen specific drugs either marketed or in late-stage clinical trials are discussed in detail, including exciting new potential mechanisms of action at trace amine-associated receptors and at muscarinic cholinergic receptors.

6 Mood Disorders and the Neurotransmitter Networks Norepinephrine and γ-Aminobutyric Acid (GABA)

Description of Mood Disorders 244
Mood Spectrum 244
Distinguishing Unipolar Depression from Bipolar Depression 249
Mixed Features: Are Mood Disorders Progressive? 251
Neurobiology of Mood Disorders 252
Neurotransmitters 252
The Monoamine Hypothesis of Depression 264
The Monoamine Receptor Hypothesis and Neurotrophic Factors 264
Beyond Monoamines: The Neuroplasticity and Neuroprogression Hypothesis of Depression 266
Symptoms and Circuits in Mood Disorders 277
Symptom-Based Treatment Selections 279
Summary 282

This chapter discusses disorders characterized by abnormalities of mood: namely, depression, mania, or mixtures of both. Included here are descriptions of a wide variety of mood disorders that occur over a broad clinical spectrum. Clinical descriptions and criteria for how to diagnose disorders of mood will only be mentioned in passing. The reader should consult standard reference sources for this material. Also included in this chapter is an analysis of how monoamine neurotransmitter systems have long been hypothetically linked to the biological basis of mood disorders. We will also cover more recent advances in neurobiology that link mood disorders to glutamate, GABA (γ-aminobutyric acid), neurotrophic factors, neuroinflammation, and stress.

Mood disorders have many symptoms and approaching them clinically involves first constructing a diagnosis from a given patient's symptom profile, but then deconstructing that patient's mood disorder into its component symptoms so each symptom can be individually targeted therapeutically. We will discuss how to combine this clinical approach to diagnosis with a neurobiological approach to treatment by first matching every symptom to its hypothetically malfunctioning brain circuit, regulated by one or more neurotransmitters. The strategy is next to select drugs that target the specific neurotransmitters in the specific symptomatic brain circuits in a given patient. The goal is to improve the efficiency of information processing in those brain circuits and thereby reduce symptoms. Covering the neurobiological basis of mood disorders in this chapter sets the stage for understanding the mechanisms of action and how to select specific drug treatments in Chapter 7.

DESCRIPTION OF MOOD DISORDERS

Mood Spectrum

Disorders of mood are often called affective disorders, since affect is the external display of mood, an emotion that is, however, felt internally and called mood. Mood disorders are not just about mood. The diagnosis of a major depressive episode requires the presence of at least five symptoms, only one of which is depressed mood (Figure 6-1). Similarly, a manic episode requires more than just an elevated, expansive, or irritable mood; there must be at least three or four additional symptoms (Figure 6-2).

Classically, the mood symptoms of mania and depression are "poles" apart (Figures 6-3 through 6-6). This concept has generated the terms "unipolar" depression (i.e., patients who experience just the *down* or depressed pole) (Figures 6-3 and 6-4) and "bipolar" (i.e., patients who at different times experience the *up* pole, or mania (Figures 6-3 and 6-5) or hypomania (Figures 6-3 and 6-6) and the *down* pole, i.e., depressed pole (Figures 6-3, 6-5, and 6-6). Bipolar I patients have full-blown manic episodes usually followed by depressive episodes (Figure 6-5). Bipolar II disorder is characterized by at least one hypomanic episode and one major depressive episode (Figure 6-6). Depression and mania may even occur simultaneously, which is

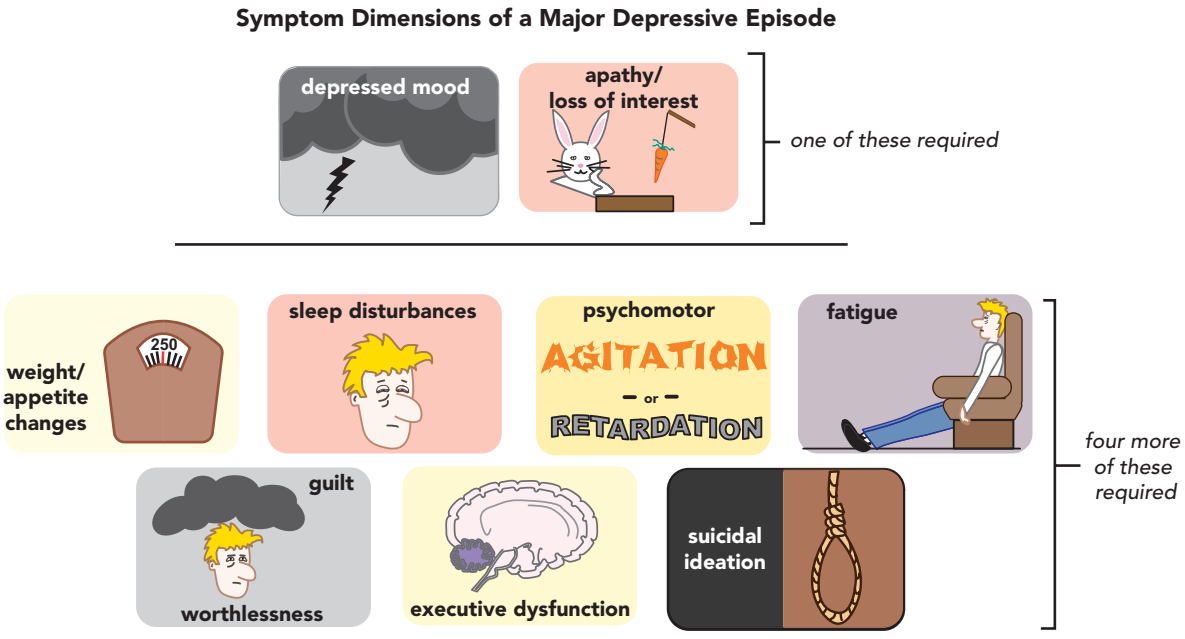


Figure 6-1 **DSM-5 symptoms of a major depressive episode.** According to the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5), a major depressive episode consists of either depressed mood or loss of interest and at least four of the following: weight/appetite changes, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of guilt or worthlessness, executive dysfunction, and suicidal ideation.

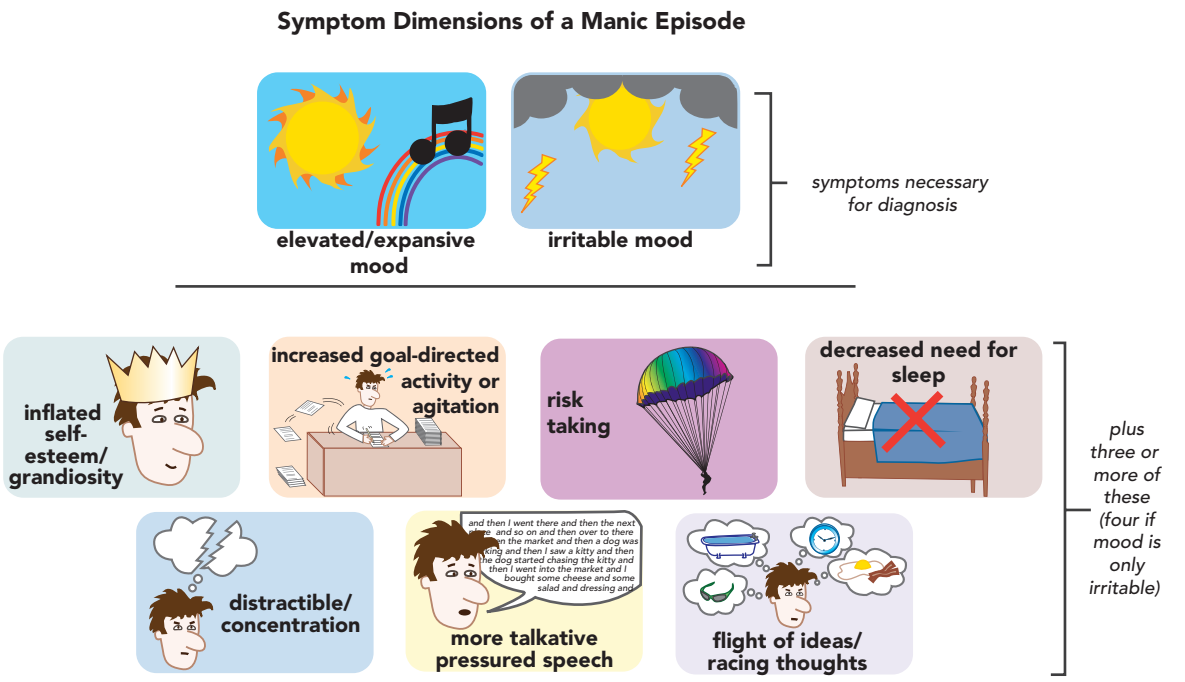


Figure 6-2 **DSM-5 symptoms of a manic episode.** According to the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5), a manic episode consists of either elevated/expansive mood or irritable mood. In addition, at least three of the following must be present (four if mood is irritable): inflated self-esteem/grandiosity, increased goal-directed activity or agitation, risk taking, decreased need for sleep, distractibility, pressured speech, and racing thoughts.

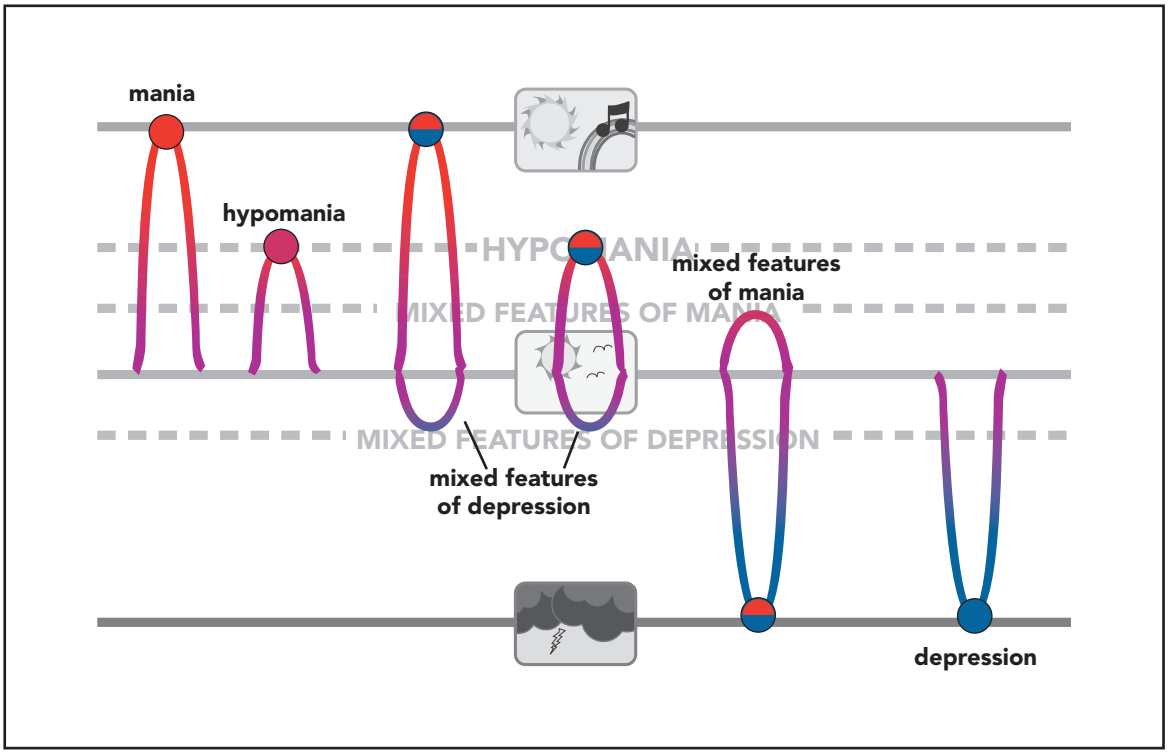


Figure 6-3 Mood episodes. Mood symptoms exist along a spectrum, with the polar ends being pure mania or hypomania ("up" pole) and pure depression ("down" pole). Patients can also experience mood episodes that include symptoms of both poles; such episodes can be described as mania/hypomania with mixed features of depression or depression with mixed features of mania. A patient may have any combination of these episodes over the course of illness; subsyndromal manic or depressive episodes also occur during the course of illness, in which case there are not enough symptoms or the symptoms are not severe enough to meet the diagnostic criteria for one of these episodes. Thus the presentation of mood disorders can vary widely.

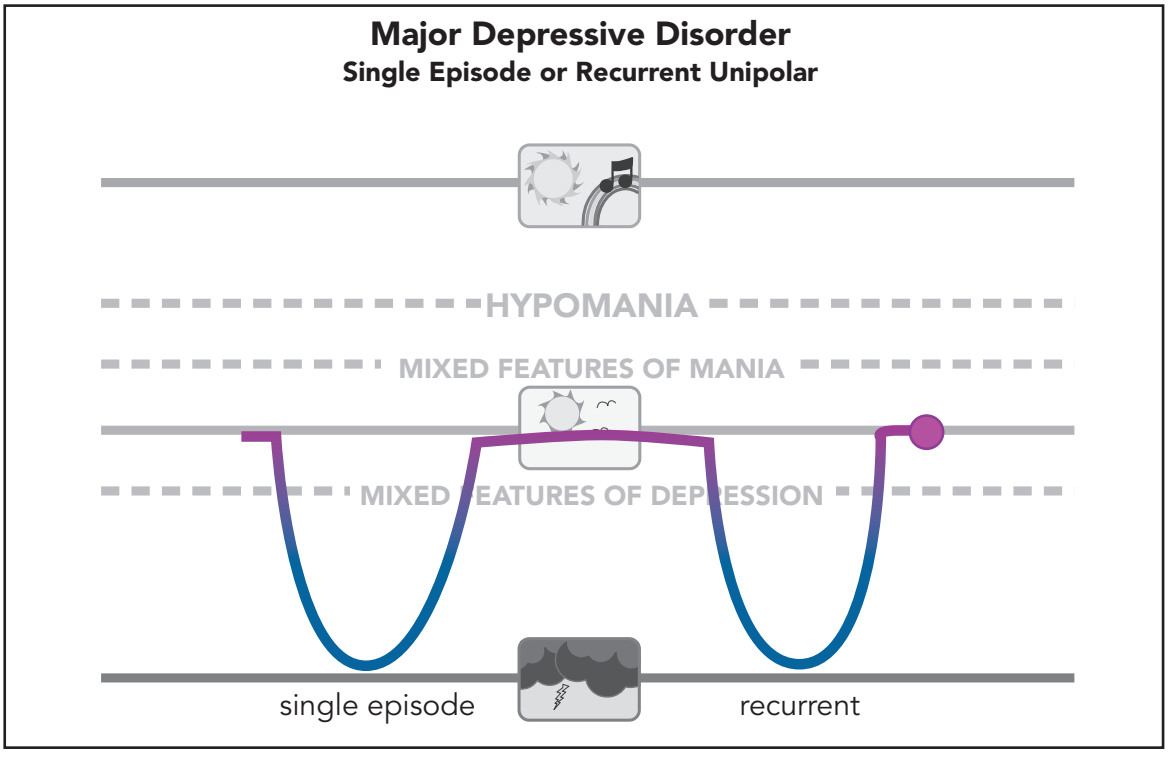


Figure 6-4 Major depressive disorder. Major depressive disorder is defined by the occurrence of at least a single major depressive episode, although most patients will experience recurrent episodes.

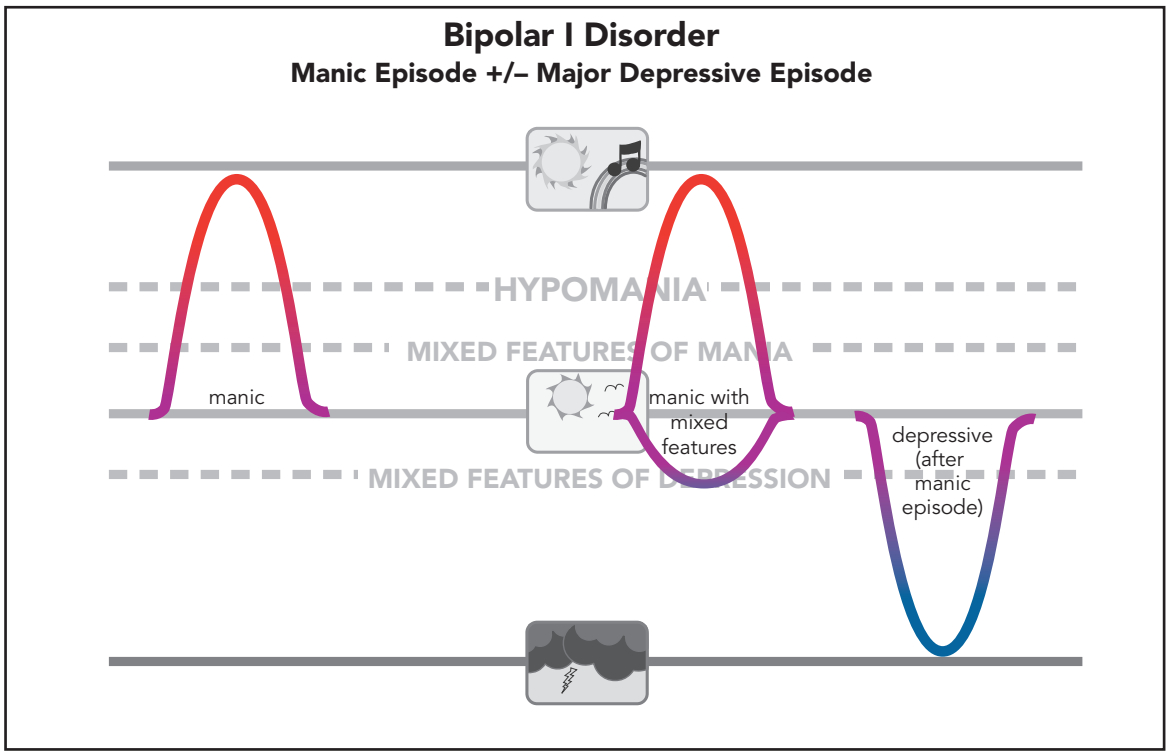


Figure 6-5 **Bipolar I disorder.** Bipolar I disorder is defined as the occurrence of at least one manic episode. Patients with bipolar I disorder typically experience major depressive episodes as well, although this is not necessary for the bipolar I diagnosis. It is also common for patients to experience manic episodes with mixed features of depression.

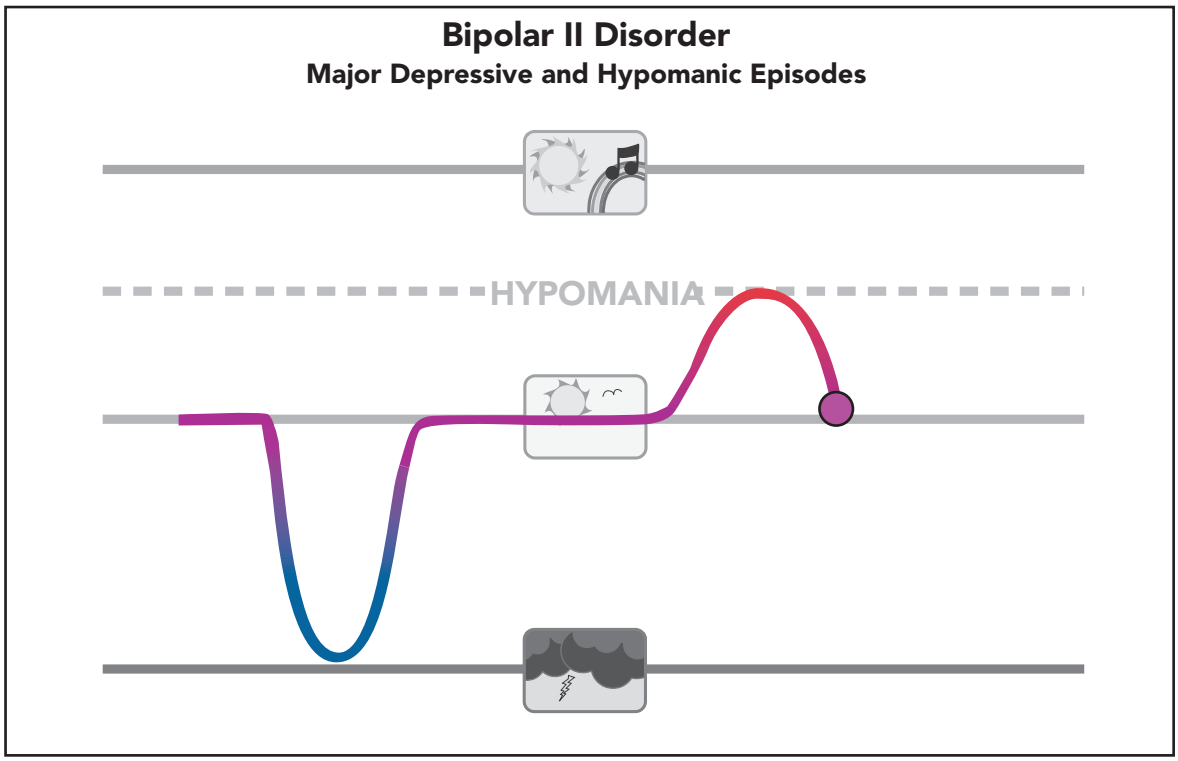


Figure 6-6 **Bipolar II disorder.** Bipolar II disorder is defined as an illness course consisting of one or more major depressive episodes and at least one hypomanic episode.

called a "mixed" mood state or, in DSM-5, "mixed features" (Figure 6-7; Table 6-1). Introduction of the mixed-features modifier has moved the field away from considering depression and mania as distinct categories and towards the concept that they are opposite ends of a spectrum, with all degrees of mixtures in between (Figure 6-7). Many real patients are neither purely depressed nor purely manic, but some mixture of both,

Table 6-1 Mixed features (DSM-5) of manic, hypomanic, and major depressive episodes

Manic or hypomanic episode, with mixed features
Full criteria for manic or hypomanic episode
At least three of the following symptoms of depression:
Depressed mood
Loss of interest or pleasure
Psychomotor retardation
Fatigue or loss of energy
Feelings of worthlessness or excessive or inappropriate guilt
Recurrent thoughts of death or suicidal ideation/actions
Depressive episode, with mixed features
Full criteria for a major depressive episode
At least three of the following manic/hypomanic symptoms:
Elevated, expansive mood (e.g., feeling high, excited, or hyper)
Inflated self-esteem or grandiosity
More talkative than usual or feeling pressured to keep talking
Flight of ideas or subjective experience that thoughts are racing
Increase in energy or goal-directed activity
Increased or excessive involvement in activities that have a high potential for painful consequences
Decreased need for sleep
(*Not included: psychomotor agitation)
(*Not included: irritability)
(*Not included: distractibility)

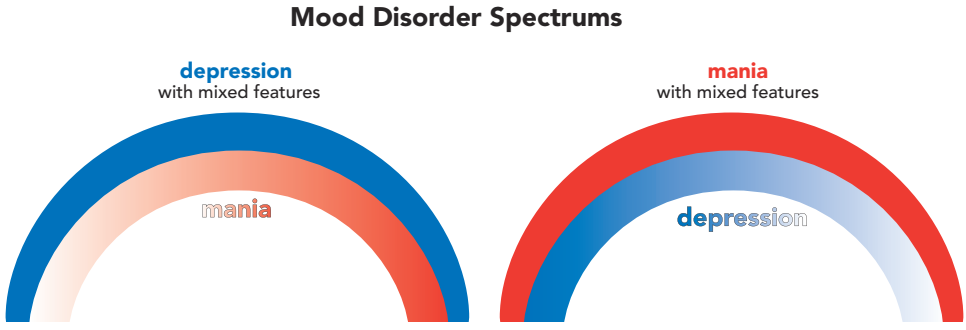


Figure 6-7 Mood-disorder spectrums. Depressive symptoms and manic symptoms can occur as part of the same episode; this is termed "mixed features" and can be defined as depression with mixed features, in which depressive symptoms dominate, or as mania with mixed features, in which manic symptoms dominate. Thus mood disorders are best understood as a spectrum, rather than as discrete categorial diagnoses.

with the specific mix of symptoms changing along the mood spectrum over the course of illness. This is similar to the evolution in the conceptualization of schizophrenia versus bipolar disorder, where the old dichotomous model (Figure 6-8) has been largely replaced with a continuous disease model spectrum, ranging from pure psychotic disorder to pure mood disorder (Figure 6-9).

Distinguishing Unipolar Depression from Bipolar Depression

Other than a history of a prior manic/hypomanic episode, patients with unipolar depressive episodes (Figure 6-4) are diagnosed using the same symptom criteria (Figure 6-1) as patients with bipolar depressive episodes (Figures 6-5 and 6-6). Despite similar symptoms, patients with

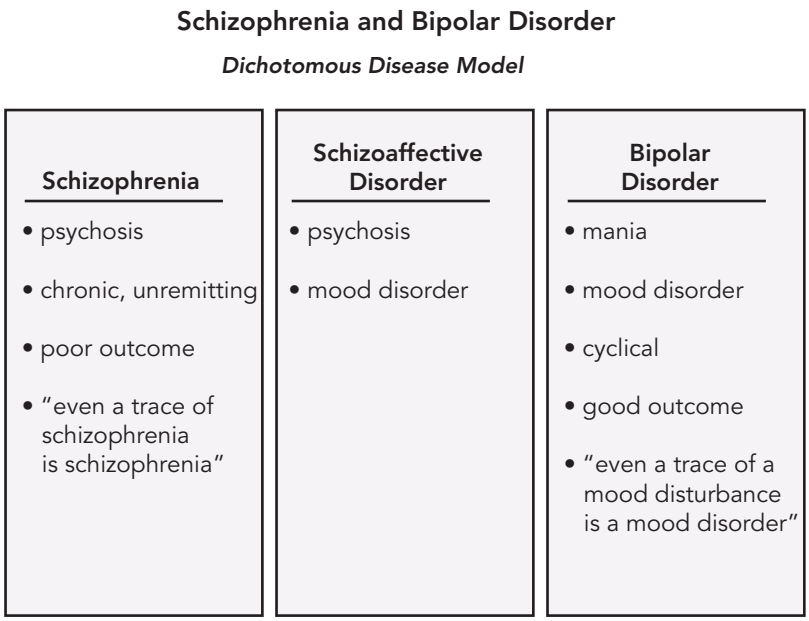


Figure 6-8 Schizophrenia and bipolar disorder: dichotomous disease model. Schizophrenia and bipolar disorder have been conceptualized both as dichotomous disorders and as belonging to a continuum. In the dichotomous disease model, schizophrenia consists of chronic, unremitting psychosis, with poor outcomes expected. Bipolar disorder consists of cyclical manic and other mood episodes and has better expected outcomes than schizophrenia. A third distinct disorder is schizoaffective disorder, characterized by both psychosis and a mood disorder.

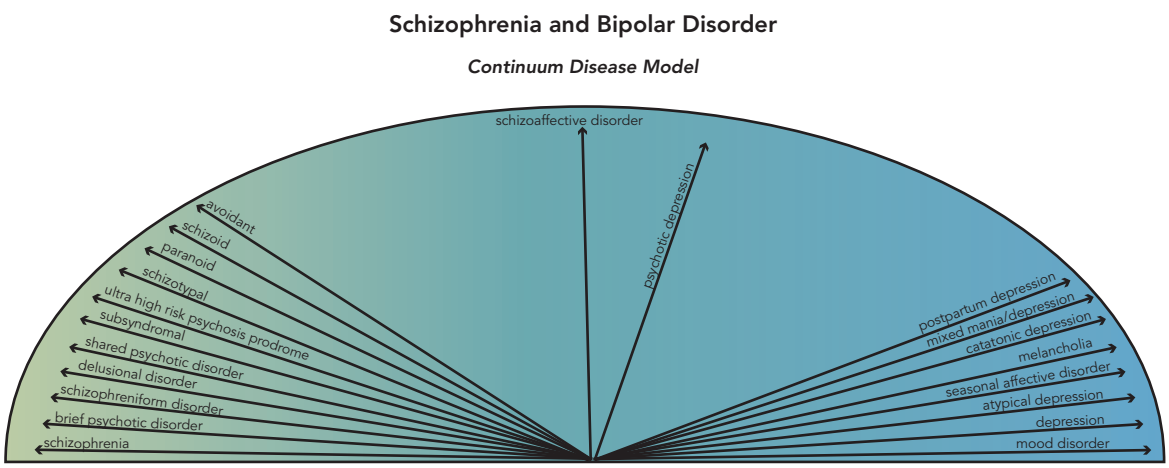


Figure 6-9 Schizophrenia and bipolar disorder: continuum disease model. Schizophrenia and bipolar disorder have been conceptualized both as dichotomous disorders and as belonging to a continuum. In the continuum disease model, schizophrenia and mood disorders fall along a continuum in which psychosis, delusions, and paranoid avoidant behavior are on one extreme and depression and other mood symptoms are on the other extreme. Falling in the middle are psychotic depression and schizoaffective disorder.

unipolar versus bipolar depression have different long-term outcomes and should generally receive different treatments. Unfortunately, missed diagnosis or delayed diagnosis of bipolar depression is all too common. Over a third of patients with unipolar depression are eventually re-diagnosed as having bipolar disorder and maybe as many as 60% of depressed patients with bipolar II disorder are initially diagnosed as having unipolar depression. In some cases, this is because the patient had depressive episodes before they had manic or hypomanic episodes, and a bipolar diagnosis could not be made. In other cases, the diagnosis of a past manic or hypomanic episode is missed because patients with bipolar disorder often present in the depressed phase and past hypomania is often pleasant for patients and may not be mentioned.

Why do you want to make an early accurate diagnosis of bipolar disorder? Although unipolar versus bipolar depression cannot be readily distinguished on the basis of a patient's current symptomatology, there are some hints that can raise suspicion of a bipolar depressive episode rather than a unipolar depressive episode (Figure 6-10). Missing the diagnosis of bipolar depression early may lead to worse quality of life due to giving the wrong treatment (for unipolar depression rather than for bipolar depression) and this may be ineffective or even dangerous. That is, delay of appropriate treatment in bipolar depression can increase the risk of mood cycling, relapse, and suicide, and even decrease the chances of responding to appropriate bipolar treatments once they are given later.

Thus, it is important to tell unipolar from bipolar depression. Is there any way to do this when the patient is in the depressed state other than to find a prior history of mania/hypomania? The short answer is no. The long answer is that there are certain clinical characteristics that favor the likelihood of a bipolar depressive episode instead of a unipolar depressive episode, and these factors can be clues to the diagnosis of a bipolar depressive episode when the past history of a manic/hypomanic episode is unclear (Figure 6-10). Some additional tips about how to determine whether a depressed patient is unipolar or bipolar might be to ask two questions (Table 6-2):

"Who's your daddy?" and "Where's your mama?"

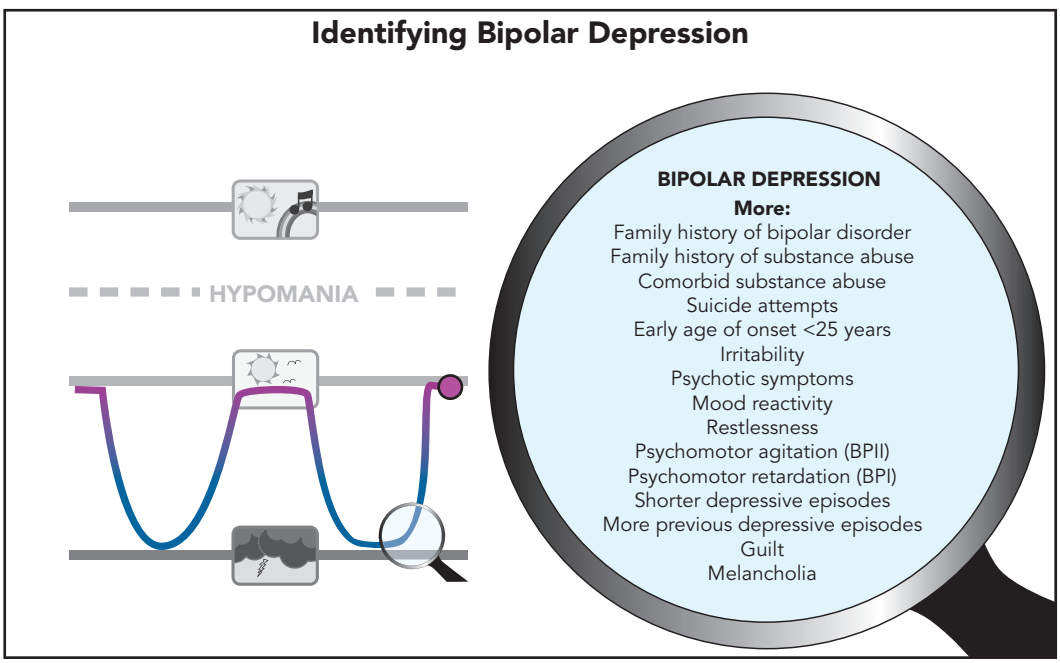


Figure 6-10 Identifying bipolar depression. Although all symptoms of a major depressive episode can occur in either unipolar or bipolar depression, some factors can provide hints if not diagnostic certainty that the patient has a bipolar spectrum disorder. These can include a family history of bipolar disorder, family history of substance abuse, comorbid substance abuse, history of suicide attempts, earlier age of onset, and shorter but more frequent depressive episodes. Some symptoms may also be more common as part of a bipolar illness, including irritability, psychotic symptoms, mood reactivity, restlessness, psychomotor agitation or retardation, guilt, and melancholia.

Table 6-2 Is it unipolar or bipolar depression? Questions to ask

Who's your daddy?
What is your family history of:
• mood disorder? • psychiatric hospitalizations? • suicide? • anyone who took lithium, mood stabilizers, drugs for psychosis or depression? • anyone who received ECT?
These can be indications of a unipolar or bipolar spectrum disorder in relatives.
Where's your mama?
I need to get additional history about you from someone close to you, such as your mother or your spouse.
Patients may especially lack insight about their manic symptoms and under-report them.

"Who's your daddy?" means more precisely, "what is your family history?" since a first-degree relative with a bipolar spectrum disorder can give a strong hint that the patient also has a bipolar spectrum disorder rather than unipolar depression. Although the majority of patients with bipolar depression do not have a family history of bipolar disorder, when it is present, it is arguably the most robust and reliable risk factor for bipolar depression. Individuals with a first-degree relative with bipolar disorder are at an 8–10-fold greater risk of developing bipolar disorder compared to the general population.

The second question, "Where's your mama?," really means "I need to get additional history from someone else close to you," since patients tend to under-report their manic symptoms. The insight and observations of an outside informant such as a mother or spouse who can give past history might indeed prove to be quite different from the one the patient is reporting, and thus help establish a bipolar spectrum diagnosis that patients themselves deny or do not perceive.

Mixed Features: Are Mood Disorders Progressive?

In addition to the importance of distinguishing unipolar depression from bipolar depression, it is also very important to look for mixed features in your depressed patients, whether those patients have a unipolar or bipolar illness. This is because there are big differences in the outcome for patients if mixed features are present. For one thing, there is evidence that unipolar depression can progress to mixed features, mixed features progress to bipolar disorder, and bipolar disorder progress to treatment resistance (Figure 6-11). The presence of even subthreshold manic symptoms is strongly associated with conversion to bipolar disorder, with each manic symptom increasing risk by 30%. We don't know if we can halt this march towards a bad outcome, but the best chance may be early recognition and effective treatment that reduces or eliminates all symptoms, whether manic or depressed, and to do this as early in the course of illness as possible.

How many depressed patients have mixed features? The estimates are about a quarter of all patients with unipolar depression and a third of all patients with bipolar I or II depression have subsyndromal symptoms of mania. Estimates of mixed features in unipolar depression in children and adolescents are even higher. Compared to those with "pure" depression, those with depression plus some manic symptoms may have a more complex illness and less favorable course and outcome. For example, mixed features may compound the already high risk of suicide in depressed patients. Non-euphoric manic symptoms such as psychomotor agitation, impulsivity, irritability, and racing/crowded thoughts combined with depressive symptoms are a recipe for suicidality. Suicide rates are twice as high in bipolar than in unipolar depression and up to 20 times higher in bipolar disorder compared to the general population. Sadly, up to a third of bipolar patients attempt suicide at least once in their life, and 10–20% of them succeed.

What about those subsyndromal manic symptoms and suicide? In the presence of mixed features there is a fourfold increased risk of suicidality in both unipolar and bipolar depression. Studies show specifically a worrisome association of mixed episodes with suicide attempts, so it is not only important to identify who has mixed features, but also to treat appropriately. Treatment for mixed features is discussed in Chapter 7 and surprisingly is NOT the same as the treatment for unipolar depression without mixed features. That is, neither unipolar nor bipolar depression with mixed features are treated first-line with standard monoamine reuptake inhibiting drugs used widely in unipolar depression and discussed in Chapter 7, but rather with serotonin/dopamine antagonists/partial agonists used widely for the treatment of psychosis and discussed in Chapter 5. Thus, it cannot be emphasized too strongly that major depressive episodes need to be correctly diagnosed as part of a unipolar or bipolar illness and as having or lacking mixed features, and that

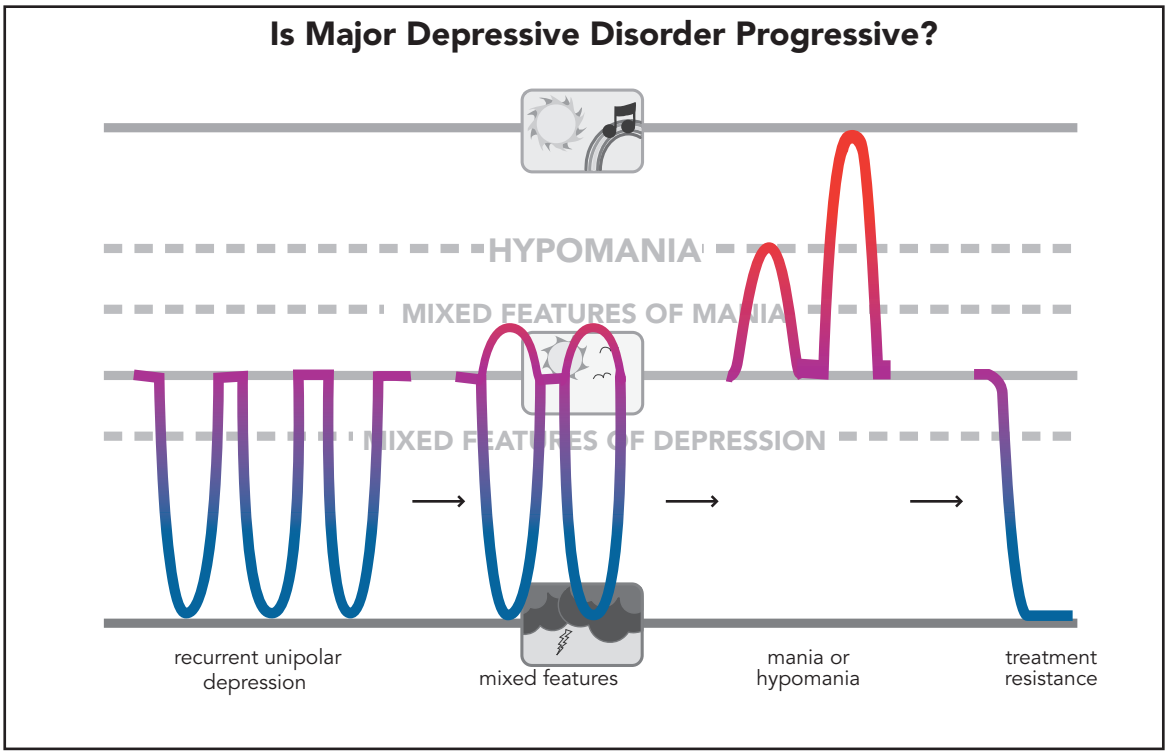


Figure 6-11 **Is major depressive disorder progressive?** There is evidence that mood disorders may be progressive. Unipolar depression with recurrent episodes may progress to depression with mixed features, which may ultimately progress to a bipolar spectrum condition and finally treatment resistance.

the correct treatment be given (details of treatment of mood disorders are given in Chapter 7). The hope is that recognition and appropriate treatment of both unipolar and bipolar depression – whether that depressive episode has mixed features or not – will cause all symptoms to remit for long periods of time and that this might prevent progression to more difficult states (Figure 6-11). This is not proven, but is a major hypothesis in the field at the present time.

NEUROBIOLOGY OF MOOD DISORDERS

Neurotransmitters

Dysfunctional neurotransmission in various brain circuits is implicated in both the pathophysiology and treatment of mood disorders. Classically, this has included the monoamine neurotransmitters norepinephrine, dopamine, and serotonin, and more recently the neurotransmitters glutamate and GABA (γ-aminobutyric acid) and their associated ion channels. Symptoms of mood disorders are hypothesized to involve dysfunction of various combinations of these neurotransmitters and ion channels, and all known treatments for mood disorders act upon one or more of them. We have extensively discussed the dopamine system (Chapter 4; Figures 4-2 through 4-13), the serotonin system (Chapter 4; Figures 4-36 through 4-51), the glutamate system (Chapter 4; Figures 4-20 through 4-28), and ion channels (Chapter 3; Figures 3-19 through 3-26). Here, we add two other neurotransmitter systems: norepinephrine and GABA. Before discussing how these various neurotransmitters and ion channels are thought to be involved in mood disorders, we will begin with a general discussion of norepinephrine, GABA, and their receptors and pathways.

Norepinephrine

The noradrenergic neuron utilizes norepinephrine (noradrenaline) as its neurotransmitter. Norepinephrine is synthesized, or produced, from the precursor amino acid tyrosine, which is transported into the nervous system from the blood by means of

an active transport pump (Figure 6-12). Once inside the neuron, tyrosine is acted upon by three enzymes in sequence: first, tyrosine hydroxylase (TOH), the rate-limiting and most important enzyme in the regulation of norepinephrine (NE) synthesis. Tyrosine hydroxylase converts the amino acid tyrosine into DOPA. The second enzyme then acts, namely, DOPA decarboxylase (DDC), which converts DOPA into dopamine (DA). Dopamine itself is a neurotransmitter in DA neurons as discussed in Chapter 4 and illustrated in Figure 4-2. However, for NE neurons, DA is just a precursor of NE. In fact, the third and final NE synthetic enzyme, dopamine β-hydroxylase (DBH), converts DA into NE. Norepinephrine is then stored in synaptic packages called vesicles until released by a nerve impulse (Figure 6-12).

Norepinephrine action is terminated by two principal destructive or catabolic enzymes that turn NE into inactive metabolites. The first is monoamine oxidase (MAO) A or B, which is located in mitochondria in the presynaptic neuron and elsewhere (Figure 6-13). The second is catechol-*O*-methyltransferase (COMT), which is thought to be located largely outside of the presynaptic nerve terminal (Figure 6-13). The action of NE can be

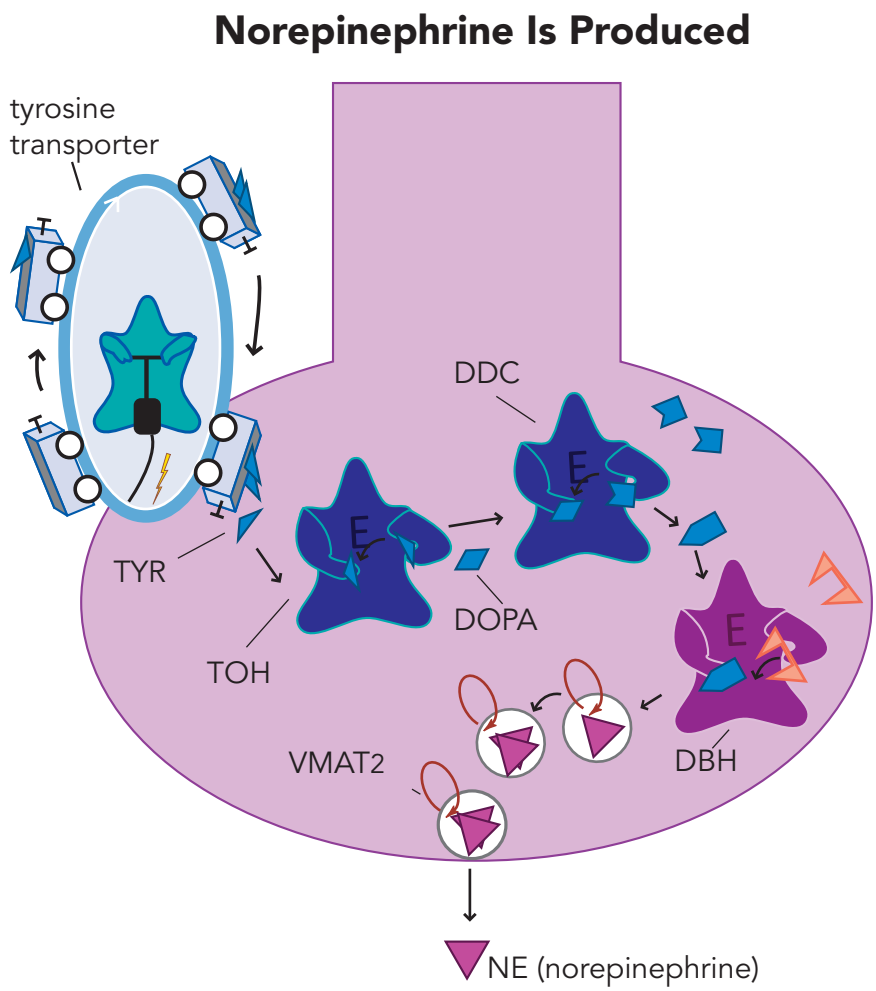


Figure 6-12 Norepinephrine is produced. Tyrosine (TYR), a precursor to norepinephrine (NE), is taken up into NE nerve terminals via a tyrosine transporter and converted into DOPA by the enzyme tyrosine hydroxylase (TOH). DOPA is then converted into dopamine (DA) by the enzyme DOPA decarboxylase (DDC). Finally, DA is converted into NE by dopamine β-hydroxylase (DBH). After synthesis, NE is packaged into synaptic vesicles via the vesicular monoamine transporter 2 (VMAT2) and stored there until its release into the synapse during neurotransmission.

terminated not only by enzymes which destroy NE, but also by a transport pump for NE that removes it from acting in the synapse without destroying it (Figure 6-14). In fact, such inactivated NE can be restored for reuse in a later neurotransmitting nerve impulse. The transport pump that terminates synaptic action of NE is sometimes called the "NE transporter" or "NET" and sometimes the "NE reuptake pump." This NE reuptake pump is located on the presynaptic noradrenergic nerve terminal as part of the presynaptic machinery of the neuron, where it acts as a vacuum cleaner whisking NE out of the synapse, off the synaptic receptors, and stopping its synaptic actions. Once inside the presynaptic nerve terminal, NE can either be stored again for subsequent reuse when another nerve impulse arrives, or it can be destroyed by NE-destroying enzymes (Figure 6-13).

The noradrenergic neuron is regulated by a multiplicity of receptors for NE (Figure 6-14). The norepinephrine transporter is one type of receptor, as is the vesicular monoamine transporter 2 (VMAT2), which transports NE in the cytoplasm of the presynaptic neuron into storage vesicles (Figure 6-14). The VMAT2 transporter was extensively discussed in Chapter 5, as the VMAT2 transporter in dopamine nerve terminals is the target of treatments for tardive dyskinesia (Figures 5-10 through 5-12). Other NE receptors are classified as α_1, α_{2A}, α_{2B}, or α_{2C}, or as β_1, β_2, or β_3 (Figure 6-14). All can be postsynaptic, but only α_2 receptors can act as presynaptic autoreceptors (Figures 6-14 through 6-16). Postsynaptic receptors convert their occupancy by NE into physiological functions, and ultimately, into changes in signal transduction and gene expression in the postsynaptic neuron (Figure 6-14).

Presynaptic α_2 receptors regulate NE release, so they are called "autoreceptors" (Figures 6-14 and 6-15). Presynaptic α_2 autoreceptors are located both on the axon terminal (i.e., terminal α_2 receptors; Figures 6-14 and 6-15) and at the cell body (soma) and nearby dendrites;

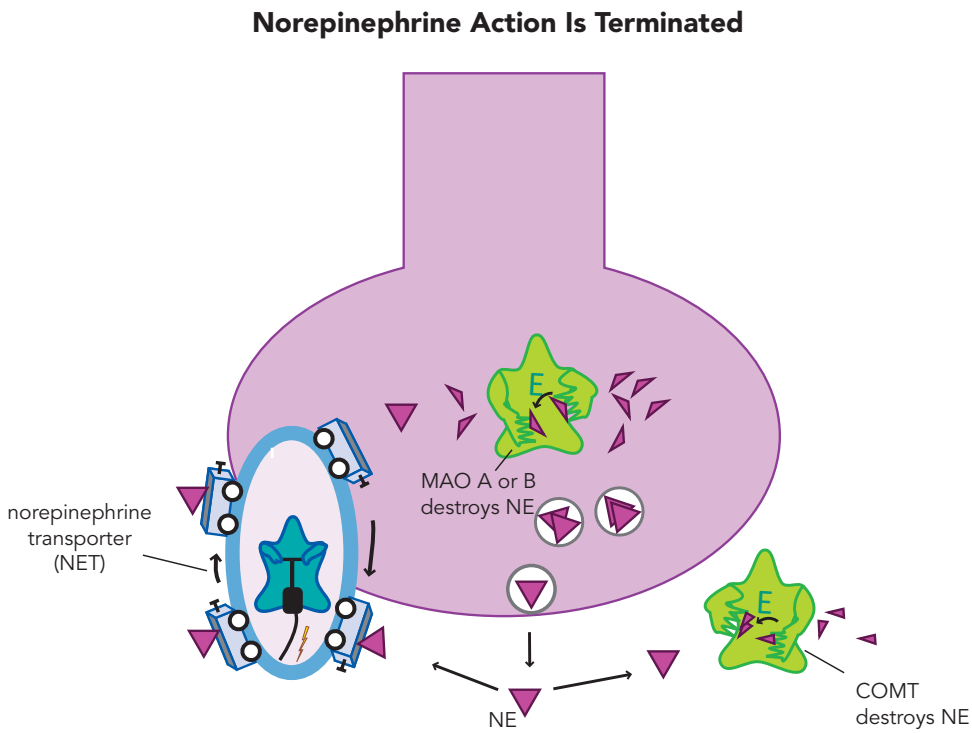


Figure 6-13 Norepinephrine's action is terminated. Norepinephrine's action can be terminated through multiple mechanisms. Norepinephrine can be transported out of the synaptic cleft and back into the presynaptic neuron via the norepinephrine transporter (NET), where it may be repackaged for future use. Alternatively, norepinephrine may be broken down extracellularly via the enzyme catechol-*O*-methyltransferase (COMT). Other enzymes that break down norepinephrine are monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B), which are present in mitochondria, both within the presynaptic neuron and in other cells, including neurons and glia.

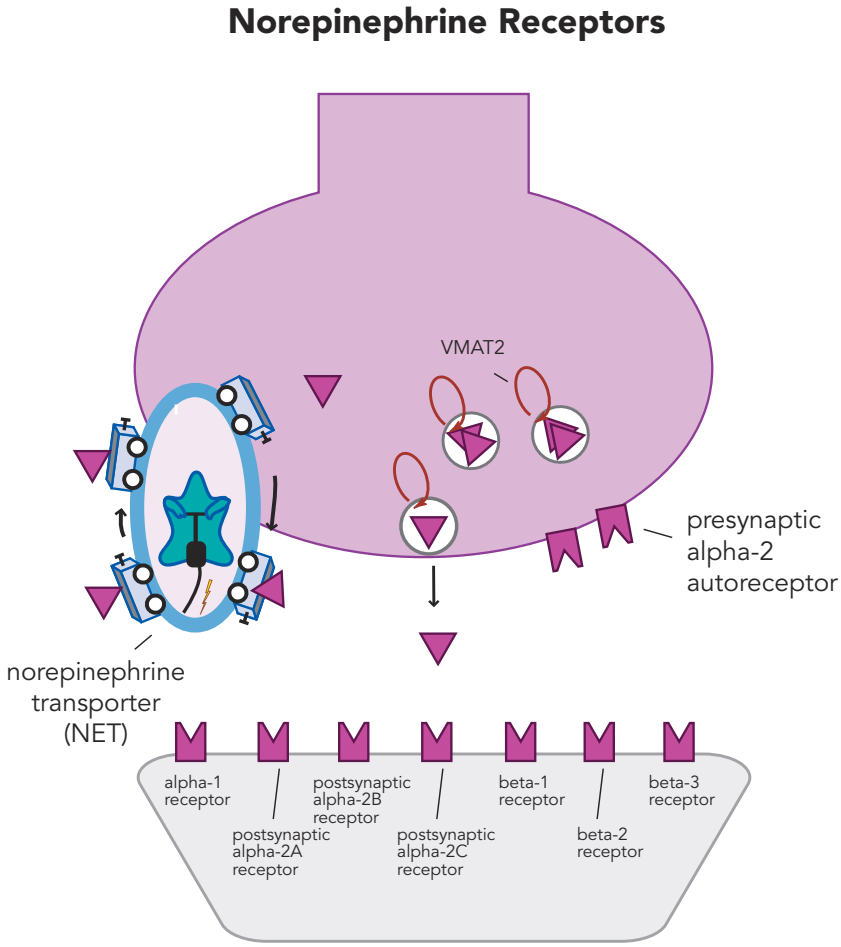


Figure 6-14 **Norepinephrine receptors.** Shown here are receptors for norepinephrine that regulate its neurotransmission. The norepinephrine transporter (NET) exists presynaptically and is responsible for clearing excess norepinephrine out of the synapse. The vesicular monoamine transporter 2 (VMAT2) takes norepinephrine up into synaptic vesicles and stores it for future neurotransmission. There is also a presynaptic α_2 autoreceptor, which regulates release of norepinephrine from the presynaptic neuron. In addition, there are several postsynaptic receptors. These include α_1, α_{2A}, α_{2B}, α_{2C}, β_1, β_2, and β_3 receptors.

thus, these latter α_2 presynaptic receptors are called somatodendritic α_2 receptors (Figure 6-16). Presynaptic α_2 receptors are important because both the terminal and the somatodendritic α_2 receptors are autoreceptors. That is, when presynaptic α_2 receptors recognize NE, they turn off further release of NE (Figures 6-14 and 6-15). Thus, presynaptic α_2 autoreceptors act as a brake for the NE neuron, and also cause what is known as a negative feedback regulatory signal. Stimulating this receptor (i.e., stepping on the brake) stops the neuron from firing. This probably occurs physiologically to prevent over-firing of the NE neuron, since it can shut itself off once the firing rate gets too high and the autoreceptor becomes stimulated. It is worthy to note that some drugs can not only mimic the natural functioning of the NE neuron by stimulating the presynaptic α_2 neuron, but other drugs that antagonize this same receptor will have the effect of cutting the brake cable, thus enhancing release of NE.

GABA (γ-Aminobutyric Acid)

GABA is the principle inhibitory neurotransmitter in the brain, and normally serves an important regulatory role in reducing the activity of many neurons. Specifically, GABA is produced, or synthesized, from the amino acid glutamate (glutamic acid) via the actions of the enzyme glutamic acid decarboxylase (GAD) (Figure 6-17). Once formed in presynaptic neurons, GABA is transported into synaptic vesicles by vesicular inhibitory amino acid transporters (VIAATs), where it is stored until released into the synapse during inhibitory neurotransmission

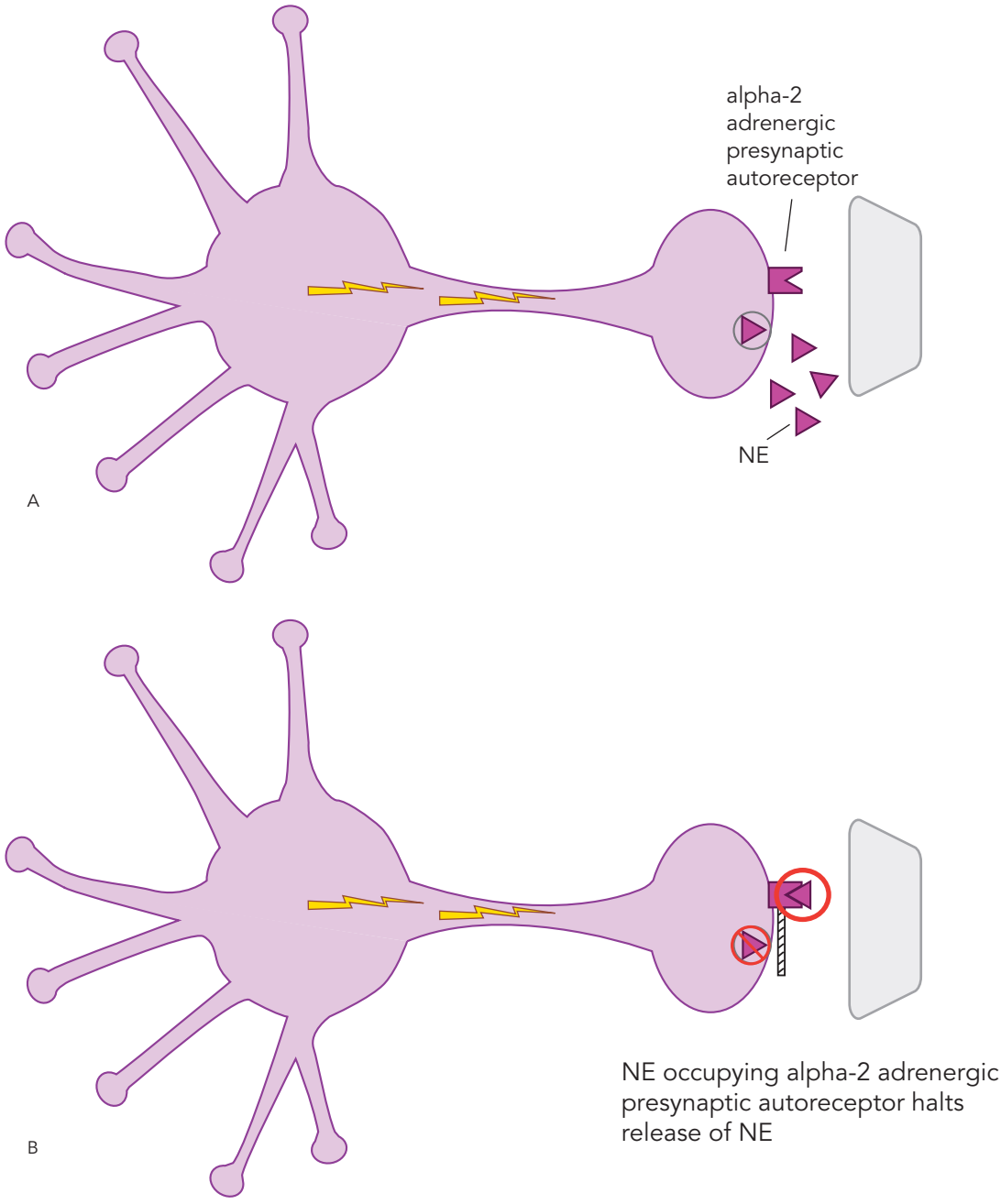


Figure 6-15 Alpha-2 receptors on axon terminal. Shown here are presynaptic α_2-adrenergic autoreceptors located on the axon terminal of the norepinephrine (NE) neuron. These autoreceptors are "gatekeepers" for norepinephrine. (A) When they are not bound by norepinephrine, they are open, allowing norepinephrine release. (B) When norepinephrine binds to the gatekeeping receptors, they close the molecular gate and prevent norepinephrine from being released.

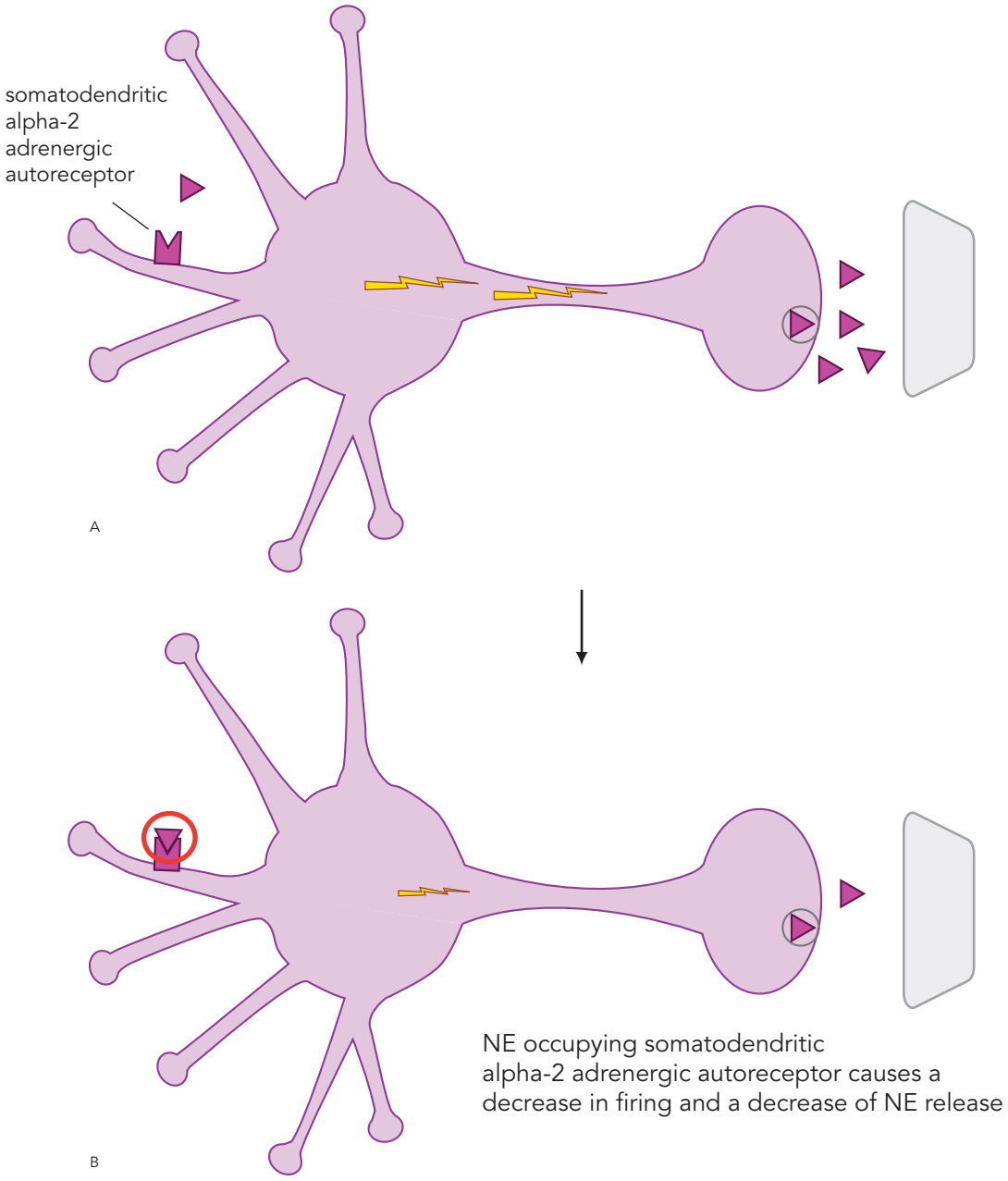


Figure 6-16 Somatodendritic α_2 receptors. Shown here are presynaptic α_2-adrenergic autoreceptors located in the somatodendritic area of the norepinephrine neuron. (A) When they are not bound by norepinephrine, there is normal neuronal impulse flow, with resultant release of norepinephrine. (B) When norepinephrine binds to these α_2 receptors, it shuts off neuronal impulse flow (see loss of lightning bolts in the neuron), and this stops further norepinephrine release.

(Figure 6-17). GABA's synaptic actions are terminated by the presynaptic GABA transporter (GAT), also known as the GABA reuptake pump (Figure 6-18), analogous to similar transporters for other neurotransmitters discussed throughout this text. GABA action can also be terminated by the enzyme GABA transaminase (GABA-T), which converts GABA into an inactive substance (Figure 6-18).

There are three major types of GABA receptors and numerous subtypes of GABA receptors. The major types are $GABA_A$, $GABA_B$, and $GABA_C$ receptors (Figure 6-19). $GABA_A$ and $GABA_C$ receptors are both ligand-gated ion channels, whereas $GABA_B$ receptors are linked to G proteins and not to ion channels (Figure 6–19).

$GABA_A$ Receptor Subtypes

The molecular structure of $GABA_A$ receptors is shown in Figure 6-20. Each subunit of a $GABA_A$ receptor has four transmembrane regions (Figure 6-20A). When five subunits cluster together, they form an intact $GABA_A$ receptor with a chloride channel in the center (Figure 6-20B). There are many different subtypes of

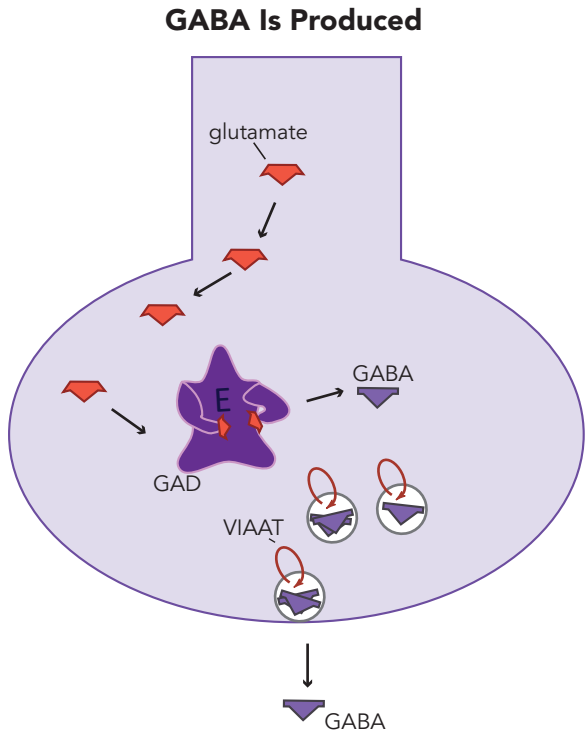


Figure 6-17 Gamma-aminobutyric acid (GABA) is produced. The amino acid glutamate, a precursor to GABA, is converted to GABA by the enzyme glutamic acid decarboxylase (GAD). After synthesis, GABA is transported into synaptic vesicles via vesicular inhibitory amino acid transporters (VIAATs) and stored until its release into the synapse during neurotransmission.

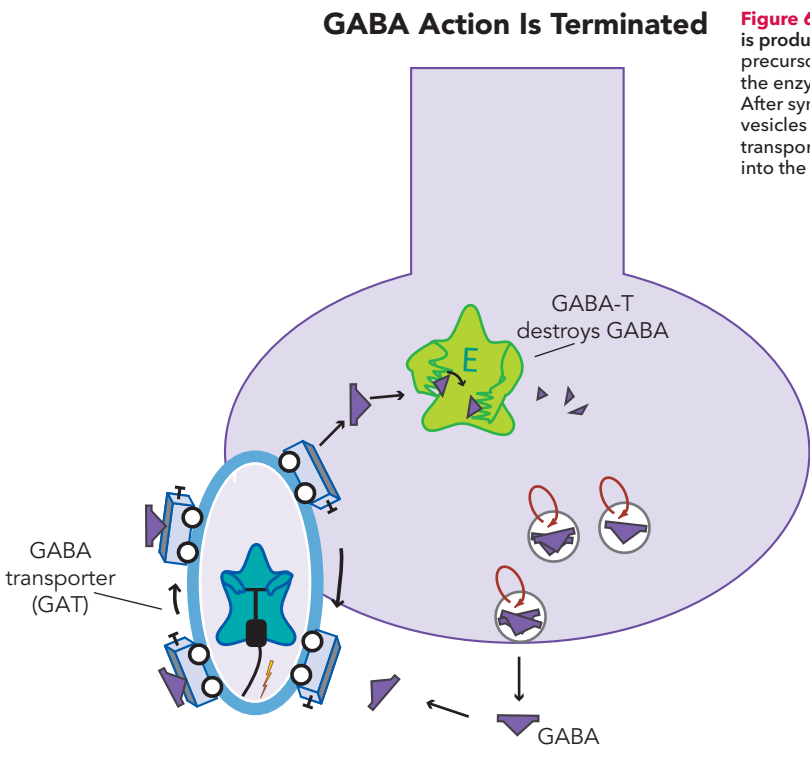


Figure 6-18 Gamma-aminobutyric acid (GABA) action is terminated. GABA's action can be terminated through multiple mechanisms. GABA can be transported out of the synaptic cleft and back into the presynaptic neuron via the GABA transporter (GAT), where it may be repackaged for future use. Alternatively, once GABA has been transported back into the cell, it may be converted into an inactive substance via the enzyme GABA transaminase (GABA-T).

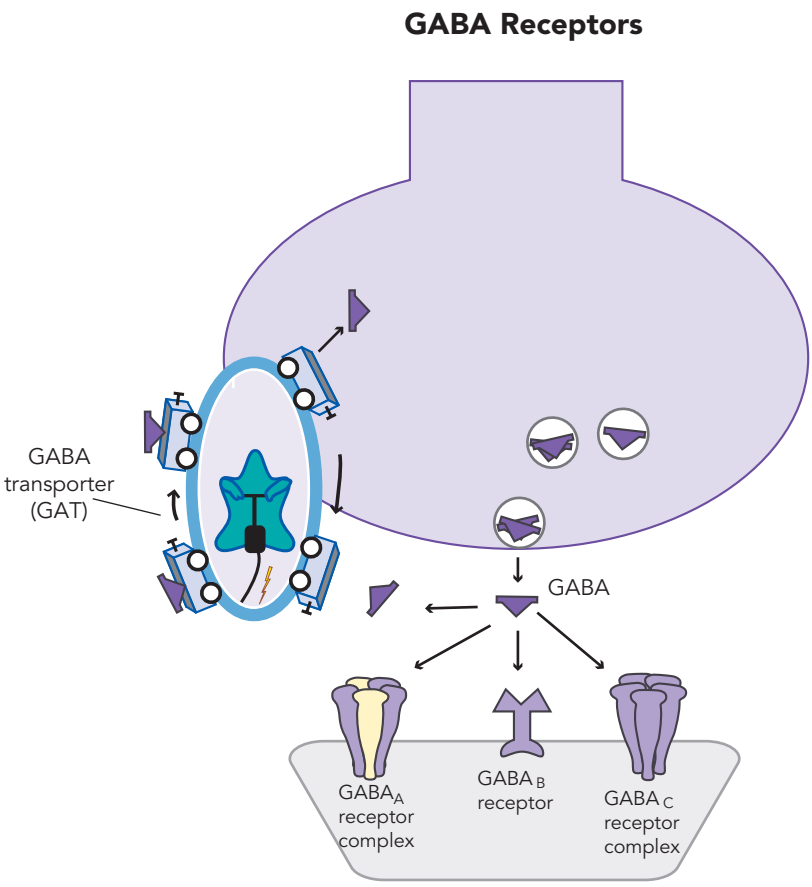


Figure 6-19 Gamma-aminobutyric acid (GABA) receptors. Shown here are receptors for GABA that regulate its neurotransmission. These include the GABA transporter (GAT) as well as three major types of postsynaptic GABA receptors: $GABA_A$, $GABA_B$, and $GABA_C$. $GABA_A$ and $GABA_C$ receptors are ligand-gated ion channels; they are part of a macromolecular complex that forms an inhibitory chloride channel. $GABA_B$ receptors are G-protein-linked receptors that may be coupled with calcium or potassium channels.

$GABA_A$ receptors, depending upon which subunits are present (Figure 6-20C). Subunits of $GABA_A$ receptors are sometimes also called isoforms, and include α (with six isoforms α_1 to α_6), β (with three isoforms β_1 to β_3), γ (with three isoforms γ_1 to γ_3), δ, ε, π, θ, and ρ (with three isoforms ρ_1 to ρ_3) (Figure 6-20C). What is important for this discussion is that depending upon which subunits are present, the functions of a $GABA_A$ receptor can vary quite significantly. Thus, $GABA_A$ receptors can be classified by the specific isoform subunits that they contain.

$GABA_A$ receptors can also be categorized into other subtypes: those that are synaptic and hypothetically mediate phasic neurotransmission, and those that are extrasynaptic and hypothetically mediate tonic neurotransmission (Figure 6-21). Other classification systems are whether GABA receptors are sensitive to the well-known benzodiazepines or insensitive to them. Some of these classifications overlap, since $GABA_A$ receptors containing a γ subunit tend to be synaptic, to mediate phasic neurotransmission, and to be *sensitive* to benzodiazepines. On the other hand, $GABA_A$ receptors containing a δ subunit tend to be extrasynaptic, to mediate tonic neurotransmission, and to be *insensitive* to benzodiazepines.

Benzodiazepine-sensitive $GABA_A$ receptors have several structural and functional features that make them distinct from benzodiazepine-insensitive $GABA_A$ receptors. For a $GABA_A$ receptor to be sensitive to benzodiazepines, there must be two β units plus a γ unit of either the γ_2 or γ_3 subtype, plus two α units of either the α_1, α_2, or α_3 subtype (Figure 6-20C). Benzodiazepines appear to bind to the region of the receptor between the γ_2/γ_3 subunit and the $\alpha_1/\alpha_2/\alpha_3$ subunit, one benzodiazepine molecule per receptor complex (Figure 6-20C). GABA itself binds with two molecules of GABA per receptor complex, to the GABA agonist sites in the

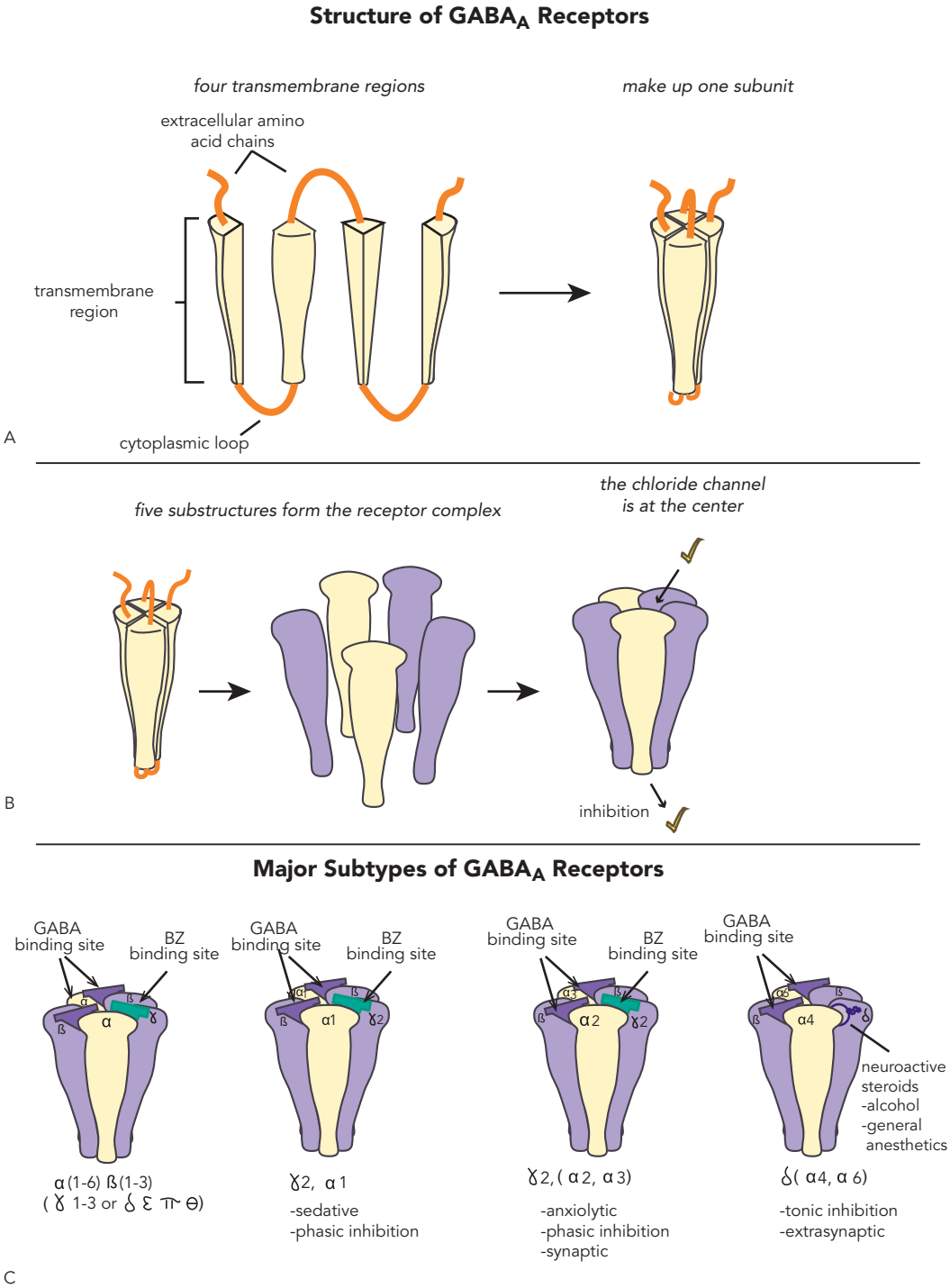


Figure 6-20 Gamma-aminobutyric acid A (GABA$_A$) receptors. (A) Shown here are the four transmembrane regions that make up one subunit of a GABA$_A$ receptor. (B) There are five copies of these subunits in a fully constituted GABA$_A$ receptor, at the center of which is a chloride channel. (C) Different types of subunits (also called isoforms or subtypes) can combine to form a GABA$_A$ receptor. These include six different α isoforms, three different β isoforms, three different γ isoforms, δ, ε, π, θ, and three different ρ isoforms. The ultimate type and function of each GABA$_A$ receptor subtype will depend on which subunits it contains. Benzodiazepine (BZ)-sensitive GABA$_A$ receptors (middle two) contain two β units, plus either γ_2 or γ_3, plus two α (α_1 through α_3) subunits. They generally mediate phasic inhibition triggered by peak concentrations of synaptically released GABA. Benzodiazepine-sensitive GABA$_A$ receptors containing α_1 subunits are involved in sleep (second from left), while those that contain α_2 and/or α_3 subunits are involved in anxiety (second from right). GABA$_A$ receptors containing α_4, α_6, or δ subunits (far right) are benzodiazepine-insensitive, are located extrasynaptically, and regulate tonic inhibition. They are bound by naturally occurring neuroactive steroids and possibly to alcohol and some general anesthetics.

regions of the receptor between the α and the β units, sometimes also referred to as the GABA orthosteric site (Figures 6-20C and 6-22).

Acting alone, GABA acting at its agonist sites can increase the frequency of opening of the chloride channel formed inside all its subunits (see Figure 6-20), but only to a limited extent (compare Figure 6-22A and 6-22B). Since the site for benzodiazepines is in a different location from the agonist sites for GABA (see Figure 6-20C and 6-22D), the modulatory site is often called allosteric (literally "other site"), and the agents that bind there "allosteric modulators." Since the modulation is "positive" in the sense that it makes GABA more effective at $GABA_A$ receptors, enhancing the frequency of opening of inhibitory chloride channels (Figure 6-22D), the action is called "positive allosteric modulation," and benzodiazepines are called $GABA_A$ positive allosteric modulators (PAMs). Interestingly, GABA must be present for the PAM to work (compare Figure 6-22C and 6-22D). The actions of benzodiazepines at benzodiazepine-sensitive $GABA_A$ receptors are essentially the actions of an agonist at their positive allosteric sites, because their actions can be reversed by the neutral antagonist flumazenil (Figure 6-23), which is sometimes used to reverse anesthesia with benzodiazepines or overdoses of benzodiazepines.

As mentioned above, benzodiazepine-sensitive $GABA_A$ receptor subtypes (with γ subunits and α_1 to α_3 subunits) are thought to be postsynaptic and to mediate a type of inhibition at the postsynaptic neuron that is phasic, occurring in bursts of inhibition that are triggered by peak concentrations of synaptically released GABA (Figure 6-21). Theoretically, benzodiazepines acting at these receptors, particularly the $\alpha_{2/3}$ subtypes clustered at postsynaptic GABA sites, should exert an anxiolytic effect due to enhancement of phasic postsynaptic inhibition. However, not all benzodiazepine-sensitive $GABA_A$ receptors are the same. Notably, on the one hand, those benzodiazepine-sensitive $GABA_A$ receptors with α_1 subunits may be most important for regulating sleep and are the presumed targets of numerous sedative hypnotic agents, including both benzodiazepine and

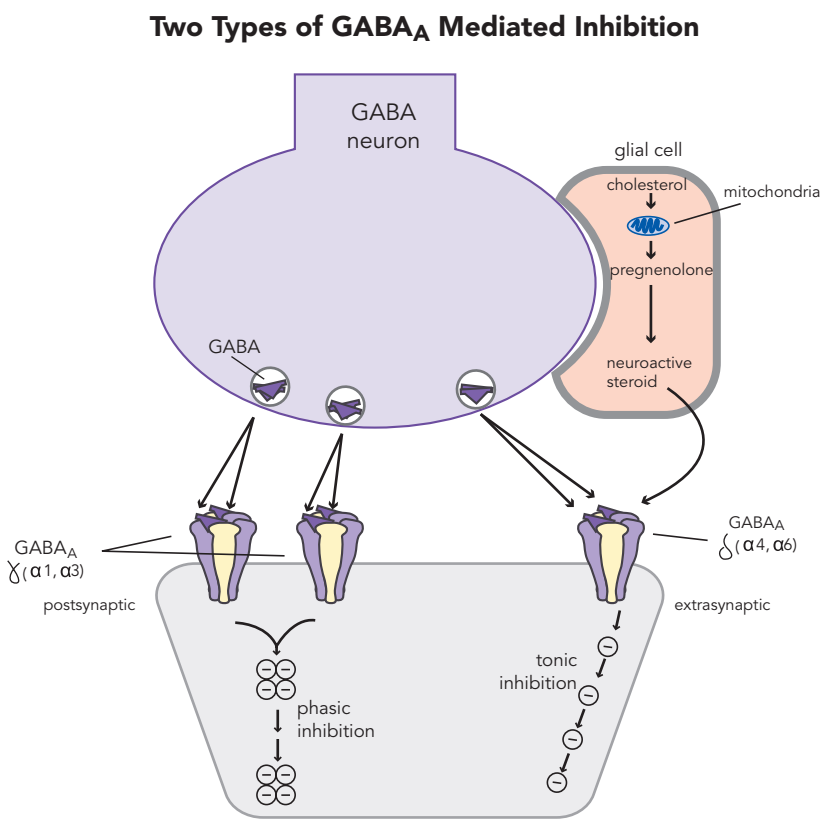


Figure 6-21 $GABA_A$ mediation of tonic and phasic inhibition. Benzodiazepine-sensitive $GABA_A$ receptors (those that contain γ and α_1 through α_3 subunits) are postsynaptic receptors that mediate phasic inhibition, which occurs in bursts triggered by peak concentrations of synaptically released GABA. Benzodiazepine-insensitive $GABA_A$ receptors (those containing δ subunits and α_4 or α_6 subunits) are extrasynaptic and capture GABA that diffuses away from the synapse as well as neuroactive steroids that are synthesized and released by glia. These receptors mediate inhibition that is tonic (i.e., mediated by ambient levels of extracellular GABA that has escaped from the synapse).

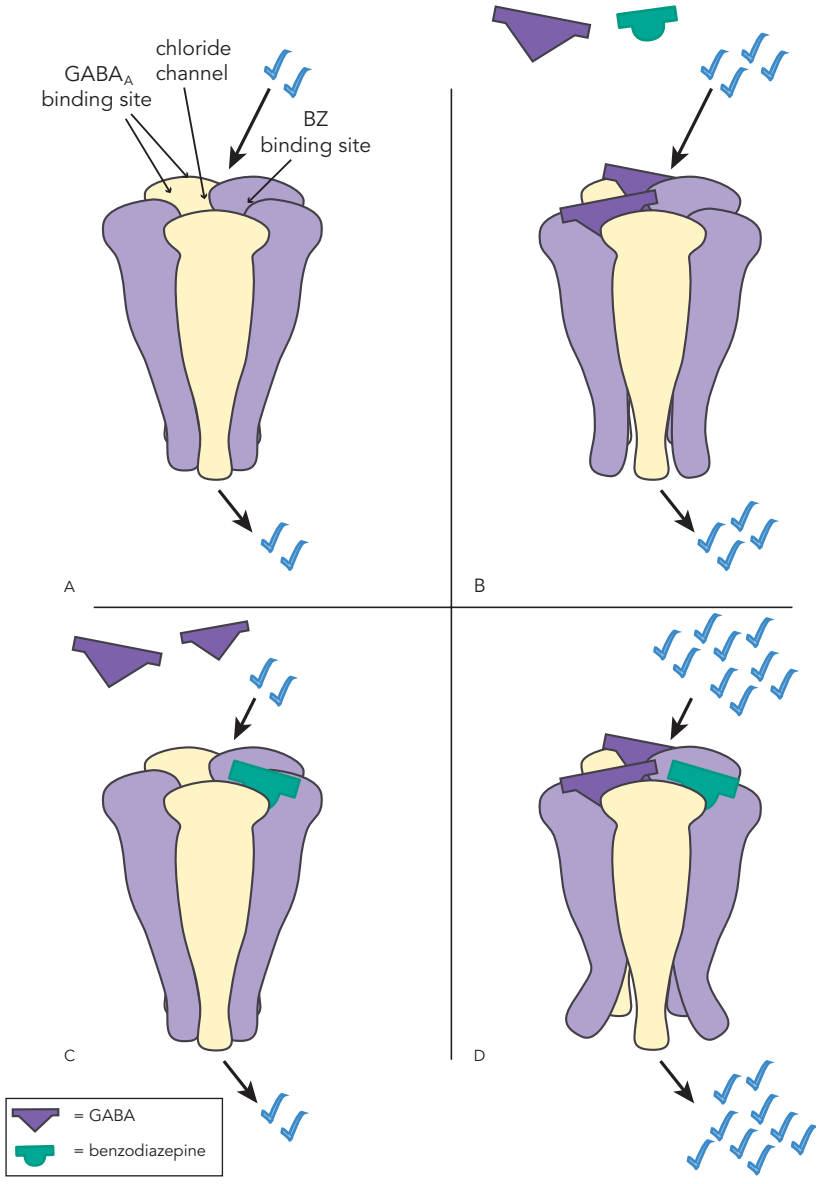


Figure 6-22 Positive allosteric modulation of GABA-A receptors. (A) Benzodiazepine (BZ)-sensitive GABA$_A$ receptors, like the one shown here, consist of five subunits with a central chloride channel and have binding sites not only for GABA but also for positive allosteric modulators (e.g., benzodiazepines). (B) When GABA binds to its sites on the GABA$_A$ receptor, it increases the frequency of opening of the chloride channel and thus allows more chloride to pass through. (C) When a positive allosteric modulator such as a benzodiazepine binds to the GABA$_A$ receptor in the absence of GABA, it has no effect on the chloride channel. (D) When a positive allosteric modulator such as a benzodiazepine binds to the GABA$_A$ receptor in the presence of GABA, it causes the channel to open even more frequently than when GABA alone is present.

non-benzodiazepine PAMs of the GABA$_A$ receptor (Figure 6-21C). The α_1 subtype of GABA$_A$ receptors and the drugs that bind to it are discussed further in Chapter 10 on disorders of sleep. Some of these agents (i.e., some Z drugs that also bind to benzodiazepine-sensitive GABA$_A$ receptors; see Chapter 10) are selective for only the α_1 subtype of GABA$_A$ receptor. On the other hand, benzodiazepine-sensitive GABA$_A$ receptors with α_2 and/or α_3 subunits may be most important for regulating anxiety and are the presumed targets of the anxiolytic and sedative hypnotic benzodiazepines (discussed in Chapter 8 on anxiety and in Chapter 10) (Figure 6-20C). Currently available benzodiazepines are nonselective for GABA$_A$ receptors with different α subunits. Abnormal expression of γ_2, α_2, or δ subunits have all been associated with different types of epilepsy. Receptor subtype expression can change in response to chronic benzodiazepine administration and withdrawal, and could theoretically be altered in patients with various psychiatric disorders, including different subpopulations of depression.

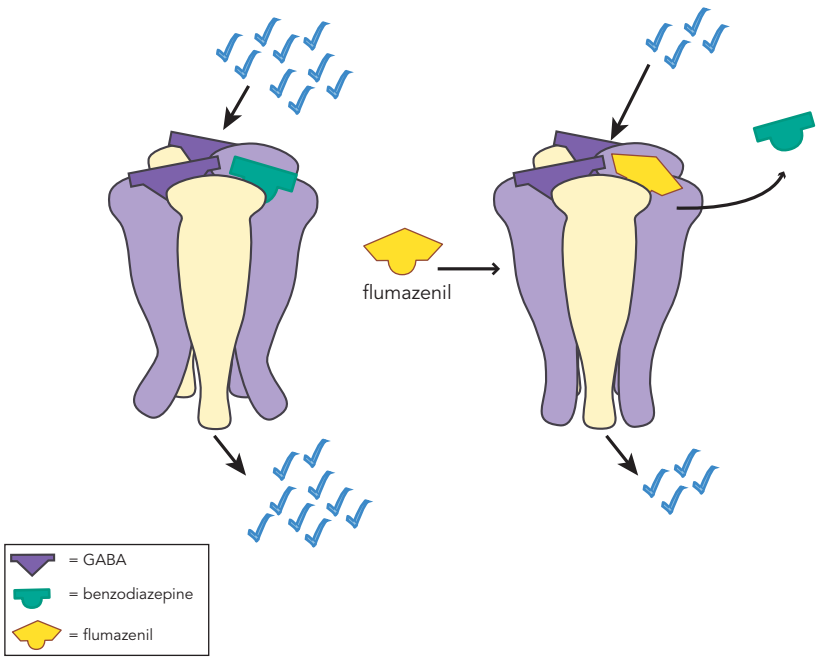


Figure 6-23 Flumazenil. The benzodiazepine receptor antagonist flumazenil is able to reverse a full agonist benzodiazepine acting at its site on the $GABA_A$ receptor. This may be helpful in reversing the sedative effects of full agonist benzodiazepines when administered for anesthetic purposes or when taken in overdose by a patient.

Benzodiazepine-insensitive $GABA_A$ receptors are those with α_4, α_6, γ_1, or δ subunits (Figure 6-20C). $GABA_A$ receptors with a δ subunit rather than a γ subunit, plus either α_4 or α_6 subunits, do not bind to benzodiazepines. Benzodiazepine-insensitive $GABA_A$ receptors bind instead to the naturally occurring neuroactive steroids, and possibly to alcohol and to some general anesthetics (Figure 6-20C). The binding site for these non-benzodiazepine modulators is located between the α and the δ subunits, one site per receptor complex (Figure 6-20C). Two molecules of GABA bind per receptor complex of benzodiazepine-insensitive $GABA_A$ receptors at the GABA agonist (orthosteric) sites located between the α and the β subunits (Figure 6-20C), just as they do at the benzodiazepine-sensitive $GABA_A$ receptors.

As already mentioned, benzodiazepine-insensitive $GABA_A$ receptor subtypes (with δ subunits and α_4 or α_6 subunits) are thought to be located extrasynaptically, where they capture not only GABA that diffuses away from the synapse, but also neuroactive steroids synthesized and released by glia (Figure 6-21). Extrasynaptic benzodiazepine-insensitive $GABA_A$ receptors are thought to mediate a type of inhibition at the postsynaptic neuron that is *tonic*, in contrast to the *phasic* type of inhibition mediated by postsynaptic benzodiazepine-sensitive $GABA_A$ receptors (Figure 6-21). Tonic inhibition may be regulated by the ambient levels of extracellular GABA molecules that have escaped presynaptic reuptake and enzymatic destruction and persist between neurotransmissions and is boosted by allosteric modulation at these sites.

Thus, tonic inhibition is thought to set the overall tone and excitability of the postsynaptic neuron, and to be important for certain regulatory events such as the frequency of neuronal discharge in response to excitatory inputs. Since neuroactive steroids have antidepressant properties (see Chapter 7), this has led to the proposal that some depressed patients may have a lack of normal tonic inhibition, and thus too much excitability in some brain circuits. Hypothetically this could be calmed by neuroactive steroid administration, causing more efficiency of information processing in those brain circuits and reduction of the symptoms of depression. It is possible that neuroactive steroids could also have important anxiolytic actions. Why would more tonic and supposedly sustained opening of chloride channels be a good thing for depression? In the case of postpartum depression, it may be potentially explainable on the basis that pregnant women have high circulating and presumably brain levels of neuroactive steroids. When they deliver, there is a precipitous decline

in circulating neuroactive steroid levels, hypothetically triggering the sudden onset of a major depressive episode when tonic inhibition is lost. Restoring neuroactive steroid levels – and tonic inhibition – for 60 hours of intravenous infusion may be enough for the patient to respond by reversing their depression and then having some additional time to accommodate to the lower levels of neuroactive steroids postpartum. This is a reasonable but not yet proven theory. It may be a bit more difficult to understand why positive allosteric modulation by a neuroactive steroid would treat other forms of depression, and treat quickly. However neuroactive steroids exert their antidepressant effects, clearly extrasynaptic benzodiazepine-insensitive $GABA_A$ sites are the targets, because benzodiazepines acting at the synaptic benzodiazepine-sensitive $GABA_A$ sites do not have robust antidepressant action. It may be worth noting that neuroactive steroids actually work at both benzodiazepine-sensitive $GABA_A$ receptors as well as at benzodiazepine-insensitive $GABA_A$ receptors. However, their unique action is at the benzodiazepine-insensitive sites and it is this action that is the focus of much interest in how neuroactive steroids hypothetically mediate their antidepressant actions.

The Monoamine Hypothesis of Depression

The classic theory about the biological etiology of depression hypothesizes that depression is due to a deficiency of monoamine neurotransmission. Mania may be the opposite, due to an excess of monoamine neurotransmission. This original conceptualization was a rather simplistic "chemical imbalance" notion that is now considered relatively unsophisticated and based mainly on observations that certain drugs that depleted monoamines could induce depression, and that all effective drugs for depression in the past acted by boosting one or more of three monoamine neurotransmitters: norepinephrine, serotonin, or dopamine. Thus, the idea was born that the "normal" amount of monoamine neurotransmitters (Figure 6-24A) somehow became depleted by an unknown disease process, stress, or drugs (Figure 6-24B), leading to the symptoms of depression. Direct evidence for the monoamine hypothesis is still largely lacking. A good deal of effort was expended especially in the 1970s and 1980s to identify the theoretically predicted deficiencies of monoamine neurotransmitters in depression and excess in mania. This effort to date has unfortunately yielded mixed results, prompting a search for better explanations of the etiology of mood disorders in general and of the potential link between monoamines and mood disorders in particular.

The Monoamine Receptor Hypothesis and Neurotrophic Factors

Because of these and other difficulties with the monoamine hypothesis, the focus of hypotheses for the etiology of mood disorders shifted next from the monoamine neurotransmitters themselves to their receptors and then to the downstream molecular events that these receptors trigger, including the regulation of gene expression and the production of growth factors. Currently, there is also great interest in the influence of nature (genes) and nurture (environment and epigenetics) on brain circuits regulated by monoamines, especially what happens when epigenetic changes from stressful life experiences are combined with inheriting various risk genes that can make an individual vulnerable to those environmental stressors.

The neurotransmitter receptor hypothesis of depression posits that an abnormality in the receptors for monoamine neurotransmitters leads to depression (Figure 6-24B). Thus, if depletion of monoamine neurotransmitters is the central theme of the monoamine hypothesis of depression (Figure 6-24B), the neurotransmitter receptor hypothesis of depression takes this theme one step further: namely, that the depletion of neurotransmitter causes compensatory upregulation of postsynaptic neurotransmitter receptors (Figure 6-24C). Direct evidence for this hypothesis is also generally lacking. However, postmortem studies do consistently show increased numbers of serotonin 2 receptors in the frontal cortex of patients who die by suicide. Also, some neuroimaging studies have identified abnormalities in serotonin receptors of depressed patients, but this approach has not yet been successful in identifying consistent and replicable molecular lesions in receptors for monoamines in depression. Thus, there is no clear and convincing evidence that monoamine deficiency accounts for depression: i.e., there is no "real" monoamine deficit. Likewise, there is no clear and convincing evidence that abnormalities in monoamine receptors account for depression even though all the classic drugs to treat depression raise monoamine levels. Although the monoamine hypothesis is obviously an overly simplified notion about mood disorders, it has been very valuable in focusing attention upon the three monoamine neurotransmitters norepinephrine, dopamine, and serotonin. This has led to a much better understanding of the physiological

Monoamine Receptor Hypothesis of Depression

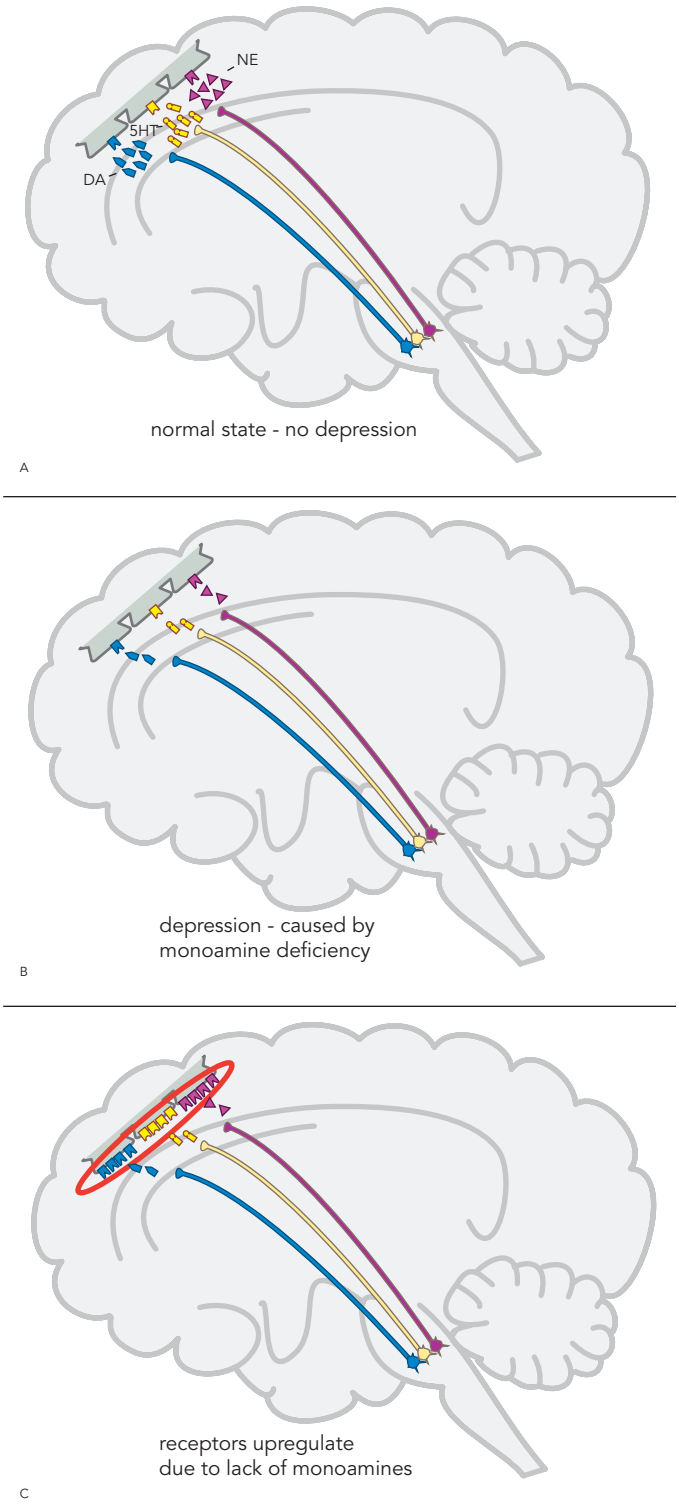


Figure 6-24 Monoamine receptor hypothesis of depression. (A) According to the classic monoamine hypothesis of depression, when there is a "normal" amount of monoamine neurotransmitter activity, there is no depression present. (B) The monoamine hypothesis of depression posits that if the "normal" amount of monoamine neurotransmitter activity becomes reduced, depleted, or dysfunctional for some reason, depression may ensue. (C) The monoamine receptor hypothesis of depression extends the classic monoamine hypothesis of depression, positing that deficient activity of monoamine neurotransmitters causes upregulation of postsynaptic monoamine neurotransmitter receptors, and that this leads to depression.

functioning of these three neurotransmitters, and for a while led to more and more pharmacological treatment options for depression, with many therapeutic variants upon the theme of monoamine targeting. These many therapeutic approaches and drugs are discussed in detail in Chapter 7.

Beyond Monoamines: The Neuroplasticity and Neuroprogression Hypothesis of Depression

One of the hints that depression is not simply due to deficient monoamines and that drugs for depression simply restored those deficient monoamines is the observation that the classic drugs for depression increased monoamines almost immediately, yet the clinical improvement in depression is delayed for weeks (Figure 6-25). This led to a search for molecular events that correlated in time with the onset of clinical antidepressant effects. Some of the earliest findings showed that delayed downregulation of neurotransmitter receptors following immediate elevation of monoamines after administration of drugs for depression correlates in time with the onset of clinical antidepressant effects (Figures 6-25 and 6-26). Downregulation of neurotransmitter receptors also correlates in time with the onset of tolerance to some of the side effects of drugs used to treat depression.

Other molecular events that correlate with the timing of onset of clinical antidepressant effects following administration of drugs for depression include the downstream synthesis of growth factors such as BDNF (brain-derived neurotrophic factor) (Figure 6-27). One notable current hypothesis is that stress, inflammation, and other genetic and environmental factors (such as early life adversity, the microbiome, and chronic medical illnesses) lead to loss of growth factors (Figure 6-28) and this leads in turn to neuroprogression, starting with lack of synaptic maintenance and then loss of synapses and dendritic arborization, and then ultimately leading to loss of neurons themselves (Figure 6-29, left), at which point neuroprogression becomes irreversible. The effect of the loss of growth factors on maintaining synaptic integrity and connectivity is shown in the microscopic inserts in Figure 6-30 (see loss of dendritic spines indicating loss of synapses on the right). Ominously, copious degrees of synaptic and neuronal loss can be observed on structural magnetic resonance imaging brain scans (Figure 6-30). Abnormal functional neuroimaging studies of connectivity of brain circuits have also been reported in depression.

The hypothetical neurobiology of neuroprogression in depression is multifactorial (Figure 6-31). In addition to possibly deficient production of growth factors (Figures 6-27 through 6-29; 6-31), there is also the longstanding theory of hypothalamic-pituitary-adrenal (HPA) axis dysregulation in depression, and it, too,

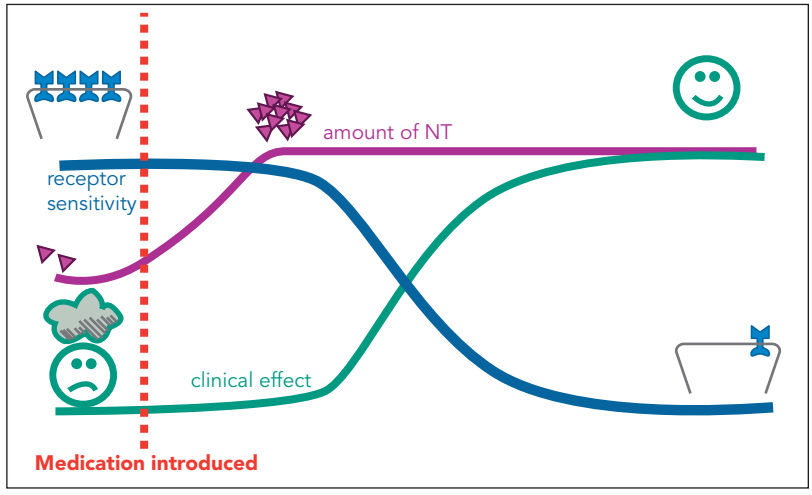


Figure 6-25 Time course of effects of drugs for depression. This figure depicts the different time courses for three effects of most drugs used to treat depression – namely, clinical changes, neurotransmitter (NT) changes, and receptor-sensitivity changes. Specifically, the amount of neurotransmitters changes relatively rapidly after a drug for depression is introduced. However, the clinical effect is delayed, as is the desensitization, or downregulation, of neurotransmitter receptors. This temporal correlation of clinical effects with changes in receptor sensitivity has given rise to the hypothesis that changes in neurotransmitter receptor sensitivity may actually mediate the clinical effects of drugs used for depression. These clinical effects include not only antidepressant and anxiolytic actions but also the development of tolerance to the acute side effects.

Neurotransmitter Receptor Hypothesis of Antidepressant Action

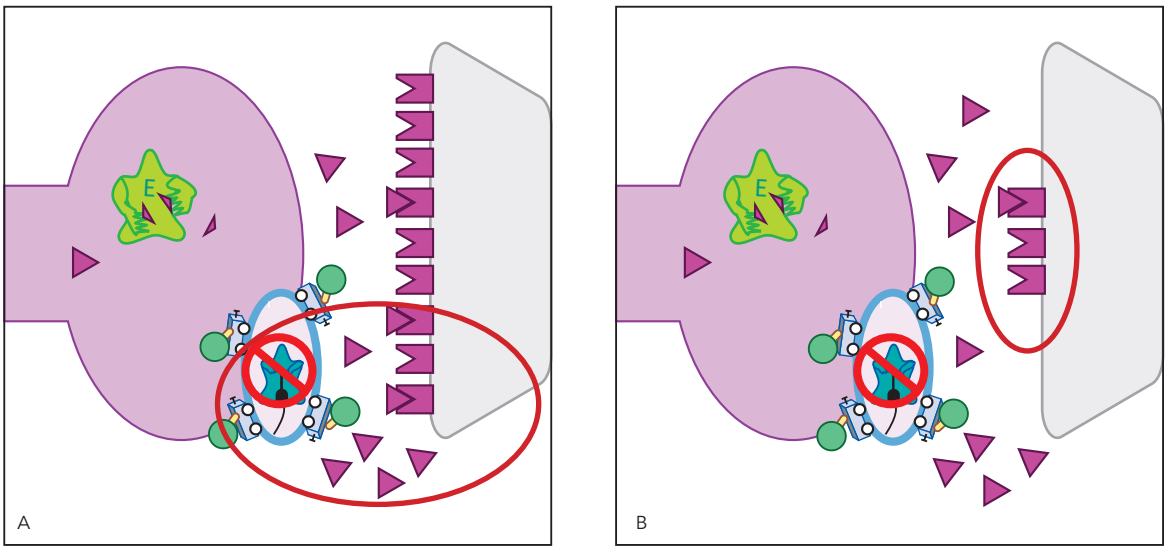


Figure 6-26 Neurotransmitter receptor hypothesis of antidepressant action. Although drugs for depression cause an immediate increase in monoamines, they do not have immediate therapeutic effects. This may be explained by the monoamine receptor hypothesis of depression, which states that depression is caused by upregulation of monoamine receptors; thus, clinical antidepressant effects would be related to downregulation of those receptors, as shown here. (A) When the monoamine reuptake pump is blocked, this causes more neurotransmitter (in this case, norepinephrine) to accumulate in the synapse. (B) The increased availability of neurotransmitter ultimately causes receptors to downregulate. The time course of receptor adaptation is consistent both with the delayed clinical effects of drugs for depression and with development of tolerance to side effects.

Monoamine Signaling Increases BDNF Release, Which Modifies Monoamine Innervation

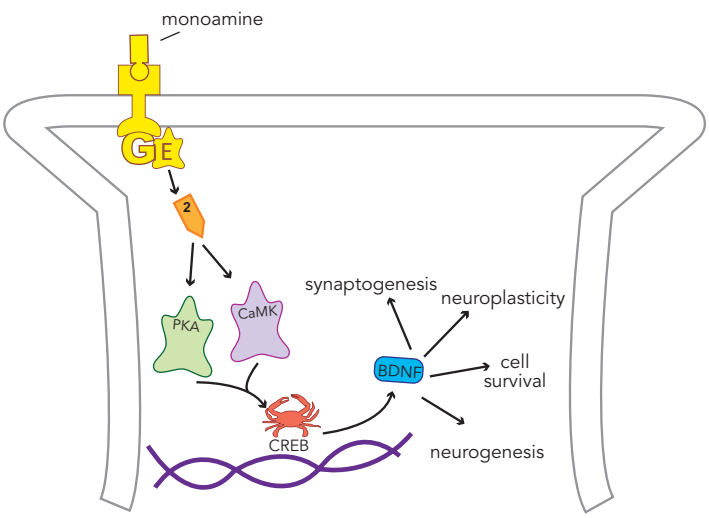


Figure 6-27 Monoamine signaling and brain-derived neurotrophic factor (BDNF) release. The neuroprogression hypothesis of depression states that depression may be caused by reduced synthesis of proteins involved in neurogenesis and synaptic plasticity. BDNF promotes the growth and development of immature neurons, including monoaminergic neurons, enhances the survival and function of adult neurons, and helps maintain synaptic connections. Because BDNF is important for neuronal survival, decreased levels may contribute to cell atrophy. In some cases, low levels of BDNF may even cause cell loss. Monoamines can increase the availability of BDNF by initiating signal transduction cascades that lead to its release. Thus, increased synaptic availability of monoamines by reuptake inhibitors may lead to downstream increases in neurotrophic factors, a molecular effect that would correlate in timing with the clinical effects.

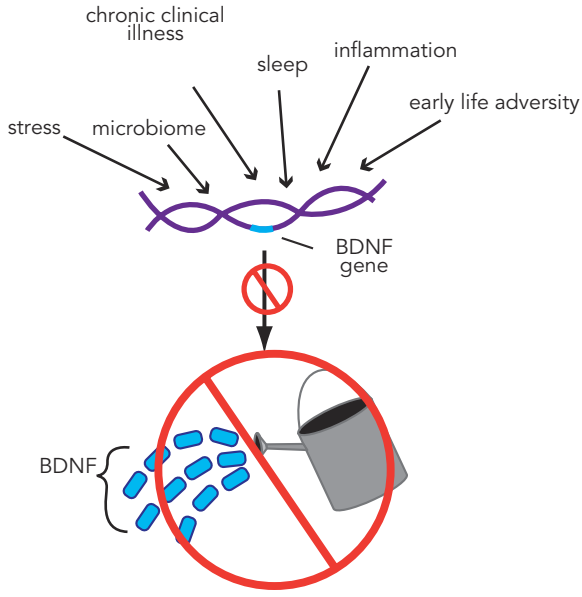


Figure 6-28 Genetic and environmental factors may lead to loss of neurotrophic factors. Neurotrophic factors such as brain-derived neurotrophic factor (BDNF) play a role in the proper growth and maintenance of neurons and neuronal connections. Multiple environmental factors, including chronic stress, inflammation, chronic illness, early life adversity, changes in the microbiome, and altered sleep could contribute to neuroprogression in depression by causing epigenetic changes that turn the genes for BDNF off, potentially reducing its production.

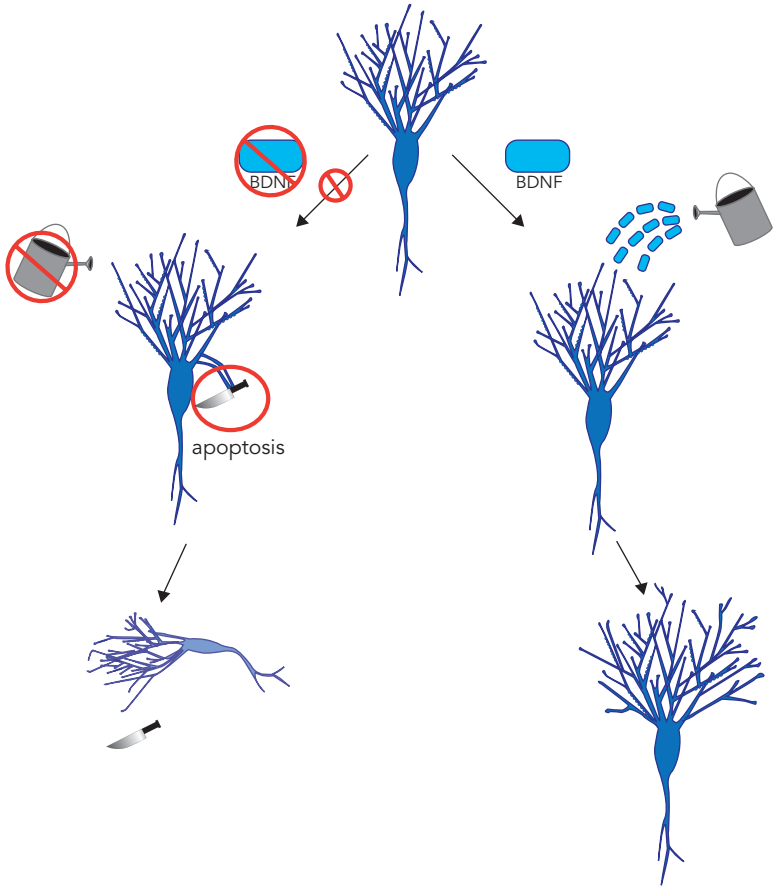


Figure 6-29 Suppression of brain-derived neurotrophic factor (BDNF) production. BDNF plays a role in the proper growth and maintenance of neurons and neuronal connections (right). If the genes for BDNF are turned off (left), the resultant decrease in BDNF could compromise the brain's ability to create and maintain neurons and their connections. This could lead to loss of synapses or even whole neurons by apoptosis.

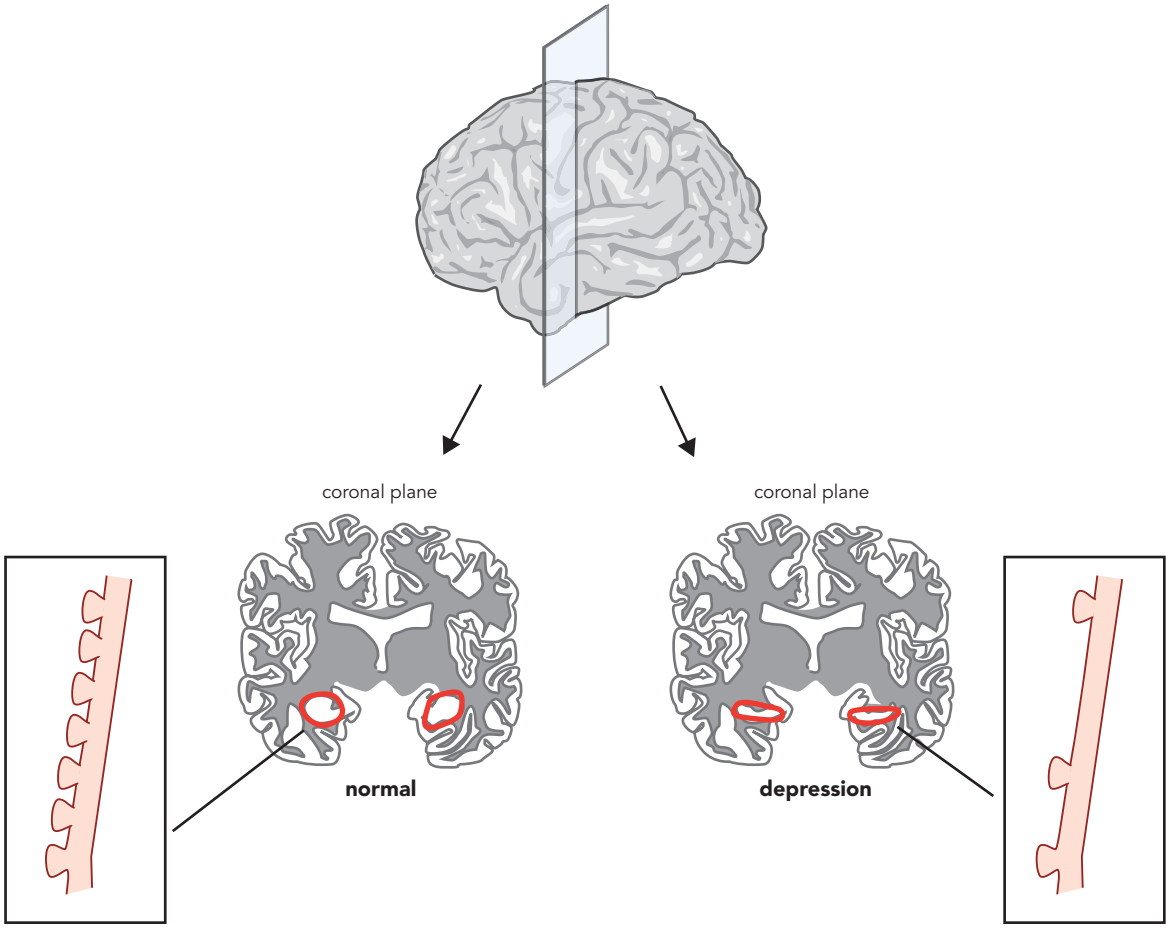


Figure 6-30 Loss of dendritic spines in depression. Reduction in neurotrophic factors compromises the maintenance of synaptic integrity and connectivity and can ultimately lead to synapse loss. This has been shown in structural magnetic resonance imaging studies of hippocampal volume, in which patients with depression have fewer dendritic spines.

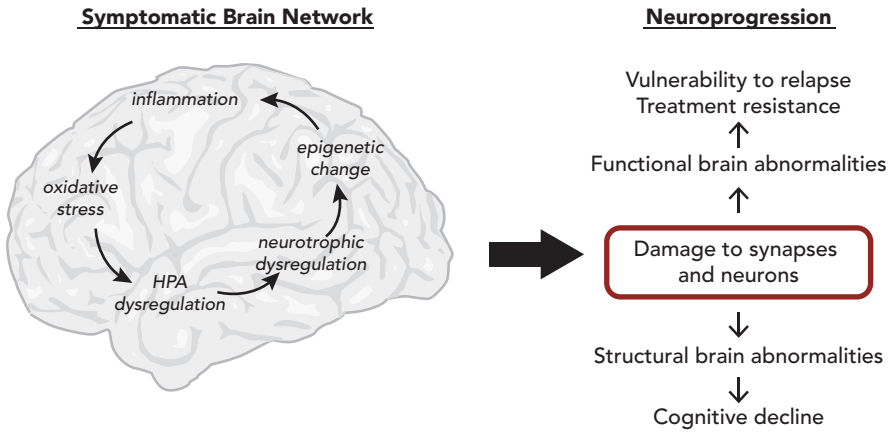


Figure 6-31 Neuroprogression in depression is multifactorial. Neuroprogression in depression may be related to multiple factors that may themselves interact. Inflammation, oxidative stress, and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis may all contribute to neurotrophic dysregulation, which may lead to epigenetic changes, which may further exacerbate inflammation, oxidative stress, and HPA axis dysfunction. All these factors may ultimately contribute to damage to synapses and neurons, which may lead to both functional and structural brain abnormalities.

may contribute to neurodegeneration (Figures 6-31, 6-32A, and 6-32B). Neurons from the hippocampal area and amygdala normally suppress the HPA axis (Figure 6-32A), so if stress causes hippocampal and amygdala neurons to atrophy, with loss of their inhibitory input to the hypothalamus, this could lead to overactivity of the HPA axis (Figure 6-32B). In depression, abnormalities of the HPA axis have long been reported, including elevated glucocorticoid and insensitivity of the HPA axis to feedback inhibition (Figure 6-32B). Some evidence suggests that glucocorticoids at high levels could even be toxic to neurons and contribute to their atrophy under chronic stress (Figure 6-32B). Novel antidepressant treatments are in testing that target CRF (corticotropin-releasing factor) receptors, vasopressin 1B receptors, and glucocorticoid receptors (Figure 6-32B), in an attempt to halt and even reverse these HPA abnormalities in depression and other stress-related psychiatric illnesses.

Yet another factor potentially contributing to neurodegeneration in at least a subset of patients with depression is neuroinflammation (Figure 6-33). That is, a number of conditions and factors contribute to inflammation invading the central nervous system in a number of psychiatric disorders, maybe especially in depression (Figure 6-33). Those factors include not only chronic stress, but also obesity, early life/childhood adversity, disruption of the microbiome, and numerous chronic inflammatory medical illnesses (Figure 6-33A). In such patients, it is hypothesized that these factors activate microglia in the brain to release proinflammatory molecules (Figure 6-33B), which in turn attract immune cells such as monocytes and macrophages into the brain (Figure 6-33C) where they disrupt neurotransmission (Figure 6-33D), cause oxidative chemical stress, mitochondrial dysfunction, HPA-axis dysfunction, reduction of neurotrophic factor availability, and

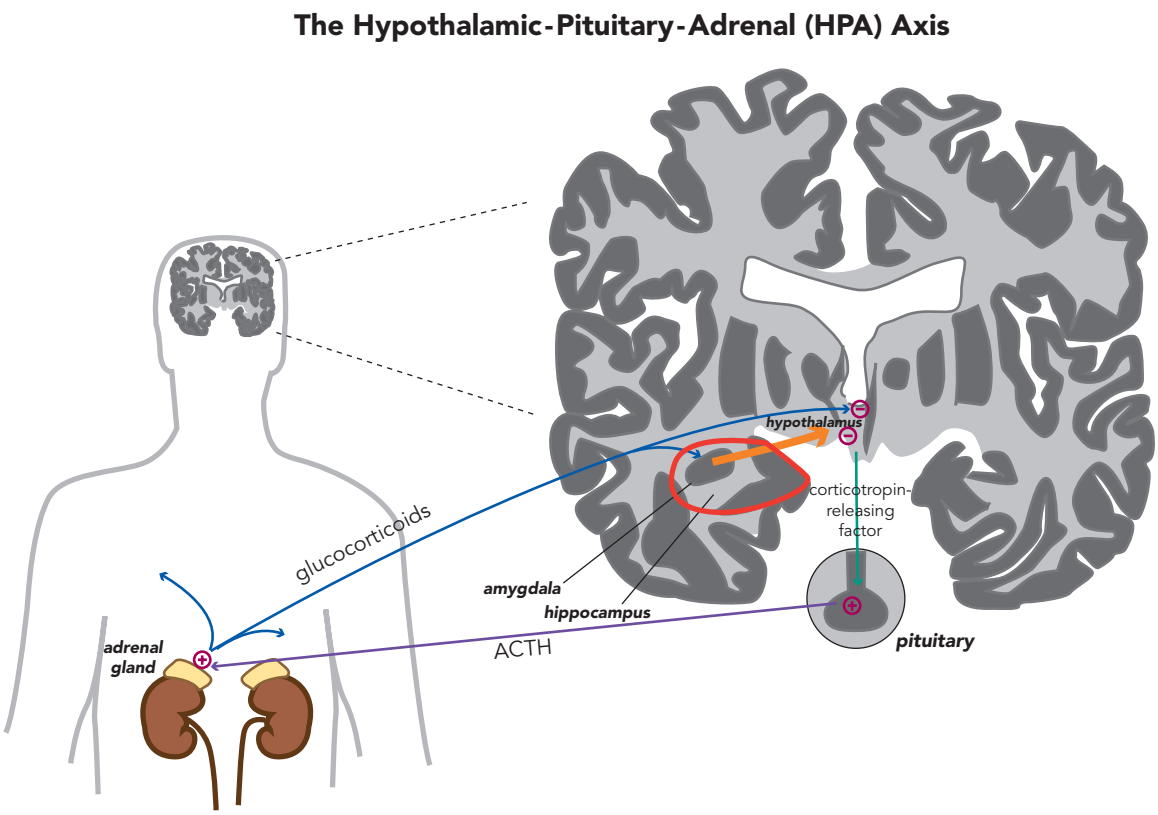


Figure 6-32A Hypothalamic-pituitary-adrenal (HPA) axis. The normal stress response involves activation of the hypothalamus and a resultant increase in corticotropin-releasing factor (CRF), which in turn stimulates the release of adrenocorticotropic hormone (ACTH) from the pituitary. ACTH causes glucocorticoid release from the adrenal gland, which feeds back to the hypothalamus and inhibits CRF release, terminating the stress response. The amygdala and hippocampus also provide input to the hypothalamus, to suppress activation of the HPA axis.

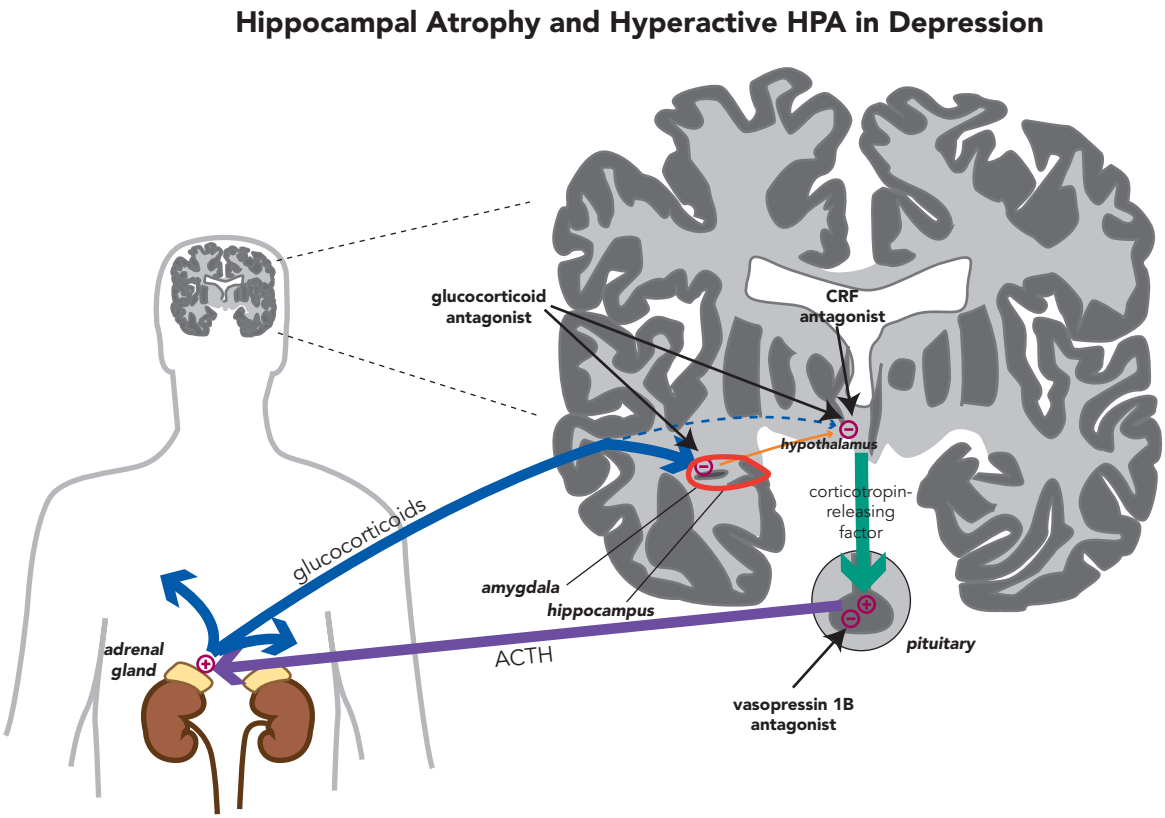


Figure 6-32B Hippocampal atrophy and hyperactive HPA axis in depression. In situations of chronic stress, hyperactivity of the HPA axis leads to excessive glucocorticoid release, which may eventually cause hippocampal atrophy. Because the hippocampus inhibits the HPA axis, atrophy in this region may lead to chronic activation of the HPA axis, which may increase risk of developing a psychiatric illness. Because the HPA axis is central to stress processing, it may be that novel targets for treating stress-induced disorders lie within the axis. Mechanisms being examined include antagonism of glucocorticoid receptors, corticotropin-releasing factor (CRF) receptors, and vasopressin 1B receptors.

epigenetic changes to unwanted gene expression (Figure 6-31), leading ultimately to loss of synapses and death of neurons (Figure 6-31 and 6-33D).

Another hypothesis for the neurobiological basis at least for some patients with depression is that it is a circadian rhythm disorder casing a phase delay in the sleep–wakefulness cycle (Figure 6-34). The degree of this phase delay correlates with the severity of depression. Numerous physiological measurements of circadian rhythms are also altered in depression, from flattening of the daily body-temperature cycle, elevation of cortisol secretion throughout the day, and also reducing melatonin secretion that also normally peaks at night and in the dark (Figure 6-35). Elevations of cortisol secretion and abnormalities of the HPA axis in depression are discussed above (Figures 6-32A and B). Other circadian rhythms that may be disrupted in depression include a reduction in BDNF and neurogenesis, also discussed above, and these normally peak at night. Desynchronization of biological processes can be so pervasive in depression that it is possible to characterize depression as fundamentally a circadian illness. It is possible, at least for some patients, that depression is due to a "broken" circadian clock. Numerous genes operate in a circadian manner, sensitive to light–dark rhythms and called clock genes. Abnormalities in various clock genes have been linked to mood disorders and for these patients with a circadian rhythm disorder (Figure 6-34), circadian rhythm treatments such as bright light (Figure 6-36A), melatonin (Figure 6-36B), phase advance, phase delay, and even sleep deprivation can have therapeutic effects.

Not only do all of these various factors triggered by neuroinflammation, stress, genetics, and the environment (Figures 6-28, 6-30, 6-31, and 6-33) contribute to synaptic dysfunction and structural brain abnormalities with functional decline, theoretically they ultimately

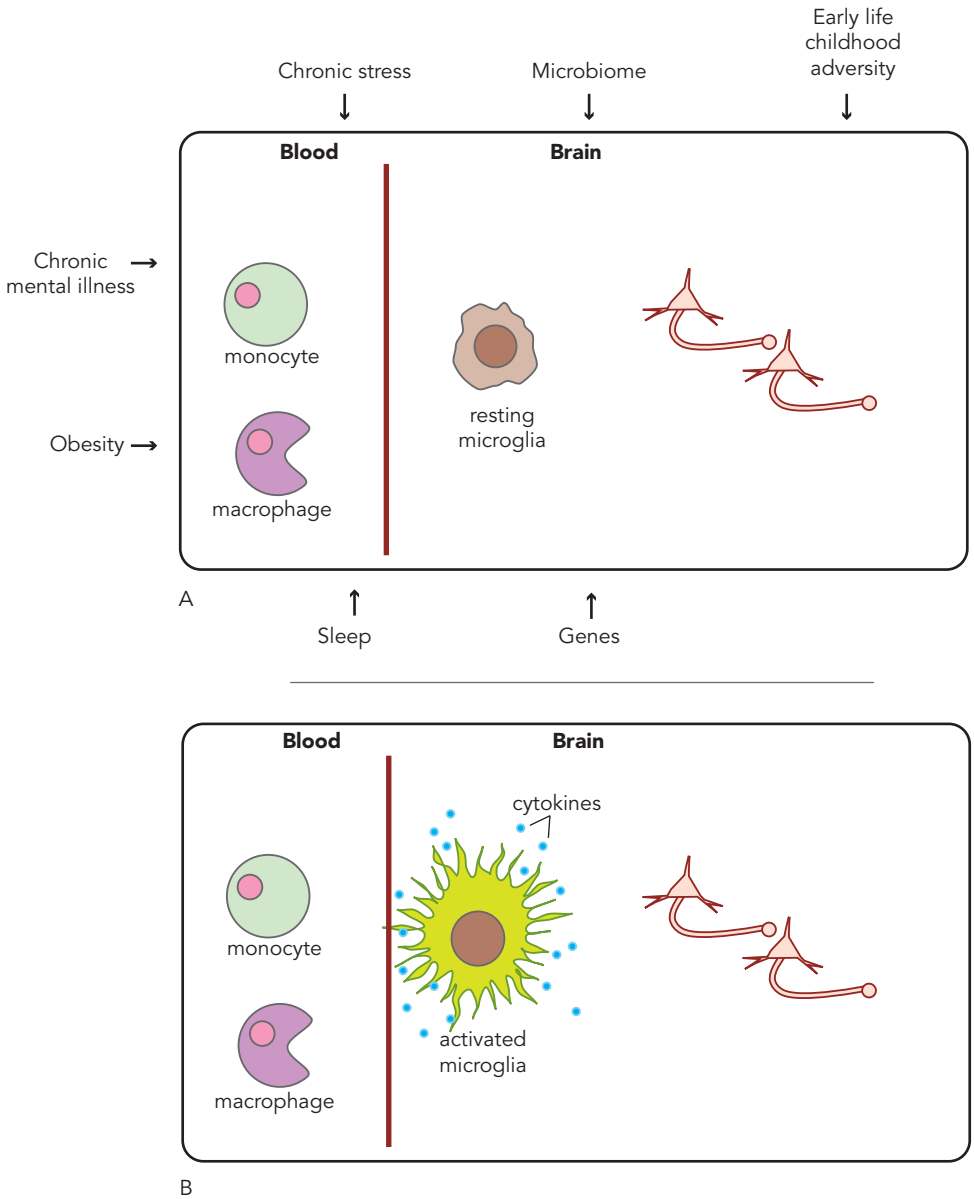
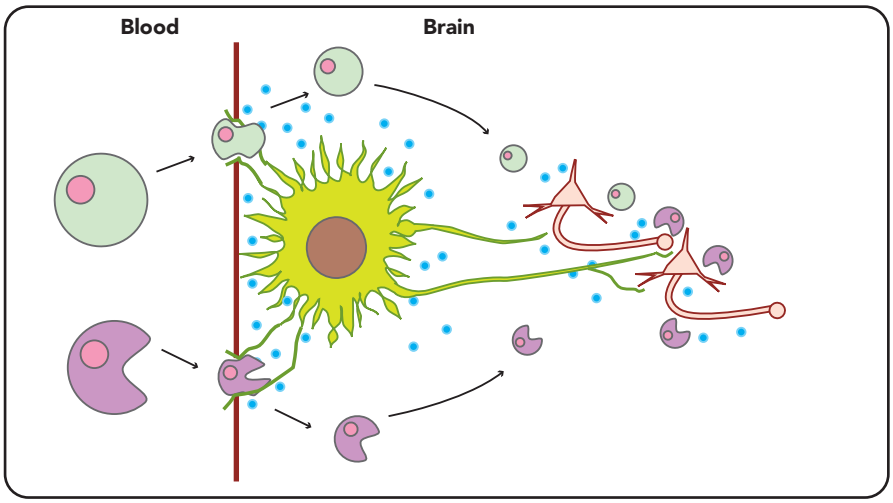


Figure 6-33 Neuroinflammation in depression. Neurodegeneration in depression could be related to the development of neuroinflammation in some patients. (A) Chronic stress, obesity, early life adversity, disruption of the microbiome, chronic sleep issues, and chronic inflammatory diseases may all contribute to the development of neuroinflammation. Shown here are immune factors in the blood and resting microglia in the brain. (B) If microglia in the brain are activated due to chronic stress, obesity, etc., they can release proinflammatory cytokines.

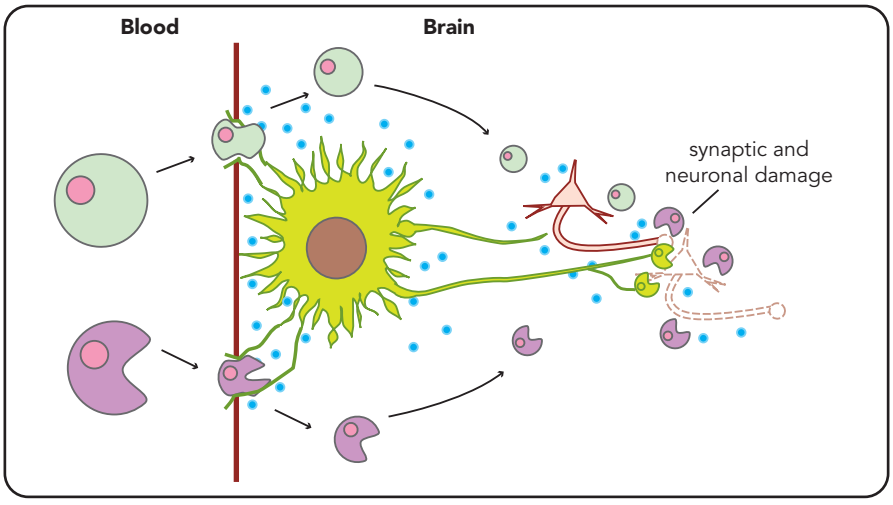
lead to at least three very unwanted clinical outcomes in depression:

- enduring cognitive decline
- increased vulnerability for further episodes of depression
- resistance to treatment with monoamine drugs for depression

Major depressive episodes of course are named for their mood symptom of sadness and depression, and indeed sad mood has the strongest association with overall impairment of functioning, but the second strongest association with impaired overall functioning is cognitive symptoms, perhaps a bit surprising for something



C



D

Figure 6-33 (cont.) **(C) Proinflammatory cytokines attract immune cells, such as monocytes and macrophages, into the brain. (D) Monocytes and macrophages can disrupt neurotransmission, cause oxidative stress and mitochondrial dysfunction, affect HPA-axis function, reduce availability of neurotrophic factors, and lead to epigenetic changes, which ultimately can lead to synaptic loss and neuronal death.**

called a "mood disorder" and not a "cognitive disorder." Functional neuroimaging studies suggest that cognitive decline may manifest in the need for more effortful thinking because depressed patients show greater activation of brain regions involved in cognitive control, such as the dorsolateral prefrontal cortex and anterior cingulate cortex. Hippocampal decline in depression is discussed above and illustrated in Figure 6-30, and is correlated with duration of untreated depression. Depressed patients with smaller hippocampal volumes have worse outcomes. A grim statistic is that memory in depression worsens as a function of the number of previous depressive episodes as though such episodes are damaging to the brain and the damage is cumulative. Interestingly, to support this haunting possibility is the observation that cognitive dysfunction in depression may be related to the number of past episodes of depression and to the duration of those episodes, and not to the

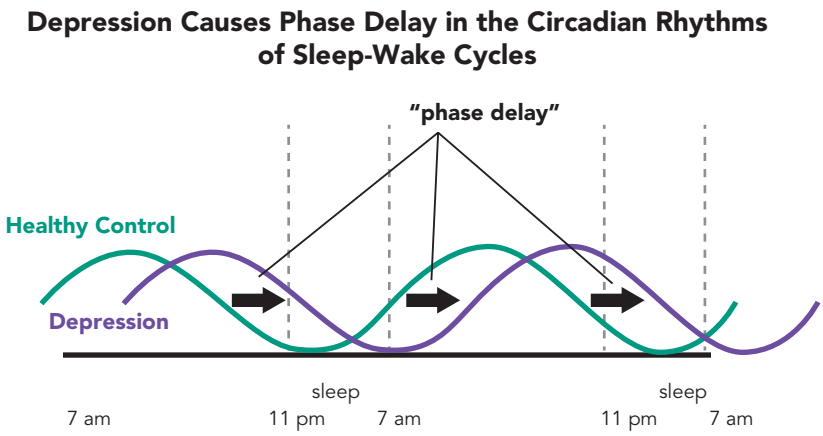


Figure 6-34 Depression can cause phase delay in circadian rhythms of sleep/wake cycles. Circadian rhythms describe events that occur on a 24-hour cycle. Many biological systems follow a circadian rhythm; in particular, circadian rhythms are key to the regulation of sleep/wake cycles. In patients with depression, the circadian rhythm is often "phase delayed," which means that because wakefulness is not promoted in the morning, such patients tend to sleep later. They also have trouble falling asleep at night, which further promotes feelings of sleepiness during the day.

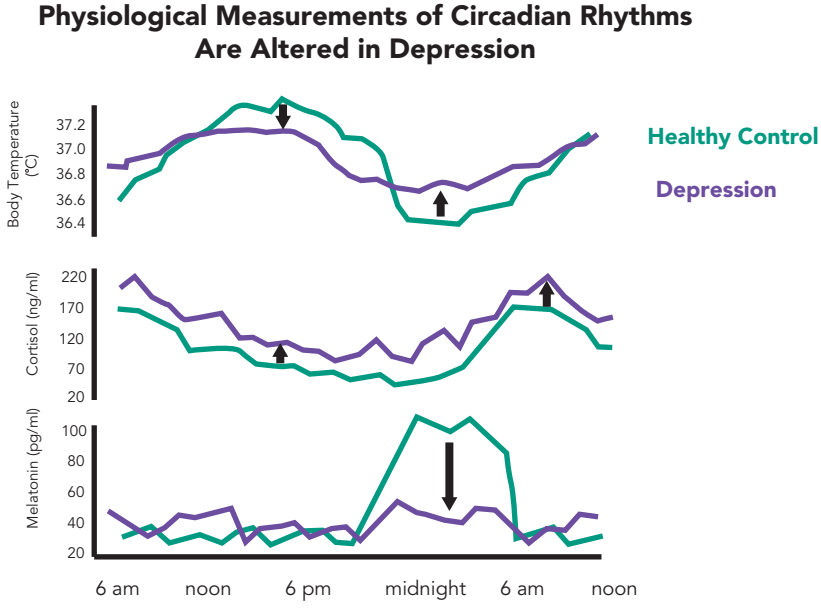


Figure 6-35 Physiological measurements of circadian rhythms are altered in some patients with depression. Circadian rhythms are evident in multiple biological functions, including body temperature, hormone levels, blood pressure, metabolism, cellular regeneration, sleep/wake cycles, and DNA transcription and translation. The internal coordination ordered by the circadian rhythm is essential to optimal health. In depression, there are altered physiological measurements of circadian rhythms, including less fluctuation in body temperature over the course of a 24-hour cycle, the same pattern but elevated cortisol levels over 24 hours, and the absence of a spike in melatonin levels at night.

severity of the symptoms in a current episode, again suggesting past damage. Cognitive symptoms are one of the most – if not the most – common residual symptom between depressive episodes once sadness and other symptoms recover. Thus, cognitive symptoms can endure longer than mood symptoms in major depressive disorder.

How bad is the cognitive dysfunction? Some estimate that it is about the same degree of impairment as one has after a night of sleep deprivation, or after being legally intoxicated with alcohol, or after taking a high dose of a benzodiazepine or antihistamine. Can you imagine living all day long, every day, with this degree of cognitive impairment? Cognitive dysfunction of this degree is not specific for patients with depression, but is very common across many psychiatric disorders, from unipolar to bipolar disorder, schizophrenia, anxiety/trauma/impulsive disorders, ADHD (attention deficit hyperactivity disorder), and beyond. Targeting cognitive symptoms with current treatments across psychiatric disorders is therefore an important therapeutic strategy, and

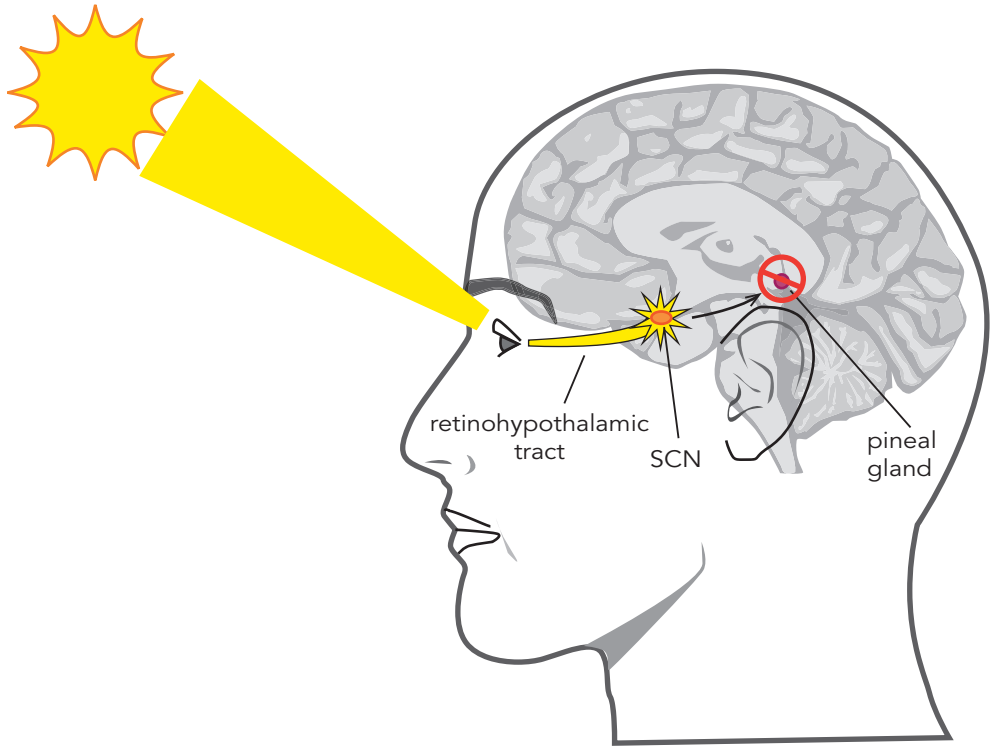


Figure 6-36A The setting of circadian rhythms, part 1. Although various factors can affect the setting of circadian rhythms, light is the most powerful synchronizer. When light enters through the eye it is translated via the retinohypothalamic tract to the suprachiasmatic nucleus (SCN) within the hypothalamus. The SCN, in turn, signals the pineal gland to turn off melatonin production. For individuals with depression who have dysregulation of circadian rhythms, bright-light therapy in the early morning may help to reset the circadian rhythm.

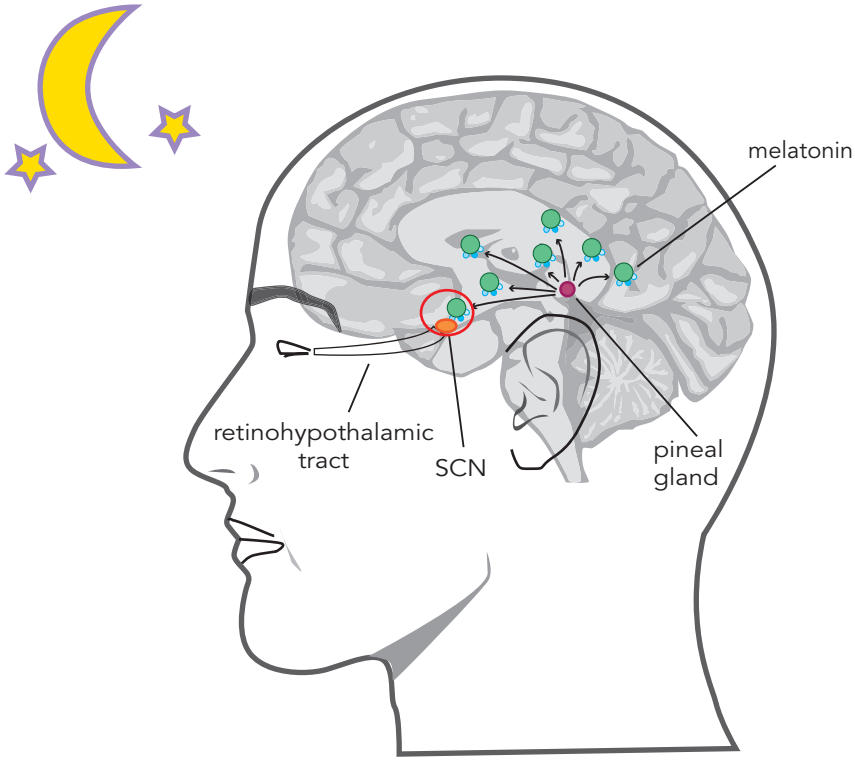


Figure 6-36B Melatonin and circadian rhythms. During darkness, there is no input from the retinohypothalamic tract to the suprachiasmatic nucleus (SCN) within the hypothalamus. Thus, darkness signals the pineal gland to produce melatonin. Melatonin, in turn, can act on the SCN to reset circadian rhythms. For individuals with depression who have dysregulated circadian rhythms, melatonin in the early evening may help to reset the circadian rhythm.

a critical need for better drugs for cognition exists. In the meantime, perhaps the best chance to prevent adverse cognitive and functional outcomes in depression is to treat early and completely, whenever possible.

Changes in structural and functional outcomes in depression in fact may be potentially reversible when captured at the stage of loss of synapses without loss of neurons, and that is what rapid-acting drugs for depression, which act on glutamate and GABA systems, hold promise for doing: namely, triggering the formation of new synapses. These drugs are discussed in Chapter 7. Here we will just mention that downstream improvement in neuroplasticity may be possible for monoamine-targeting drugs when those drugs are effective. More recently it has been discovered that improvements in animal models of neuroplasticity can be observed after boosting glutamatergic neurotransmission with novel drugs for depression (Figure 6-37). It is possible that this may also be occurring with the novel GABAergic drugs currently being developed. If so, these newer agents have the potential for rapid onset of an antidepressant effect since their molecular effects (Figure 6-37) can reverse synaptic loss and show new synapse formation within minutes to hours (reversal of synapse loss is shown in depression in Figure 6-30; see also Chapter 7). It is also possible that agents targeting glutamate, GABA, and other non-monoaminergic targets will hold promise for treating patients who do not respond to monoaminergic therapeutics. Restoration of neurotransmitter-related signal transduction cascades by drugs of any mechanism that can successfully treat depression can also hypothetically increase BDNF and other trophic factors and therefore potentially restore lost synapses. In some brain areas, such as the hippocampus, not only can synapses potentially be restored, but it is possible that some lost neurons might even be replaced by neurogenesis.

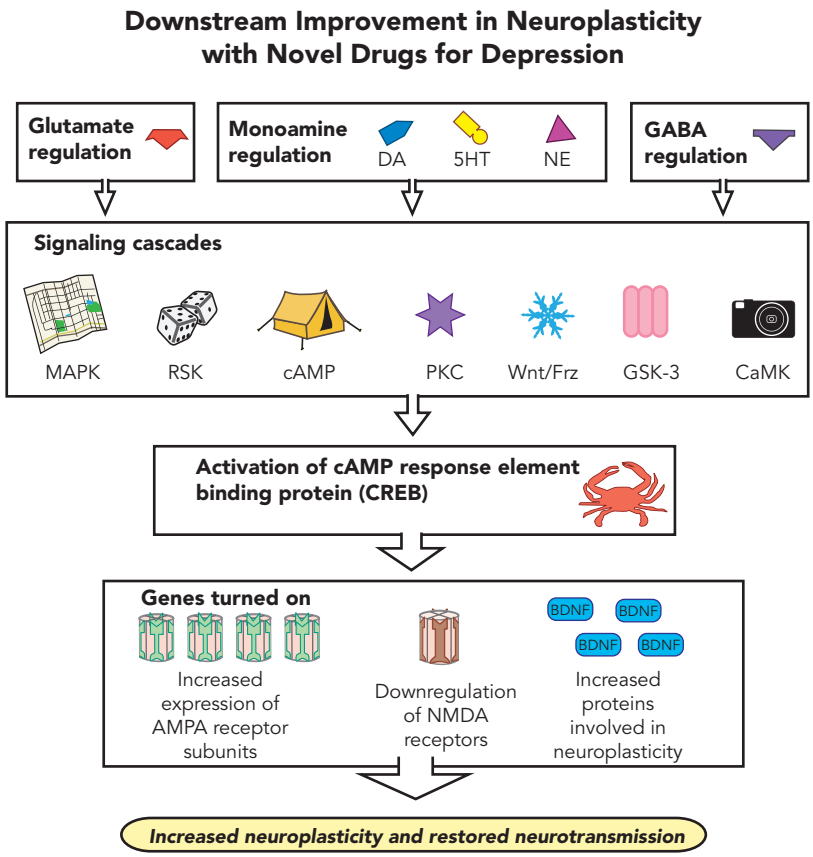


Figure 6-37 Downstream effects on neuroplasticity. In depression, there may be a deficiency in downstream signal transduction, leading to reduced synthesis of proteins involved in neurogenesis and synaptic plasticity, such as brain-derived neurotrophic factor (BDNF). Treatment with drugs for depression, both traditional monoamine reuptake inhibitors as well as novel agents that affect glutamate or GABA, can stimulate a variety of signaling cascades. Each of the signaling cascades depicted is capable of activating cAMP response element binding protein (CREB), which can elicit the expression of numerous genes involved in neuroplasticity, including BDNF. Another form of synaptic plasticity, long-term potentiation (LTP), involves the strengthening of synapses through the modulation of glutamate receptors. The activation of CREB increases the expression of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor subunits and downregulates *N*-methyl-D-aspartate (NMDA) receptors. Modifying the AMPA:NMDA receptor ratio by increasing AMPA while reducing NMDA input may restore glutamate homeostasis and facilitate neuroplasticity in the depressed brain.

SYMPTOMS AND CIRCUITS IN MOOD DISORDERS

Currently, a major hypothesis in psychiatry is that psychiatric symptoms are linked to inefficient information processing in specific brain circuits, with different circuits mediating different symptoms according to an evolving understanding of the topographical distribution of different functions across different brain regions, sometimes called nodes, and across different brain circuits, with connections forming networks. If possibly reductionistic and oversimplified, the theoretical notion is to associate specific nodes in the network with specific psychiatric symptoms. Here we will discuss how this idea might apply to doing this for the nine symptoms of a major depressive episode (Figure 6-1) and the nine symptoms of a manic episode (Figure 6-2).

Why do this if our information is still incomplete and evolving about domains of psychopathology and the circuits underlying them? It is because it helps us better understand the presenting symptoms of our patients as well as their symptoms that persist after treatment. The goal of this approach is to have a strategy for relieving all symptoms in order to get to complete remission, and to do so as rationally as possible based upon how those specific circuits are currently thought to be regulated by neurotransmitters in normal functioning and in psychiatric disorders. That strategy also involves rational use of the available drugs that are known to target the regulation of those same neurotransmitters, and, therefore, to target improvement of the symptoms those neurotransmitters regulate.

Let's now explain how this strategy works. Each of the nine symptoms listed for the diagnosis of a major depressive episode can be mapped onto brain circuits whose inefficient information processing theoretically mediates these symptoms (compare Figure 6-1 and Figure 6-38). Each of the symptoms listed for the diagnosis of a manic episode can similarly be mapped onto some of these same but also some different brain circuits (compare Figure 6-2 and 6-39). Note the innervation of these various brain areas by the three monoamine neurotransmitter systems (Figure 6-40). Glutamate and GABA are ubiquitous throughout essentially every area of the brain. This pattern of monoamine innervation provides the opportunity to target various neurotransmitters in order to improve the efficiency of information processing in these brain areas, and thus, reduce symptoms. Each node in the networks regulating psychiatric symptoms has neurotransmitters distributed to it in a unique if partially overlapping pattern that regulates each specific hypothetically malfunctioning brain region (see Figures 6-38 through 6-40). Targeting each region with drugs which act on

Match Each Diagnostic Symptom for a Major Depressive Episode to Hypothetically Malfunctioning Brain Circuits

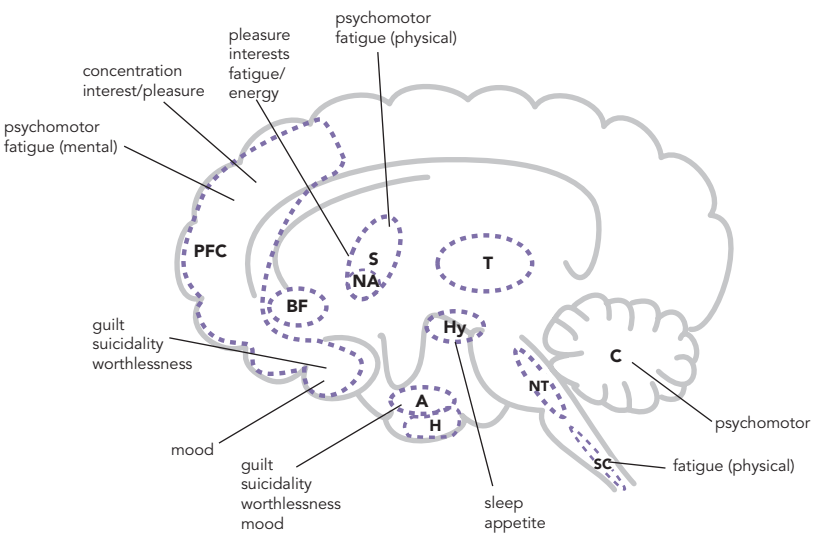


Figure 6-38 Matching depression symptoms to circuits. Alterations in neuronal activity and in the efficiency of information processing within each of the brain regions shown here can lead to symptoms of a major depressive episode. Functionality in each brain region is hypothetically associated with a different constellation of symptoms. PFC, prefrontal cortex; BF, basal forebrain; S, striatum; NA, nucleus accumbens; T, thalamus; Hy, hypothalamus; A, amygdala; H, hippocampus; NT, brainstem neurotransmitter centers; SC, spinal cord; C, cerebellum.

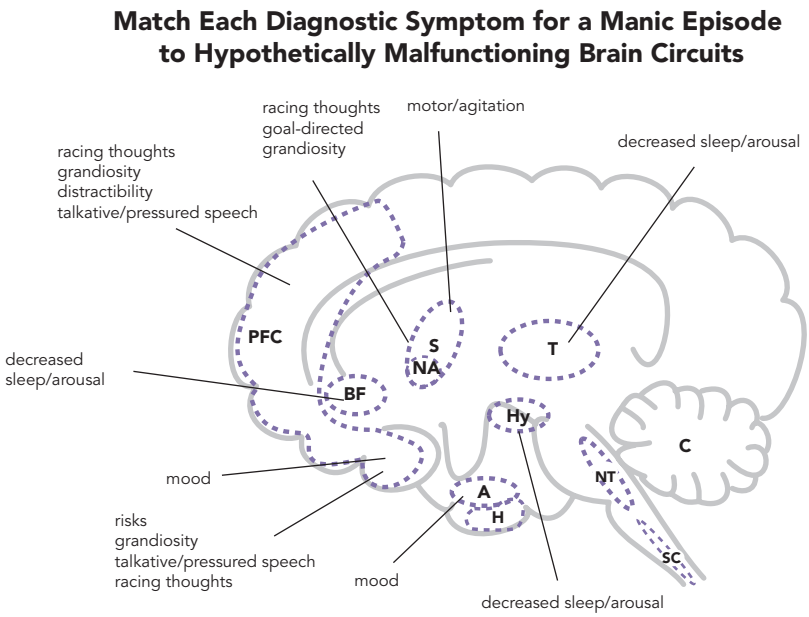


Figure 6-39 Matching mania symptoms to circuits. Alterations in neurotransmission within each of the brain regions shown here can be hypothetically linked to the various symptoms of a manic episode. Functionality in each brain region may be associated with a different constellation of symptoms. PFC, prefrontal cortex; BF, basal forebrain; S, striatum; NA, nucleus accumbens; T, thalamus; Hy, hypothalamus; A, amygdala; H, hippocampus; NT, brainstem neurotransmitter centers; SC, spinal cord; C, cerebellum.

the relevant neurotransmitters that regulate those brain regions potentially leads to reduction of each individual symptom. The idea is that whenever adjustment of specific neurotransmitter-mediated neurotransmission can enhance the efficiency of information processing in the hypothetically malfunctioning circuits for each specific symptom, it will relieve that symptom. If successful, this targeting of neurotransmitters in specific brain areas could even eliminate all symptoms and cause a major depressive episode to go into remission.

Many of the mood-related symptoms of depression can be categorized as having either too little positive affect or too much negative affect (Figure 6-41). This idea is linked to the fact that there are diffuse anatomic connections of monoamines throughout the brain, with diffuse dopamine dysfunction in this system driving predominantly the reduction of positive affect, diffuse serotonin dysfunction driving predominantly the increase in negative affect, and norepinephrine dysfunction being involved in both. Thus, reduced positive affect includes such symptoms as depressed mood but also loss of happiness, joy, interest, pleasure, alertness, energy, enthusiasm, and self-confidence (Figure 6-41, left). Enhancing dopamine function and possibly also norepinephrine function may improve information processing in the circuits mediating this cluster of symptoms. On the other hand, increased negative affect includes not only depressed mood but guilt, disgust, fear, anxiety, hostility, irritability, and loneliness (Figure 6-41, right). Enhancing serotonin function, and possibly also norepinephrine function, may improve information processing in the circuits that hypothetically mediate this cluster of symptoms. For patients with symptoms of both clusters, they may require triple-action treatments that boost all three of the monoamines.

The same general paradigm of neurotransmitter regulation of the efficiency of information processing in specific brain circuits can be applied to mania and to mixed states as well as depression. Although a simplistic notion is that the circuit problem in mania may be the opposite of that for depression, namely too much in mania versus too little neurotransmitter and neuronal activity in depression, the reality is that you can have manic and depressive symptoms at the same time, and can traverse the entire mood spectrum from full depression, with increasing amounts of mania, until arriving at pure mania (Figure 6-7). A more sophisticated and modern notion of mood disorder is that neuronal transmission in inefficient brain circuits may be chaotic and not just too high or too low. The illustrations drawn in this chapter sometimes imply there is a single neuron going from one node to another in the network (see for example Figure 6-40), but the reality is that each node in the network is connected by a vast bundle of neurons, and not all of them are hypothetically functioning the same way in a mood disorder. Some may have

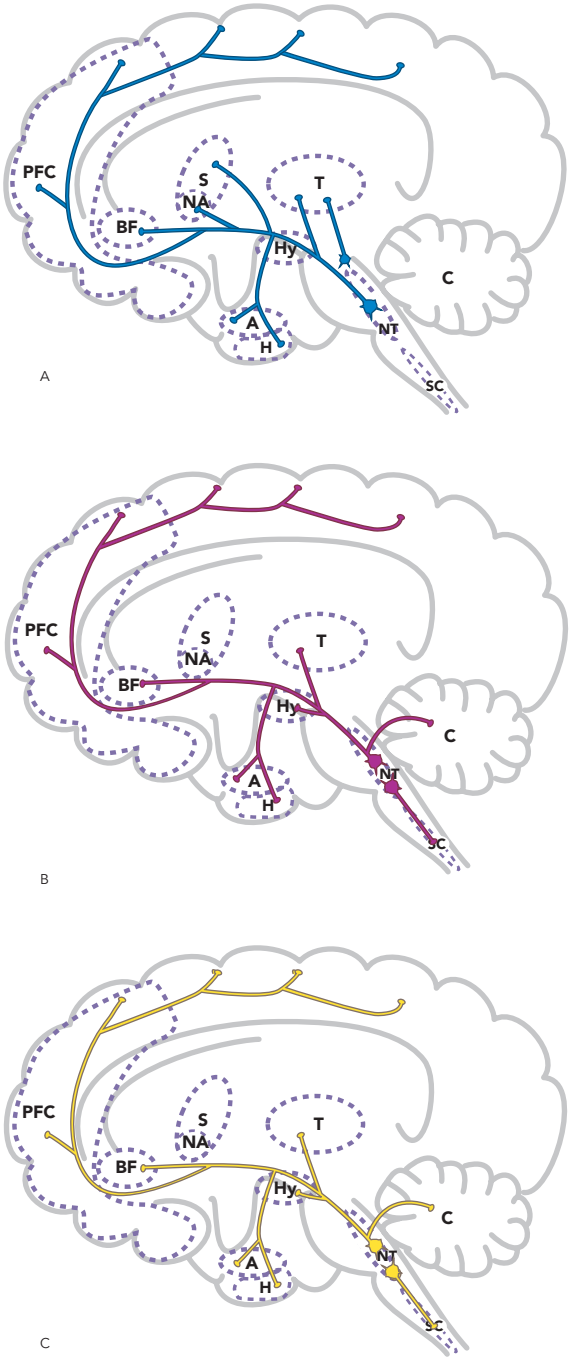


Figure 6-40 Major monoamine projections. (A) Dopamine has widespread ascending projections that originate predominantly in the brainstem (particularly the ventral tegmental area and substantia nigra) and extend via the hypothalamus to the prefrontal cortex, basal forebrain, striatum, nucleus accumbens, and other regions. Dopaminergic neurotransmission is associated with movement, pleasure and reward, cognition, psychosis, and other functions. In addition, there are direct projections from other sites to the thalamus, creating the "thalamic dopamine system," which may be involved in arousal and sleep. (B) Norepinephrine has both ascending and descending projections. Ascending noradrenergic projections originate mainly in the locus coeruleus of the brainstem; they extend to multiple brain regions, as shown here, and regulate mood, arousal, cognition, and other functions. Descending noradrenergic projections extend down the spinal cord and regulate pain pathways. (C) Like norepinephrine, serotonin has both ascending and descending projections. Ascending serotonergic projections originate mainly in the raphe nucleus in the brainstem and extend to many of the same regions as noradrenergic projections. These ascending projections may regulate mood, anxiety, sleep, and other functions. Descending serotonergic projections extend down the brainstem and through the spinal cord; they may regulate pain. PFC, prefrontal cortex; BF, basal forebrain; S, striatum; NA, nucleus accumbens; T, thalamus; Hy, hypothalamus; A, amygdala; H, hippocampus; NT, brainstem neurotransmitter centers; SC, spinal cord; C, cerebellum.

neurotransmission that is perhaps up, others down, others normal, and still others vacillating chaotically from up to down in activity. No wonder a patient can appear to have varying symptoms of concomitant mania during a full depressive episode, not only from one episode to the next, but even within an episode over time. This situation presents a challenge to find treatments that can stabilize rather than simply increase or reduce neurotransmitter action. Treatments for mood disorders are discussed in detail in Chapter 7.

Symptom-Based Treatment Selections

The neurobiologically informed psychopharmacologist may opt for a symptom-based approach to selecting or combining a series of drugs for treatment of depression, mania, and mixed states (Figures 6-42 through 6-44). This strategy leads to the construction of a portfolio of multiple psychopharmacological mechanisms in order to treat all residual symptoms of a mood disorder until the patient achieves sustained remission. Specific drugs and treatment choices are discussed in Chapter 7. Here we cover the rationale for thinking in neurobiological terms, namely, the anatomy of brain circuits regulating specific symptoms (Figures 6-38 and 6-39) and the neurotransmitters that regulate the circuits (Figure 6-40). The purpose of this approach is to apply understanding of how a given drug works on neurotransmitters, so a clinician can make rational treatment choices. Using this approach, those treatment choices are based upon addressing those specific symptoms of a given patient by targeting the unique collection of hypothetically malfunctioning brain circuits. This "tailored" approach

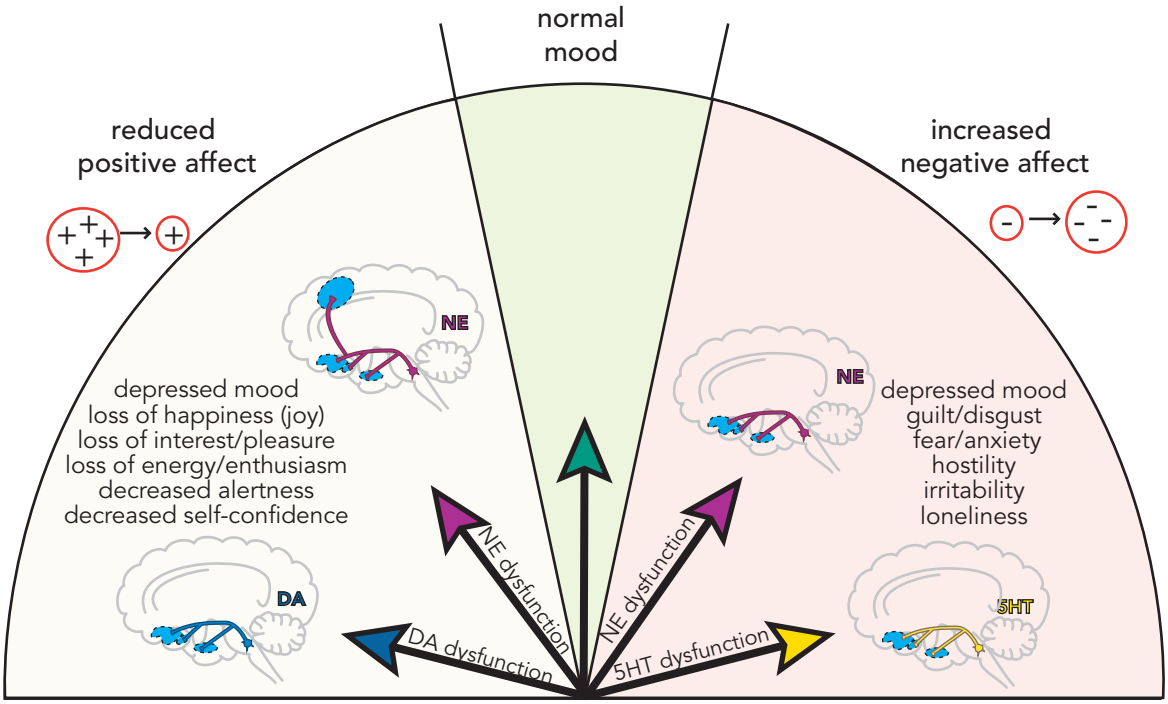


Figure 6-41 **Positive and negative affect.** Mood-related symptoms of depression can be characterized by their affective expression – that is, whether they cause a reduction in positive affect or an increase in negative affect. Symptoms related to reduced positive affect include depressed mood; loss of happiness, interest, or pleasure; loss of energy or enthusiasm; decreased alertness; and decreased self-confidence. Reduced positive affect may be hypothetically related to dopaminergic dysfunction, with a possible role of noradrenergic dysfunction as well. Symptoms associated with increased negative affect include depressed mood, guilt, disgust, fear, anxiety, hostility, irritability, and loneliness. Increased negative affect may be linked hypothetically to serotonergic dysfunction and perhaps also noradrenergic dysfunction.

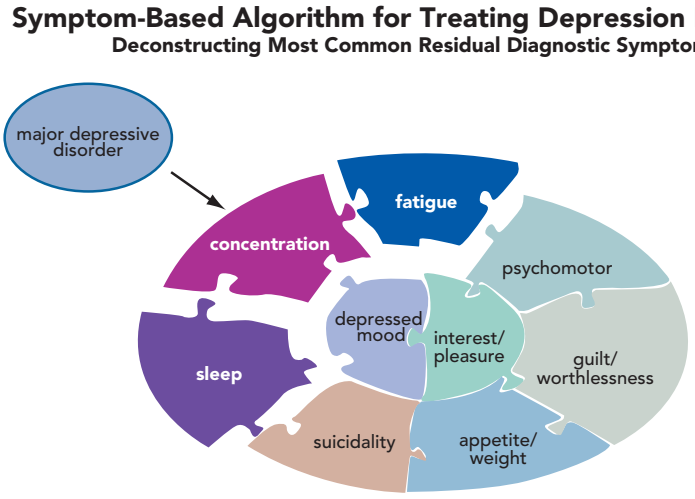


Figure 6-42 **Symptom-based algorithm for treating depression, part 1.** Shown here is the diagnosis of major depressive disorder deconstructed into its symptoms (as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition [DSM-5]). Of these, sleep disturbances, problems concentrating, and fatigue are the most common residual symptoms.

attempts to address the individual patient's needs and thereby provide relief of the specific symptoms of that individual patient rather than treating all patients with a given diagnosis the same.

How is this approach implemented? First, symptoms are evaluated and a diagnosis constructed by putting them all together, but then that diagnosis is deconstructed into a list of specific symptoms that the individual patient is experiencing (Figure 6-42). Next, these symptoms are matched with the brain circuits that hypothetically mediate these symptoms (Figure 6-43) and then with the known neuropharmacological regulation of these circuits by neurotransmitters (Figure 6-44). Finally, available treatment options that target these neuropharmacological

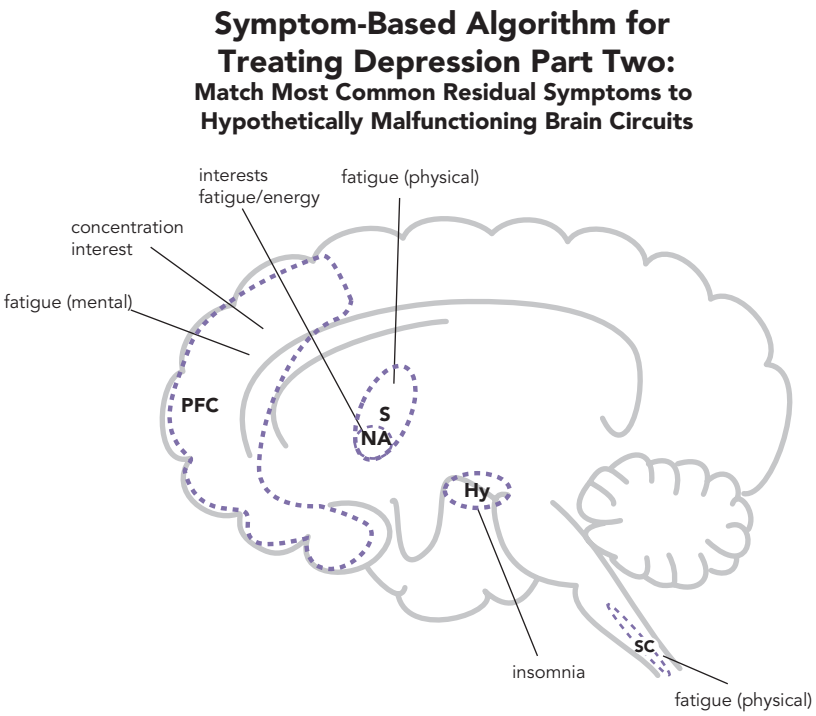


Figure 6-43 Symptom-based algorithm for treating depression, part 2. In this figure the most common residual symptoms of major depression are linked to hypothetically malfunctioning brain circuits. Insomnia maybe linked to the hypothalamus (Hy), problems concentrating to the dorsolateral prefrontal cortex (PFC), reduced interest to the PFC and nucleus accumbens (NA), and fatigue to the PFC, striatum (S), NA, and spinal cord (SC).

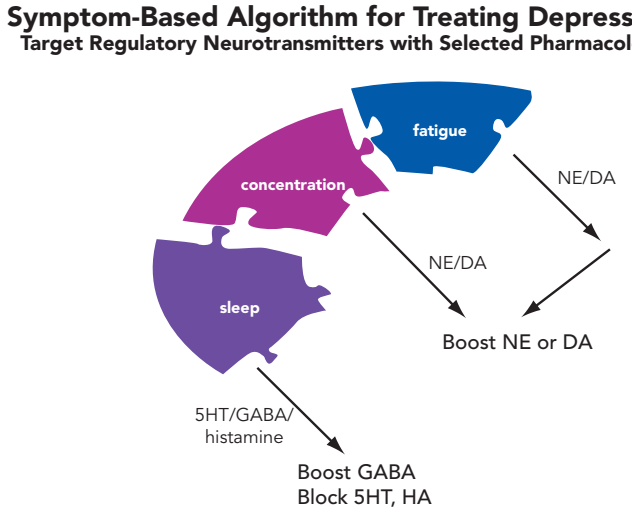


Figure 6-44 Symptom-based algorithm for treating depression, part 3. Residual symptoms of depression can be linked to the neurotransmitters that regulate them and then, in turn, to pharmacological mechanisms. Fatigue and concentration are regulated in large part by norepinephrine (NE) and dopamine (DA), and therefore may be treated by agents that boost NE and/or DA. Sleep disturbance is regulated by serotonin (5HT), γ-aminobutyric acid (GABA), and histamine (HA) and can be treated with agents that boost GABA or block 5HT or HA.

mechanisms are chosen to eliminate symptoms one by one (Figure 6-44). When symptoms persist despite treatment, another treatment with a different mechanism is added or switched. No evidence proves that this is a superior approach, but it appeals not only to clinical intuition but also to neurobiological reasoning as well as to the goal of individualizing psychopharmacological treatment rather than treating all patients with the same diagnosis the same way in the hope that this will lead to a better outcome.

For example, for the symptoms of "problems concentrating" and "fatigue," this approach suggests targeting both NE and DA (Figure 6-44). This can also call for stopping the use of a serotonergic medication if this is partially the cause of these symptoms. On the other hand, for "insomnia," this symptom is hypothetically associated with an entirely different malfunctioning circuit regulated by different neurotransmitters (Figure 6-43); therefore, the treatments for this symptom call for a different approach, namely the use of agents that act on the GABA system or that work to block rather than boost the serotonin or histamine system (Figure 6-44). It is possible that any of the symptoms shown in Figure 6-44 would respond to whatever drug is administered, but this symptom-based approach can tailor the treatment portfolio to each individual patient, possibly finding a faster way of reducing specific symptoms with more tolerable treatment selections for that patient than a purely random approach.

The symptom-based approach for selecting treatments for depression can also be applied to treating common associated symptoms of depression that are not components of the formal diagnostic criteria, such as anxiety and pain. Sometimes it is said that for a good clinician to get patients into remission, it requires targeting at least a dozen of the nine symptoms of a mood disorder!

Fortunately, psychiatric drug treatments do not respect psychiatric disorders. Treatments that target pharmacological mechanisms in specific brain circuits do so no matter what psychiatric disorder is associated with the symptom linked to that circuit. Thus, symptoms of one psychiatric disorder may be treatable with a proven agent that is known to treat the same symptom in another psychiatric disorder. For example, *anxiety* can be reduced in patients with major depression who do not have a full-criteria anxiety disorder with the same serotonin and GABA mechanisms proven to work in anxiety disorders (see Chapter 8 on anxiety disorders and their treatments). *Painful physical symptoms* can be treated with serotonin–norepinephrine reuptake inhibitors (SNRIs) and other approaches (see Chapter 9 on chronic pain and its treatment).

In conclusion, the symptom-based algorithm for selecting and combining treatments of mood disorders, and using them to build a portfolio of mechanisms until each symptom of a mood disorder is abolished, is the modern psychopharmacologist's approach to mental illnesses in general and to mood disorders in particular. This approach follows contemporary notions of neurobiological disease and drug mechanisms, with the goal of treatment being sustained remission.

SUMMARY

This chapter has described the mood disorders across a spectrum from depression to mania with many mixed states in between. For prognostic and treatment considerations, it is important not only to distinguish unipolar depression from bipolar depression, but also to detect mixed states of subsyndromal mania or depression whenever they exist. Although mood disorders are indeed disorders of mood, they are much more, and several different symptoms in addition to a mood symptom are required to make a diagnosis of a major depressive episode or a manic episode. The classic monoamine hypothesis of depression, suggesting that dysfunction of one or more of the three monoamines dopamine, norepinephrine, or serotonin, or their receptors, may be linked to symptoms in major depression, has been updated and expanded to include the notion of abnormalities in neurotrophic factors, sleep, circadian rhythms, neuroinflammation, stress, genes, and the environment in the complex etiology of mood disorders. Also discussed is the troubling notion that mood disorders may be progressive, especially if not adequately treated. Finally, each symptom of a mood disorder can be matched to a hypothetically malfunctioning neuronal circuit. Targeting one or more of the neurotransmitters in specific brain regions may improve the efficiency of information processing there and reduce the symptom caused by that area's malfunctioning. Other brain areas associated with the symptoms of a manic episode can similarly be mapped to various hypothetically malfunctioning brain circuits. Understanding the localization of symptoms in circuits, as well as the neurotransmitters that regulate these circuits in different brain regions, can set the stage for choosing and combining treatments for each individual symptom of a mood disorder, with the goal being to reduce all symptoms and lead to remission.

7 Treatments for Mood Disorders: So-Called "Antidepressants" and "Mood Stabilizers"

Definitions of Clinical Effects of Treatment in Depression 284
How Well Do Classic Monoamine Reuptake Blockers Work in Unipolar Depression? 285
Redefining "Mood Stabilizers": A Labile Label 288
Drugs for Unipolar Depression 289
Selective Serotonin Reuptake Inhibitors (SSRIs) 289
Serotonin Partial Agonist Reuptake Inhibitors (SPARIs) 296
Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs) 298
Norepinephrine–Dopamine Reuptake Inhibitors (NDRIs): Bupropion 303
Agomelatine 306
Mirtazapine 308
Serotonin Antagonist/Reuptake Inhibitors (SARIs) 311
Vortioxetine 315
Neuroactive Steroids 320
Treatment Resistance in Unipolar Depression 323
Choosing Treatment for Treatment Resistance in Depression on the Basis of Genetic Testing 323
Augmenting Strategies for Unipolar Depression 325
Second-Line Monotherapies Used for Treatment-Resistant Depression 333
Drugs for Bipolar Disorder Spectrum 338
Serotonin/Dopamine Blockers: Not Just for Psychosis and Psychotic Mania 338
Lithium, the Classic "Antimanic" and "Mood Stabilizer" 345
Anticonvulsants as "Mood Stabilizers" 346
Anticonvulsants with Proven Efficacy in Bipolar Disorder 347
Combinations are the Standard for Treating Bipolar Disorder 353
Future Treatments for Mood Disorders 353
Dextromethorphan–Bupropion and Dextromethorphan–Quinidine 353
Dextromethadone 355
Hallucinogen-Assisted Psychotherapy 355
Summary 358

In this chapter, we will review pharmacological concepts underlying the use of drugs used to treat mood disorders, from depression, to mixed states, to mania. These agents have classically been called "antidepressants" and "mood stabilizers" but this terminology is now considered out of date and confusing since not all drugs classically called "antidepressants" are used to treat all forms of depression – especially not bipolar depression or depression with mixed features. Furthermore, many of the classic so-called "antidepressants" are also used to treat a whole range of disorders from anxiety disorders, to eating disorders, traumatic disorders, obsessive compulsive and impulsive disorders, pain, and beyond. Finally, many of the drugs used for psychosis and discussed extensively in Chapter 5 are used even more commonly to treat depression, unipolar, bipolar, and mixed depression, as well as mania, yet are not generally classed as "antidepressants" although they are certainly "drugs for depression." To eliminate confusion about how to discuss categories of drugs, throughout this textbook we strive to utilize modern neuroscience-based nomenclature, where drugs are named for their pharmacological mechanism of action and not for their clinical indication.

Thus, drugs discussed in this chapter have "antidepressant action" but are not called "antidepressants." Other drugs have mood-stabilizing and antimanic action but are not called "mood stabilizers." What is a "mood stabilizer"? Originally, a mood stabilizer was a drug that treated mania and prevented recurrence of mania, thus "stabilizing" the manic pole of bipolar disorder. Others use this term for a drug that treats depression and recurrence of depression in bipolar disorder thus stabilizing the depressed pole of bipolar disorder. Rather than use the term for stabilizing either mania or depression, here we will use terms to describe

and categorize agents that treat bipolar disorder based upon presumed mechanism of therapeutic action.

This chapter will review some of the most extensively prescribed psychotropic agents in psychiatry today, namely those that target neurotransmitter transporters, receptors, and ion channels. The goal of this chapter is to acquaint the reader with current and evolving ideas about how the various drugs used to treat disorders of mood work. We will explain the mechanisms of action of these drugs by building upon general pharmacological concepts introduced in earlier chapters. We will also discuss concepts about how to use these drugs in clinical practice, including strategies for what to do if initial treatments fail and how to rationally combine one drug with another. Finally, we will introduce the reader to several new agents targeting mood disorders, which have recently been approved or are in clinical development.

Our discussion of drugs for the treatment of mood disorders in this chapter is at the conceptual level, and not at the pragmatic level. The reader should consult standard drug handbooks (such as the companion *Stahl's Essential Psychopharmacology: the Prescriber's Guide*) for details of doses, side effects, drug interactions, and other issues relevant to the prescribing of these drugs in clinical practice. Here we will discuss putting together a "portfolio" of two or more mechanisms of action, often requiring more than one drug, as a strategy for patients who have not responded to single pharmacological mechanisms. This treatment strategy for mood disorders is very different than that for schizophrenia, discussed in Chapter 5, where single antipsychotic drugs as treatments are the rule and the expected improvement in symptomatology may be only 20% to 30% reduction of symptoms, with few, if any, patients with schizophrenia becoming truly asymptomatic. By contrast, in mood disorders there is a greater chance to reach a genuine state of sustained and asymptomatic remission and the challenge for those who treat these patients is to help them attain this best outcome whenever possible. That is the reason for learning the mechanisms of action of so many drugs, the complex biological rationale for combining specific sets of drugs, and the practical tactics for tailoring a unique drug treatment portfolio to fit the needs of an individual patient.

DEFINITIONS OF CLINICAL EFFECTS OF TREATMENT IN DEPRESSION

For patients who have a major depressive episode, unipolar, bipolar, or mixed, and who receive treatment and improve to the level 50% reduction of symptoms or more, this outcome is called a response (Figure 7-1). This used to be the goal of treatment with drugs for depression: namely, reduce symptoms substantially, and by at least 50%. However, the paradigm for depression treatment has shifted dramatically in recent years so that now the goal is complete remission of symptoms (Figure 7-2), and maintaining that level of improvement so that the patient's major depressive episode does not relapse shortly after remission, nor does the patient have a recurrent episode in the future (Figure 7-3). Given the known limits to the efficacy of available drugs to treat depression, especially when multiple treatment options

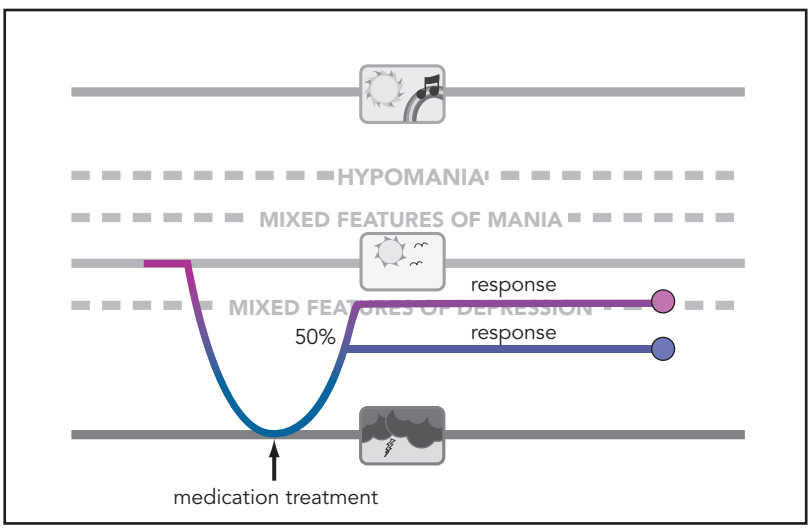


Figure 7-1 Response in depression. When treatment of a major depressive episode results in at least 50% improvement in symptoms, it is called a response. Such patients are better but not well. Previously, this was considered the goal of depression treatment.

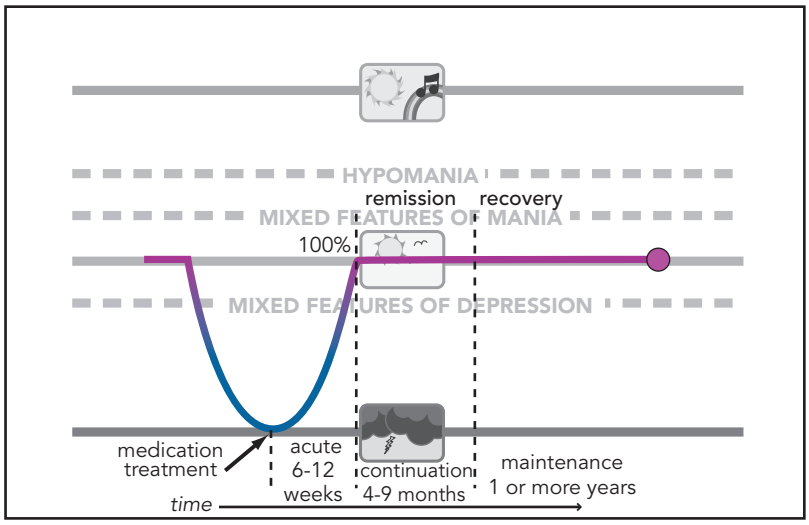


Figure 7-2 Remission in depression. When treatment of major depressive episode results in removal of essentially all symptoms, it is called remission for the first several months and then recovery if it is sustained for longer than several months. Such patients are not just better – they are well. However, they are not cured, since depression can still recur. Remission and recovery are now the goals when treating patients with depression.

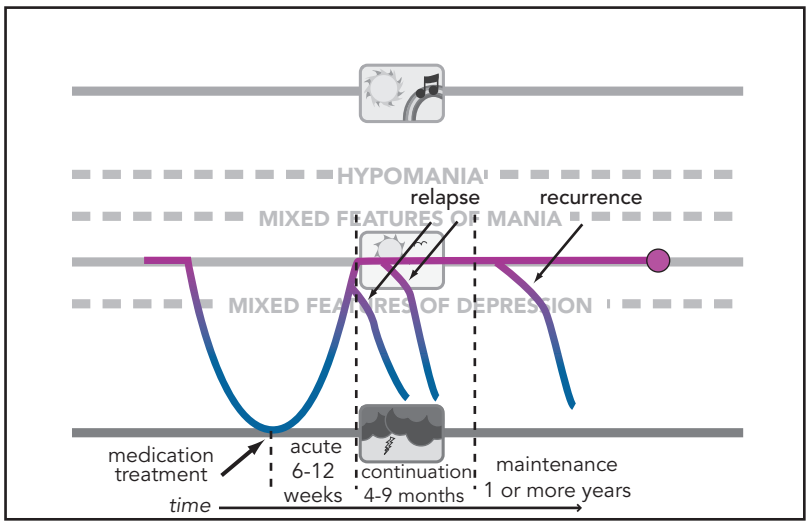


Figure 7-3 Relapse and recurrence in depression. When depression returns before there is a full remission of symptoms or within the first several months following remission of symptoms, it is called a relapse. When depression returns after a patient has recovered, it is called a recurrence.

are not deployed aggressively and early in the course of this illness, the goal of sustained remission can be difficult to reach. Unfortunately, remission is usually not reached with the first agent chosen to treat depression.

HOW WELL DO CLASSIC MONOAMINE REUPTAKE BLOCKERS WORK IN UNIPOLAR DEPRESSION?

The mechanism of action of drugs for unipolar depression is predominantly inhibition of monoamine reuptake as explained in detail in the following several sections. Before tackling the mechanism, we can ask, how well do they work? Real-world trials suggest that only a third of patients with unipolar depression remit on their first treatment with a drug from this class, and even after about a year of total treatment with a sequence of four different drugs for unipolar depression, each given for 12 weeks, only about two-thirds of patients with unipolar depression ever achieve remission of their symptoms (Figure 7-4).

If patients do not fully remit after treatment, what are the most common symptoms that persist? The answer is shown in Figure 7-5, and the symptoms include insomnia, fatigue, multiple painful physical complaints (even though these are not part of the formal diagnostic criteria for depression), cognitive problems including difficulty concentrating, and lack of interest or motivation. Drugs for unipolar depression often appear

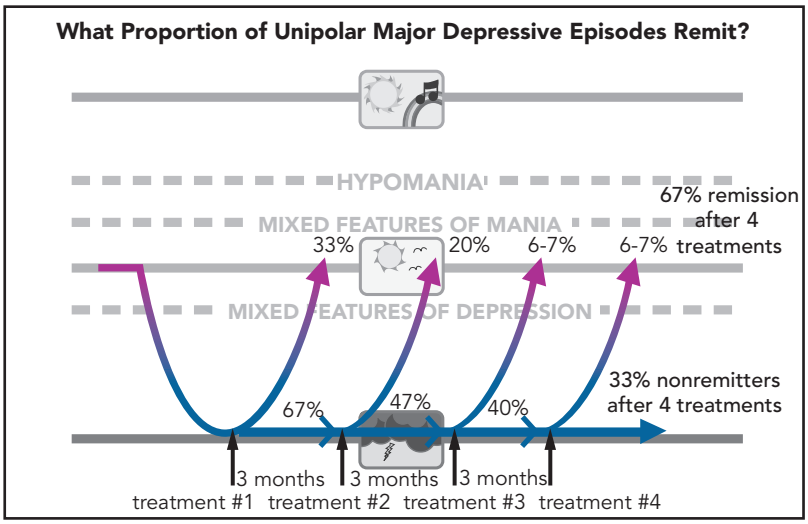


Figure 7-4 Remission rates in unipolar depression. Approximately one-third of patients with unipolar depression will remit during treatment with any treatment initially. Unfortunately, for those who fail to remit, the likelihood of remission with another monotherapy goes down with each successive trial. Thus, after a year of treatment with four sequential monotherapies taken for 12 weeks each, only two-thirds of patients will have achieved remission.

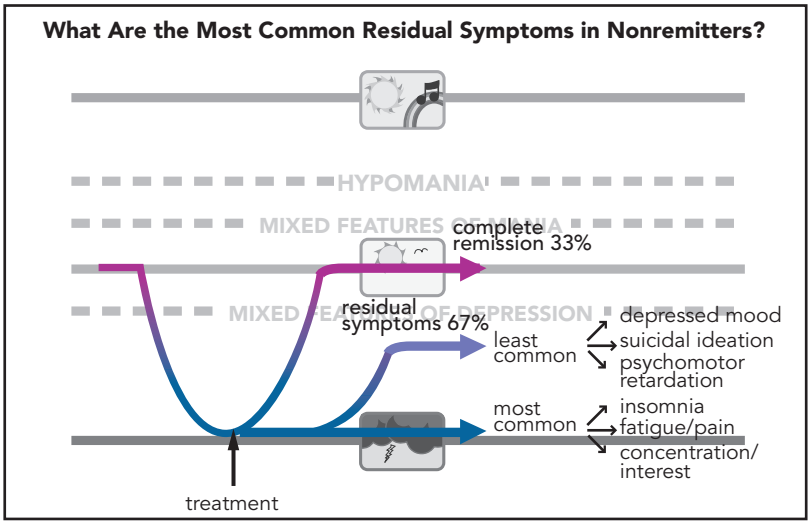


Figure 7-5 Common residual symptoms. In patients who do not achieve remission, the most common residual symptoms are insomnia, fatigue, painful physical complaints, problems concentrating, and lack of interest. The least common residual symptoms are depressed mood, suicidal ideation, and psychomotor retardation.

to work better in improving depressed mood, suicidal ideation, and psychomotor retardation (Figure 7-5).

Why should we care whether a patient is in remission from major depression or has just a few persistent symptoms? Part of the answer can be found in Chapter 6 in the discussion of neuroprogression from persisting symptoms to loss of synapses, loss of neurons, and treatment resistance (Figures 6-11, 6-28 through 6-33). The other part of the answer can be found in Figure 7-6, which illustrates the evolution of treatment resistance over time, mostly because symptoms persist or return. On the one hand, Figure 7-6 shows that if a drug for unipolar depression gets your patient into remission, that patient has a significantly lower relapse rate than if no treatment was given at all. On the other hand, the bad news is that there are still very frequent relapses in the remitters, and these relapse rates are more frequent and come quicker the more treatments the patient needs in order to get into remission (Figure 7-6).

Data like these have galvanized researchers and clinicians alike to treat patients to the point of remission of all symptoms whenever possible, and to try to intervene as early as possible in this illness of unipolar major depression, not only to be merciful in trying to relieve current suffering from all depressive symptoms, but also because of the possibility that aggressive treatment may prevent disease progression (see Chapter 6 and Figures 6-11, 6-28 through 6-33). The concept of disease progression in

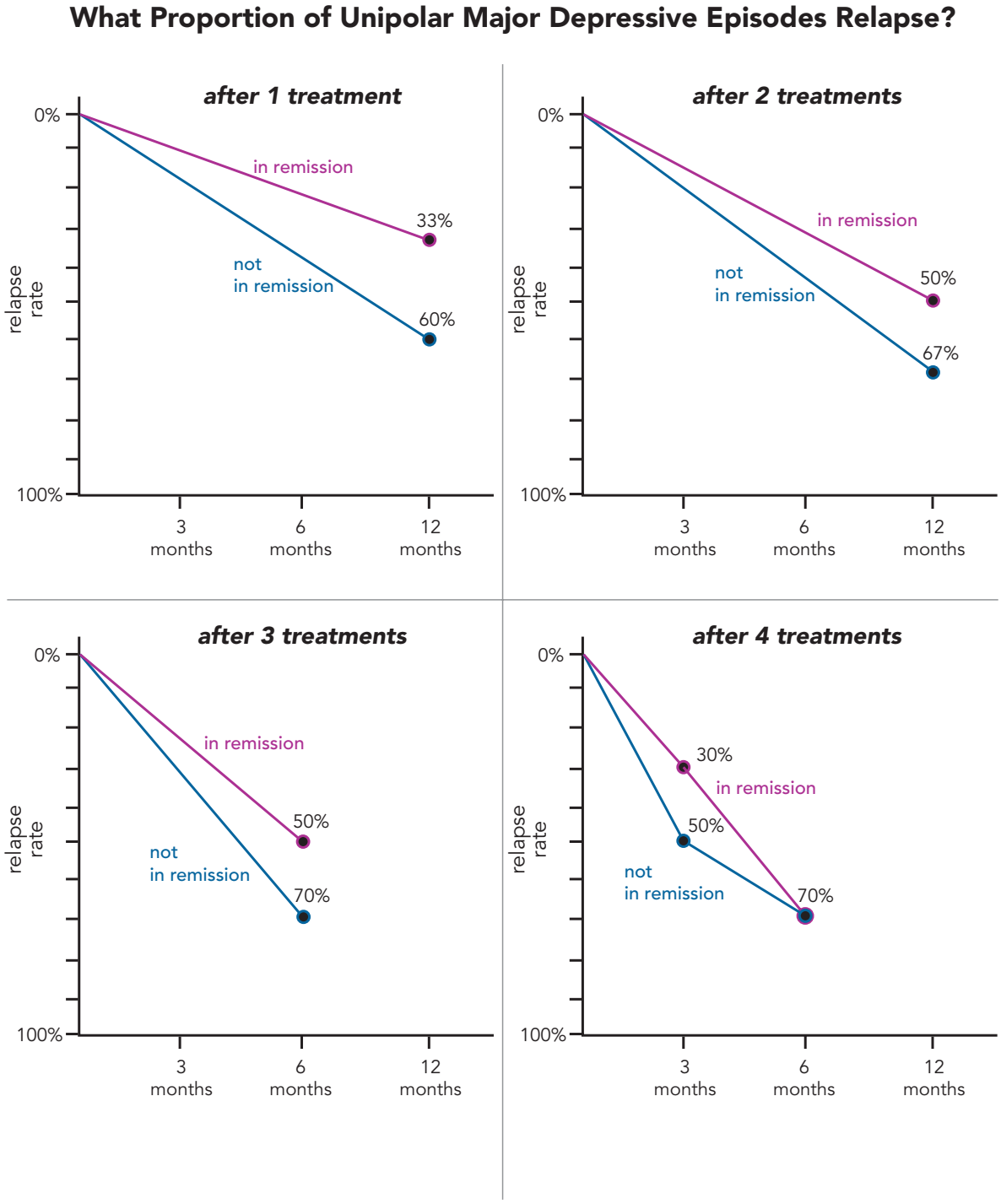


Figure 7-6 **Relapse rates.** The rate of relapse of major depression is significantly less for patients who achieve remission. However, there is still a risk of relapse even in remitters, and the likelihood increases with the number of treatments it takes to get the patient to remit. Thus, the relapse rate for patients who do not remit ranges from 60% at 12 months after one treatment to 70% at 6 months after four treatments. For those who do remit, the relapse rate ranges from only 33% at 12 months after one treatment all the way to 70% at 6 months after four treatments. In other words, the protective nature of remission virtually disappears once it takes four treatments to achieve remission.

mood disorders is unproven and provocative, but makes a good deal of sense intuitively to many clinicians and investigators. The idea is that chronicity of a mood disorder, relapses of a mood disorder, and development of treatment resistance could all be reduced, with a better overall outcome in patients with aggressive treatment that leads to remission of all symptoms, thus potentially modifiying the course of this illness.

REDEFINING "MOOD STABILIZERS": A LABILE LABEL

"There is no such thing as a mood stabilizer."

– US FDA

"Long live the mood stabilizers."

– Prescribers

What is a "mood stabilizer?" As mentioned above, originally, a mood stabilizer was a drug that treated mania and prevented recurrence of mania, thus "stabilizing" the manic pole of bipolar disorder. More recently, the concept of mood stabilizer has been defined in a wide-ranging manner, from "something that acts like lithium," to "an anticonvulsant used to treat bipolar disorder," to "an antipsychotic used to treat bipolar disorder," to "stabilizing both mania and depression in bipolar disorder." Rather than using the term mood stabilizers, regulatory authorities consider that there are drugs that can treat any or all of four distinct phases

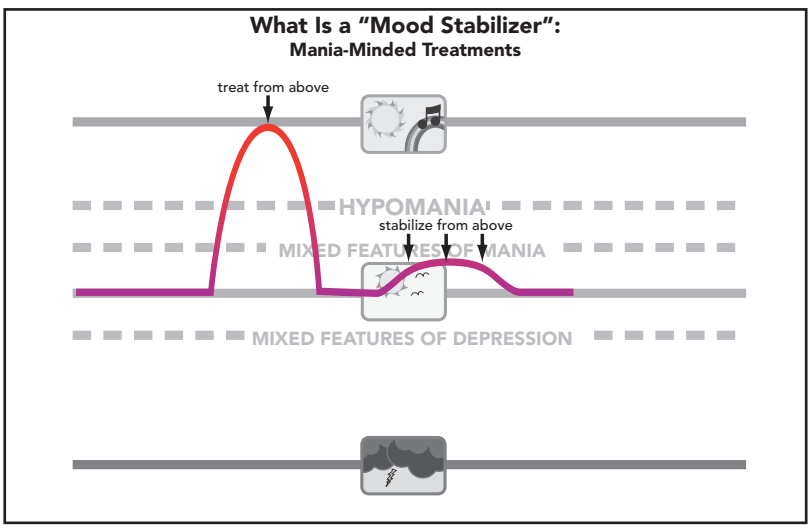


Figure 7-7 Mania-minded treatments. Although the ideal "mood stabilizer" would treat both mania and bipolar depression while also preventing episodes of either pole, in reality different agents may be efficacious for different phases of bipolar disorder. Some agents may be "mania-minded" and thus able to "treat from above" and/or "stabilize from above" – in other words, to reduce and/or prevent symptoms of mania.

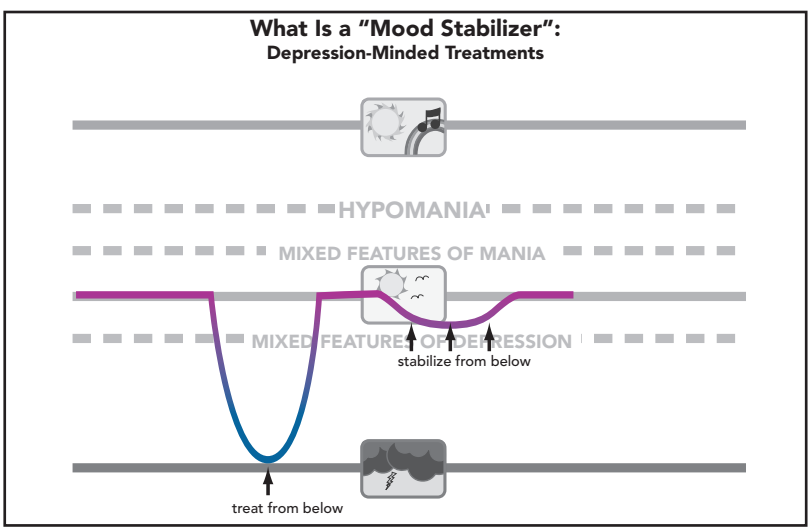


Figure 7-8 Depression-minded treatments. Although the ideal "mood stabilizer" would treat both mania and bipolar depression while also preventing episodes of either pole, in reality different agents may be efficacious for different phases of bipolar disorder. Some agents may be "depression-minded" and thus able to "treat from below" and/or "stabilize from below" – in other words, to reduce and/or prevent symptoms of bipolar depression.

of the illness (Figures 7-7 and 7-8). Thus, a drug can be "mania-minded" and "treat from above" to reduce symptoms of mania, and/or "stabilize from above" to prevent relapse and recurrence of mania (Figure 7-7). Furthermore, drugs can be "depression-minded" and "treat from below" to reduce symptoms of bipolar depression, and/or "stabilize from below" to prevent relapse and recurrence of depression (Figure 7-8). Not all drugs proven to work in bipolar disorder have all four therapeutic actions. In this chapter, we will discuss agents that have one or more of these actions in bipolar disorder, but will not refer to any of these agents as "mood stabilizers" but instead to their presumed pharmacological mechanism of action.

DRUGS FOR UNIPOLAR DEPRESSION

Selective Serotonin Reuptake Inhibitors (SSRIs)

Rarely has a class of drugs transformed a field as dramatically as the SSRIs have transformed clinical psychopharmacology. Some estimate that SSRI prescriptions in the US alone occur at the rate of 7 prescriptions per second: over 225 million a year. Clinical indications for use of SSRIs range far beyond unipolar major depressive disorder, to a number of anxiety disorders, posttraumatic stress disorder (PTSD), obsessive–compulsive disorder (OCD), and also to premenstrual dysphoric disorder, eating disorders, and others. There are six principal agents in this group, described below, and all share the common property of serotonin reuptake inhibition; thus, they all belong to the same drug class, known as SSRIs. However, each of these six drugs also has additional unique pharmacological properties that allow them to be distinguished from each other. First, we will discuss what these six drugs share in common, and then we will explore their distinctive individual properties that allow sophisticated prescribers to match specific drug profiles to individual patient symptom profiles.

What the Six SSRIs Have in Common

All the six SSRIs have the same major pharmacological feature in common: selective and potent inhibition of serotonin reuptake, also known as inhibition of the serotonin transporter (SERT). This simple concept is shown in Figures 7-9 and 7-10. Although the action of SSRIs at the *presynaptic axon terminal* has classically been emphasized (Figure 7-10), it now appears that events occurring at the *somatodendritic* end of the serotonin neuron (near the cell body) may be more important in explaining the therapeutic actions of the SSRIs (Figures 7-11 through 7-15). That is, in the

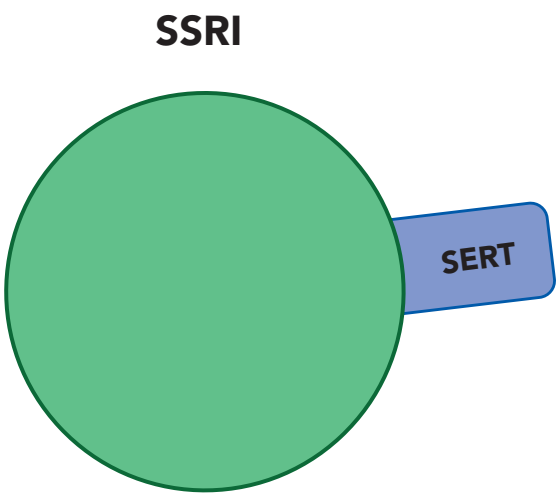


Figure 7-9 Selective serotonin reuptake inhibitors. Shown here is an icon depicting the core feature of selective serotonin reuptake inhibitors (SSRIs), namely serotonin reuptake inhibition. Although the agents in this class have unique pharmacological profiles, they all share the common property of serotonin transporter (SERT) inhibition.

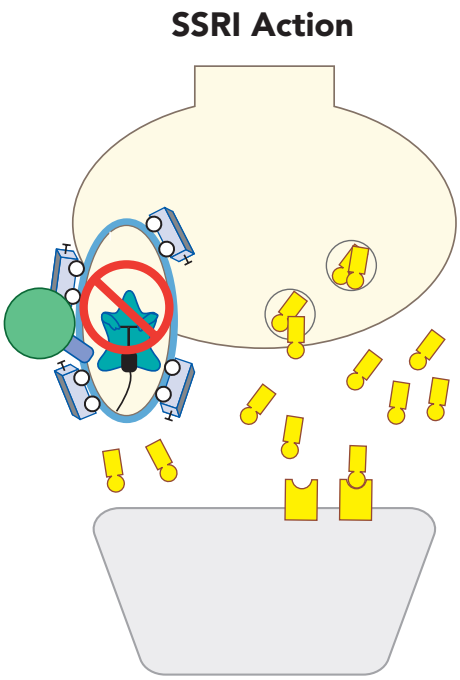
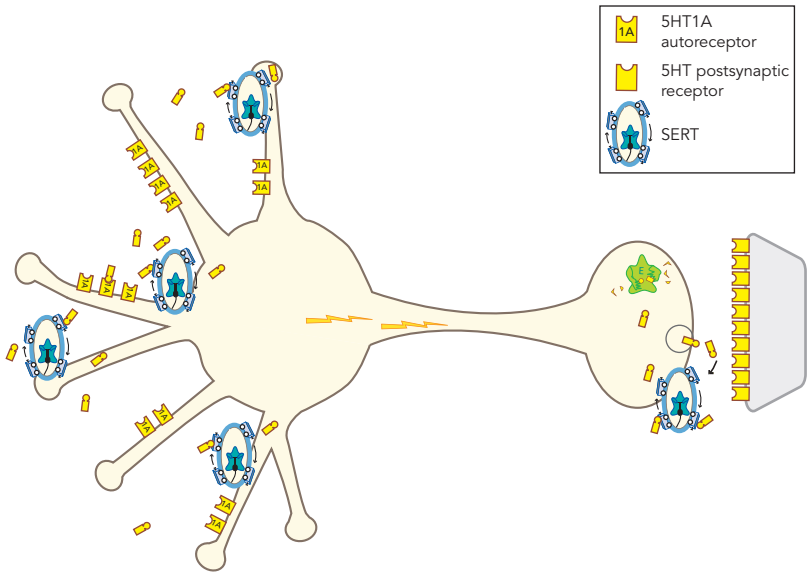
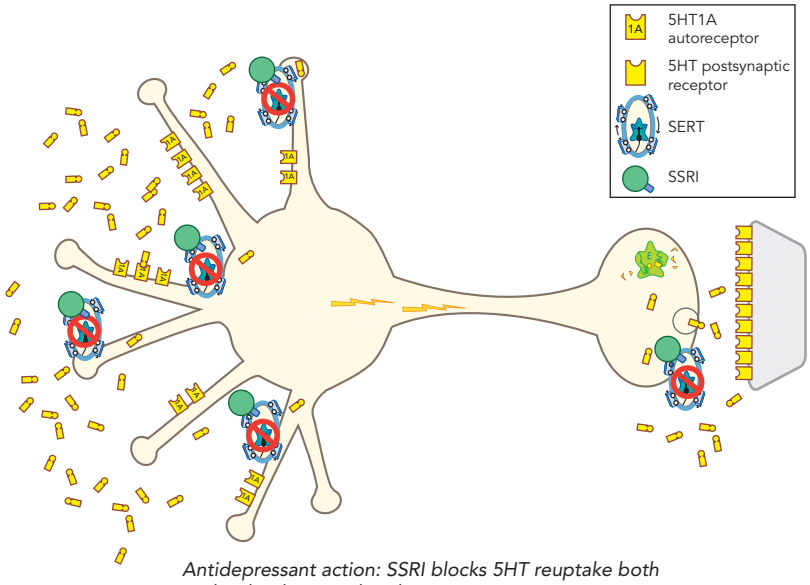


Figure 7-10 SSRI action. The serotonin reuptake inhibitor (SRI) portion of the SSRI molecule is shown inserted into the serotonin reuptake pump (the serotonin transporter, or SERT), blocking it, and causing increased synaptic availability of serotonin.



Depressed state: low 5HT, upregulated receptors, low number of signals in the neuron to release more 5HT

Figure 7-11 Mechanism of action of selective serotonin reuptake inhibitors (SSRIs), part 1. According to the monoamine hypothesis of depression, there is a relative deficiency of serotonin (5HT) (see levels of 5HT both in the synapse near the axon terminal [right] and at somatodendritic areas [left]. According to the neurotransmitter receptor hypothesis of depression, the number of 5HT receptors is upregulated, including presynaptic $5HT_{1A}$ autoreceptors as well as postsynaptic 5HT receptors.



Antidepressant action: SSRI blocks 5HT reuptake both at the dendrites and at the axon

Figure 7-12 Mechanism of action of selective serotonin reuptake inhibitors (SSRIs), part 2. When an SSRI is administered, it immediately blocks the serotonin reuptake pump or transporter (SERT) (see icon of an SSRI blocking SERT). However, this causes serotonin (5HT) to increase initially only in the somatodendritic area of the 5HT neuron (left) and not very much in the areas of the brain where the axons terminate (right). When 5HT levels rise in the somatodendritic area, this stimulates nearby $5HT_{1A}$ autoreceptors.

depressed state, the monoamine hypothesis of depression states that serotonin may be deficient, both at presynaptic somatodendritic areas near the cell body (Figure 7-11, left) and in the synapse itself, near the axon terminal (Figure 7-11, right). The neurotransmitter receptor hypothesis proposes that monoamine receptors may be upregulated, as shown in Figure 7-11, representing the depressed state before treatment. Neuronal firing rates for this neuron may also be dysregulated in depression, contributing to regional abnormalities in information processing, and the development of specific symptoms, depending upon the region affected, as discussed in Chapter 6 and shown in Figure 6-38.

When an SSRI is given acutely, it is well known that serotonin (5HT) rises due to blockade of SERT. What is somewhat surprising, however, is that blocking the

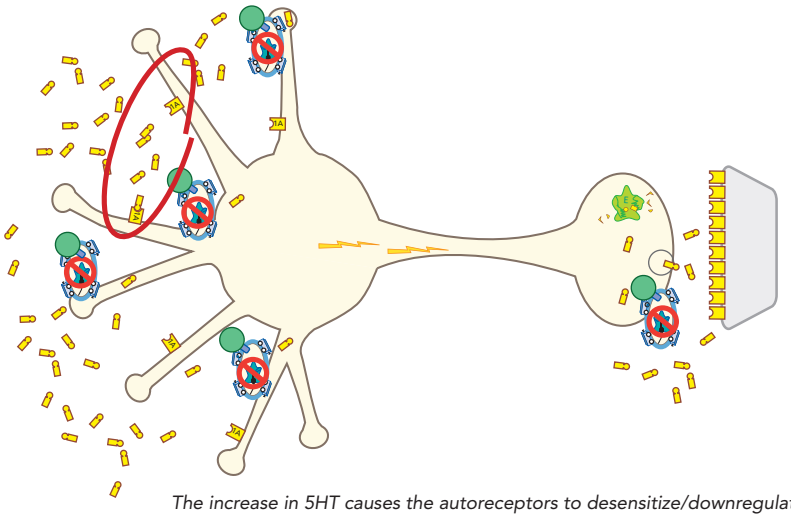


Figure 7-13 Mechanism of action of selective serotonin reuptake inhibitors (SSRIs), part 3. The consequence of increased serotonergic binding at somatodendritic $5HT_{1A}$ autoreceptors is that they desensitize or downregulate (red circle, compare to Figure 7-12).

presynaptic SERT does *not* immediately lead to a great deal of serotonin in many synapses. In fact, when SSRI treatment is initiated, 5HT rises immediately at the somatodendritic area located in the midbrain raphe (Figure 7-12, left) due to blockade of SERTs there, rather than in the areas of the brain where the axons terminate (Figure 7-12, right).

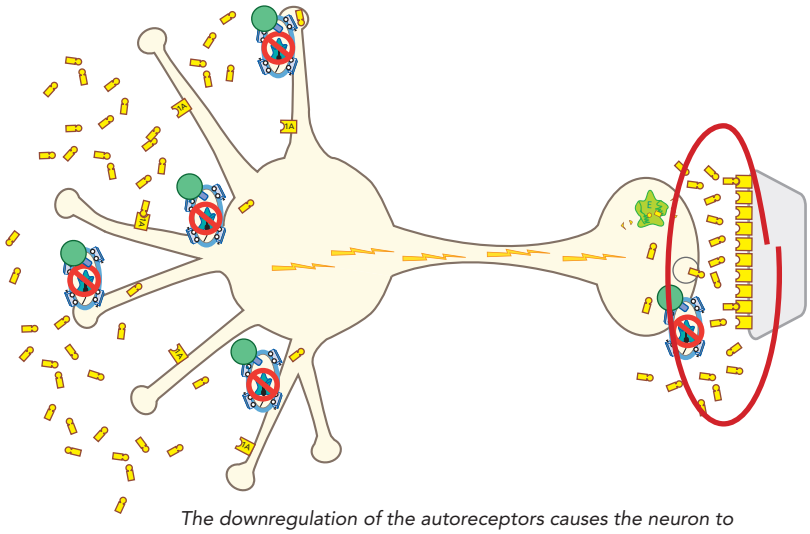
The somatodendritic area of the serotonin neuron is therefore where 5HT increases first (Figure 7-12, left). Serotonin receptors in this brain area have $5HT_{1A}$ pharmacology, as discussed in Chapter 4 and illustrated in Figure 4-39. When serotonin levels rise in the somatodendritic area, this stimulates nearby $5HT_{1A}$ autoreceptors (also on the left in Figure 7-12). These immediate pharmacological actions obviously cannot explain the delayed therapeutic actions of the SSRIs. However, these immediate actions may explain the immediate side effects that are caused by the SSRIs when treatment is initiated.

Over time, the increased 5HT levels acting at the somatodendritic $5HT_{1A}$ autoreceptors causes them to downregulate and become desensitized (Figure 7-13, left). This desensitization occurs because the increase in serotonin is recognized by these presynaptic $5HT_{1A}$ receptors, and this information is sent to the cell nucleus of the serotonin neuron. The genome's reaction to this information is to issue instructions that cause these same receptors to become desensitized over time. The time course of this desensitization correlates with the onset of therapeutic actions of the SSRIs (Figure 6-25).

Once the $5HT_{1A}$ somatodendritic autoreceptors are desensitized, 5HT can no longer effectively turn off its own release. Since 5HT is no longer inhibiting its own release, the serotonin neuron is therefore disinhibited (Figure 7-14). This results in a flurry of 5HT release from axons and an increase in neuronal impulse flow (shown as lightning in Figure 7-14 and release of serotonin from the axon terminal on the right). This is just another way of saying the serotonin release is "turned on" at the axon terminals. The serotonin that now pours out of the various projections of serotonin pathways in the brain is what theoretically mediates the various therapeutic actions of the SSRIs.

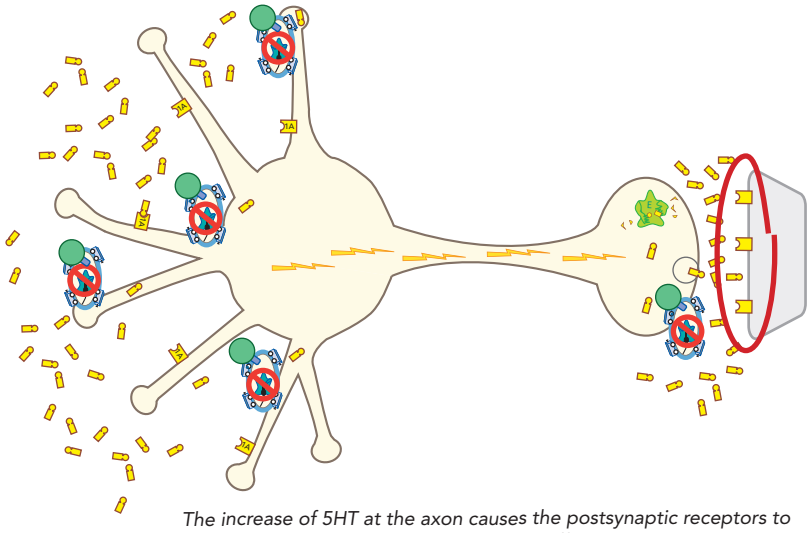
While the presynaptic somatodendritic $5HT_{1A}$ autoreceptors are desensitizing (Figure 7-13), 5HT is building up in synapses (Figure 7-14), and causes the postsynaptic 5HT receptors to desensitize as well (Figure 7-15, right). These various postsynaptic 5HT receptors in turn send information to the cell nucleus of the *postsynaptic* neuron that serotonin is targeting (on the far right of Figure 7-15). The reaction of the genome in the postsynaptic neuron is also to issue instructions to downregulate or desensitize some of these receptors as well. The time course of this desensitization correlates with the onset of tolerance to the side effects of the SSRIs (Figure 7-15).

This theory thus suggests a pharmacological cascading mechanism whereby the SSRIs exert their therapeutic actions: namely, powerful but delayed disinhibition of serotonin release in key pathways throughout the brain. Furthermore, side effects are hypothetically caused by the acute actions of serotonin at undesirable receptors in



The downregulation of the autoreceptors causes the neuron to release more 5HT at the axon

Figure 7-14 Mechanism of action of selective serotonin reuptake inhibitors (SSRIs), part 4. Once the somatodendritic $5HT_{1A}$ receptors downregulate, there is no longer inhibition of impulse flow in the serotonin (5HT) neuron. Thus, neuronal impulse flow is turned on. The consequence of this is release of 5HT in the axon terminal (red circle). This increase is delayed compared with the increase of 5HT in the somatodendritic areas of the 5HT neuron; the delay is the result of the time it takes for somatodendritic 5HT to downregulate the $5HT_{1A}$ autoreceptors and turn on neuronal impulse flow in the 5HT neuron. This delay may explain why SSRIs do not relieve depression immediately. It is also the reason why the mechanism of action of SSRIs may be linked to increasing neuronal impulse flow in 5HT neurons, with 5HT levels increasing at axon terminals before an SSRI can exert its therapeutic effects.



The increase of 5HT at the axon causes the postsynaptic receptors to desensitize/downregulate, reducing side effects

Figure 7-15 Mechanism of action of selective serotonin reuptake inhibitors (SSRIs), part 5. Finally, once the SSRIs have blocked the reuptake pump (or serotonin transporter [SERT]), increased somatodendritic serotonin (5HT), desensitized somatodendritic $5HT_{1A}$ autoreceptors, turned on neuronal impulse flow, and increased release of 5HT from axon terminals, the final step may be the desensitization of postsynaptic 5HT receptors (red circle). This desensitization may mediate the reduction of side effects of SSRIs as tolerance develops.

undesirable pathways. Finally, side effects may attenuate over time by desensitization of the very receptors that mediate them.

Unique Properties of Each SSRI: The Not-So-Selective Serotonin Reuptake Inhibitors

Although the six SSRIs clearly share the same mechanism of action, individual patients often react very differently to one SSRI versus another. This is not generally observed in large clinical trials where mean group differences between two SSRIs either in efficacy or side effects are very difficult to document. Rather, such differences are seen by prescribers treating patients one at a time, with some patients experiencing a therapeutic response to one SSRI and not another, and other patients tolerating one SSRI and not another.

If blockade of SERT explains the shared clinical and pharmacological actions of SSRIs, what explains their differences? Although there is no generally accepted explanation that accounts for the commonly observed clinical phenomena of different efficacy and tolerability of various SSRIs in individual patients, it makes sense to consider those unique pharmacological characteristics of the six SSRIs that are not shared with each other as candidates to explain the broad range of individual patient reactions to different SSRIs (Figures 7-16 through 7-21). Each SSRI has secondary pharmacological actions other than SERT blockade, and no two SSRIs have identical secondary pharmacological characteristics. Whether these secondary binding profiles can account for the differences in efficacy and tolerability in individual patients remains to be proven. However, it does lead to provocative hypothesis generation and gives a rational basis for psychopharmacologists trying more than one of these agents rather than thinking "they are all the same." Sometimes only an empiric trial of different SSRIs will lead to the best match of drug to an individual patient.

Fluoxetine: An SSRI with $5HT_{2C}$ Antagonist Properties

In addition to serotonin reuptake inhibition, fluoxetine also has $5HT_{2C}$ antagonist actions that may explain many of its unique clinical properties (Figure 7-16). $5HT_{2C}$ antagonism may contribute to its antidepressant actions and also to its efficacy in other disorders, especially in eating disorders. Other drugs for unipolar depression with $5HT_{2C}$ antagonist properties include trazodone, mirtazapine, agomelatine, and some tricyclic antidepressants, and these will be described below. Finally, two serotonin 2A/dopamine 2 antagonists, quetiapine (Figure 5-45) and olanzapine (Figure 5-44), also have potent $5HT_{2C}$ antagonist properties. Both agents are used to treat psychosis (see Chapter 5) but are also approved for augmenting other drugs for unipolar depression, treatment-resistant unipolar depression, and bipolar depression. Blocking serotonin action at $5HT_{2C}$ receptors disinhibits (i.e., enhances) release of both norepinephrine and dopamine, actions theoretically beneficial for the treatment of depression (see Chapter 6 and Figure 6-24B and also the discussion below on agomelatine).

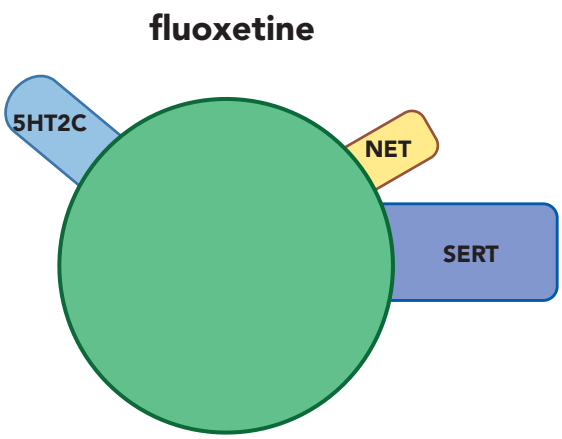


Figure 7-16 Fluoxetine. In addition to serotonin reuptake inhibition, fluoxetine has norepinephrine reuptake inhibition (NRI) and serotonin 2C antagonist actions ($5HT_{2C}$). $5HT_{2C}$ antagonism can lead to disinhibition of norepinephrine and dopamine; this action may be responsible for fluoxetine's activating effects. NRI may be clinically relevant only at very high doses.

The good news about $5HT_{2C}$ antagonism may be that it is generally activating, and the reason why many patients, even from the first dose, detect an energizing and fatigue-reducing effect of fluoxetine, with improvement in concentration and attention as well. This mechanism is perhaps best matched to depressed patients with reduced positive affect (Figure 6-41), hypersomnia, psychomotor retardation, apathy, and fatigue. Fluoxetine is also approved in some countries in combination with olanzapine for treatment-resistant unipolar depression and for bipolar depression. Since olanzapine also has $5HT_{2C}$ antagonist actions (Figure 5-44), it may be that adding the $5HT_{2C}$ antagonist actions of olanzapine to those of fluoxetine could theoretically lead to further enhanced dopamine and norepinephrine release in the cortex to mediate the antidepressant actions of this combination. $5HT_{2C}$ antagonism may also contribute to the anti-bulimia effect of higher doses of fluoxetine, the only SSRI approved for the treatment of this eating disorder. The bad news could be that $5HT_{2C}$ antagonist actions of fluoxetine may contribute to this agent being sometimes less well matched to patients with agitation, insomnia, and anxiety, who may experience unwanted activation and even a panic attack if given an agent that further activates them.

Fluoxetine also has weak norepinephrine reuptake blocking properties (Figure 7-16), which may become clinically relevant at very high doses. Fluoxetine has a long half-life (2–3 days), and its active metabolite an even longer half-life (2 weeks). The long half-life is advantageous in that it seems to reduce the withdrawal reactions that are characteristic of sudden discontinuation of some SSRIs, but it also means that it takes a long time to clear the drug and its active

metabolite after discontinuing fluoxetine, and prior to starting other agents such as a monoamine oxidase (MAO) inhibitor. Fluoxetine is not only available as a once-daily formulation, but also as a once-weekly oral dosage formulation.

Sertraline: An SSRI with Dopamine Transporter (DAT) Inhibition and σ_1 Binding

This SSRI has two candidate mechanisms that distinguish it: dopamine transporter (DAT) inhibition and σ_1 receptor binding (Figure 7-17). The DAT inhibitory actions are controversial since they are weaker than the SERT inhibitory actions, thus leading some experts to suggest that there is not sufficient DAT occupancy by sertraline to be clinically relevant. However, as will be discussed later in the section on norepinephrine–dopamine reuptake inhibitors (NDRIs), it is not clear that high degrees of DAT occupancy are necessary or even desirable in order to contribute to antidepressant actions. That is, perhaps only a small amount of DAT inhibition is sufficient to cause improvement in energy, motivation, and concentration, especially when added to another action such as SERT inhibition. In fact, high-impact DAT inhibition is the property of reinforcing stimulants, including cocaine and methamphetamine, and would not generally be desired in a drug for depression (see discussion of DAT inhibitors in Chapter 11 on ADHD and Chapter 13 on impulsivity, compulsivity, and addiction).

Anecdotally, clinicians have observed the mild and desirable activating actions of sertraline in some patients with "atypical depression," improving symptoms of hypersomnia, low energy, and mood reactivity. A favorite combination of some clinicians for depressed patients is to add bupropion to sertraline (i.e., Wellbutrin to Zoloft, sometimes called "Well-oft"), adding together the weak DAT inhibitory properties of each agent. Clinicians have also observed the overactivation of some patients with panic disorder by sertraline, thus requiring slower dose titration in some patients with anxiety symptoms. All of these actions of sertraline are consistent with weak DAT inhibitory actions contributing to its clinical portfolio of actions.

The σ_1 actions of sertraline are not well understood, but might contribute to its anxiolytic effects and especially to its effects in psychotic and delusional depression, where sertraline may have advantageous therapeutic effects compared to some other SSRIs.

Paroxetine: An SSRI with Muscarinic Anticholinergic and Norepinephrine Transporter (NET) Inhibitory Actions

This SSRI tends to be more calming, even sedating, early in treatment compared to the more activating actions of both fluoxetine and sertraline discussed above. Perhaps the mild anticholinergic actions of paroxetine contribute to this clinical profile (Figure 7-18). Paroxetine also has weak norepinephrine transporter (NET) inhibitory properties, which could contribute to its efficacy in depression, especially at high doses. The advantages of

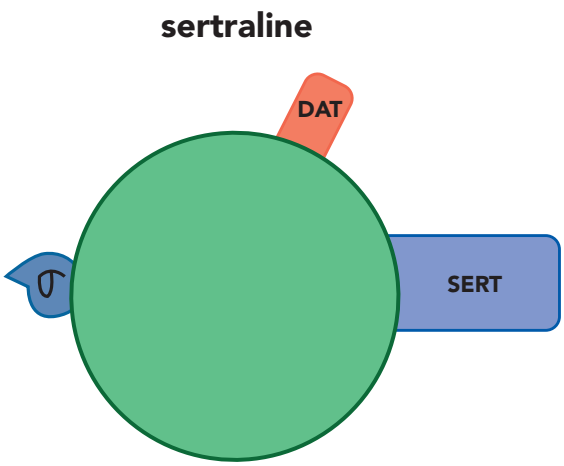


Figure 7-17 Sertraline. Sertraline has dopamine transporter (DAT) inhibition and σ_1 receptor binding in addition to serotonin reuptake inhibition (SRI). The clinical relevance of sertraline's DAT inhibition is unknown, although it may improve energy, motivation, and concentration. Its sigma properties may contribute to anxiolytic actions and may also be helpful in patients with psychotic depression.

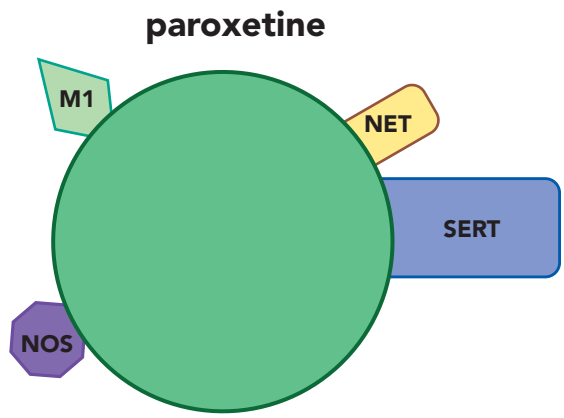


Figure 7-18 Paroxetine. In addition to serotonin reuptake inhibition, paroxetine has mild anticholinergic actions (M_1), which can be calming or possibly sedating; weak norepinephrine transporter (NET) inhibition, which may contribute to further antidepressant actions; and inhibition of the enzyme nitric oxide synthase (NOS), which may contribute to sexual dysfunction.

dual serotonin plus norepinephrine reuptake inhibiting properties, or SNRI actions, are discussed below in the section on SNRIs. It is possible that weak to moderate NET inhibition of paroxetine may contribute importantly to its antidepressant actions.

Paroxetine also inhibits the enzyme nitric oxide synthase, which could theoretically contribute to sexual dysfunction, especially in men. Paroxetine is also notorious for causing withdrawal reactions upon sudden discontinuation, with symptoms such as akathisia, restlessness, gastrointestinal symptoms, dizziness, and tingling, especially when suddenly discontinued from long-term high-dose treatment. This is possibly due not only to SERT inhibition properties, since all SSRIs can cause discontinuation reactions, but also to anticholinergic rebound when paroxetine is rapidly discontinued. Paroxetine is available in a controlled-release formulation, which may mitigate some of its side effects, including discontinuation reactions.

Fluvoxamine: An SSRI with σ_1 Receptor Binding Properties

This SSRI was among the first to be launched for the treatment of depression worldwide, but was never officially approved for depression in the US, so it has been considered more of an agent for the treatment of OCD in the US. Like sertraline, fluvoxamine binds at σ_1 sites, but this action is more potent for fluvoxamine than for sertraline (Figure 7-19). The physiological function of σ_1 sites is still a mystery, and thus sometimes called the "sigma enigma," but has been linked both to anxiety and psychosis. Preclinical studies suggest that fluvoxamine may be an agonist at σ_1 receptors, and that this property may contribute an additional pharmacological action to help explain fluvoxamine's well-known anxiolytic properties. Fluvoxamine also has shown therapeutic activity in both psychotic and delusional depression, where it, like sertraline, may have advantages over other SSRIs.

Fluvoxamine is now available as a controlled-release formulation, which makes once-daily administration possible, unlike immediate-release fluvoxamine, whose shorter half-life often requires twice-daily administration. In addition, recent trials of controlled-release fluvoxamine show impressive remission rates in both OCD and social anxiety disorder, as well as possibly less peak-dose sedation.

Citalopram: An SSRI with a "Good" and a "Bad" Enantiomer

This SSRI is comprised of two enantiomers, R and S, which are mirror images of each other (Figure 7-20). The mixture of these enantiomers is known as racemic citalopram, or commonly just as citalopram, and has mild antihistamine properties that reside in the R enantiomer. Racemic citalopram is generally one of the better-tolerated SSRIs, and has favorable findings in the treatment of depression in the elderly, but has a somewhat inconsistent therapeutic action at the lowest dose, often requiring dose increase to optimize treatment.

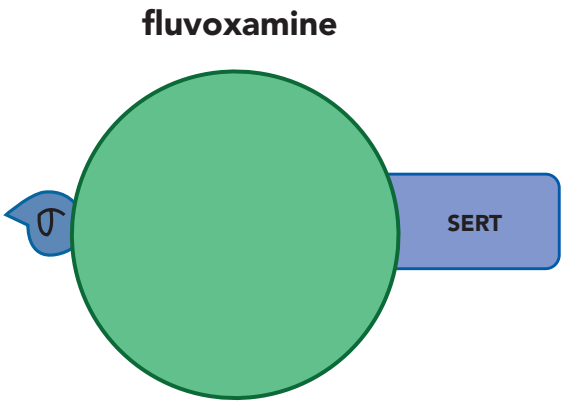


Figure 7-19 Fluvoxamine. Fluvoxamine's secondary properties include actions at σ_1 receptors, which may be anxiolytic as well as beneficial for psychotic depression.

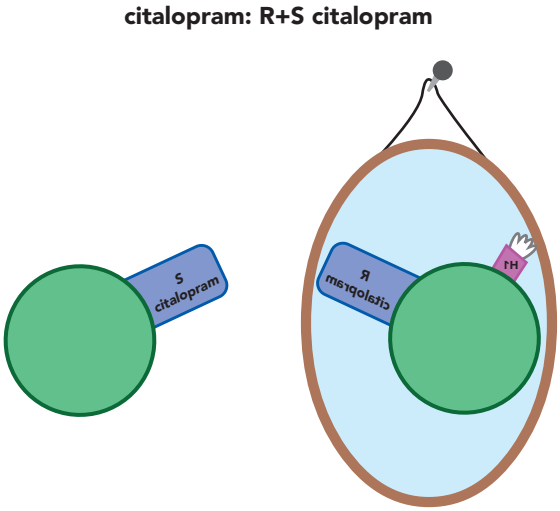


Figure 7-20 Citalopram. Citalopram consists of two enantiomers, R and S. Some pharmacological evidence suggests that the R enantiomer may be pharmacologically active at SERTs in a manner that does not inhibit SERTs but actually interferes with the ability of the active S enantiomer to inhibit SERTs. The R enantiomer also has weak antihistamine properties.

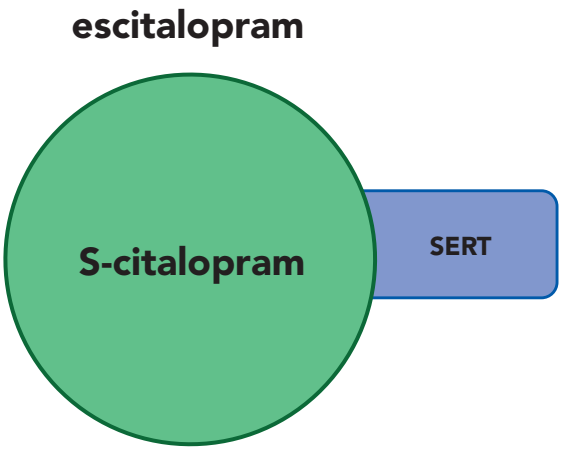


Figure 7-21 Escitalopram The R and S enantiomers of citalopram are mirror images of each other but have slightly different clinical properties. The R enantiomer is the one with weak antihistamine properties; the R and S enantiomers may also differ in their effects at the serotonin transporter. The S enantiomer of citalopram has been developed and marketed as escitalopram.

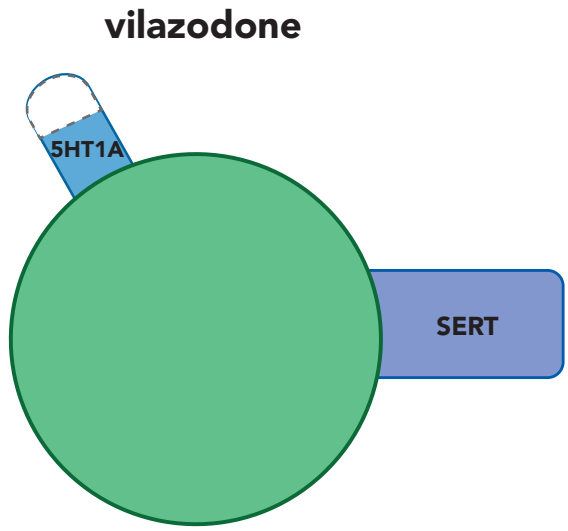


Figure 7-22 Vilazodone. Vilazodone is a partial agonist at the serotonin 1A receptor and also inhibits serotonin reuptake; thus, it is referred to as a serotonin partial agonist reuptake inhibitor (SPARI).

However, dose increase is limited due to the potential of QTc prolongation at higher doses. These findings all suggest that it is not favorable for citalopram to contain the R enantiomer. In fact, some pharmacological evidence suggests that the R enantiomer may be pharmacologically active at SERTs in a manner that does not inhibit SERTs but actually interferes with the ability of the active S enantiomer to inhibit SERTs. This could lead to reduced SERT inhibition, reduced synaptic 5HT, and possibly reduced net therapeutic actions, especially at low doses.

Escitalopram: The Quintessential SSRI

The solution to improving the properties of racemic citalopram is to remove the unwanted R enantiomer. The resulting drug is known as escitalopram, as it is comprised of only the pure active S enantiomer (Figure 7-21). This maneuver appears to remove the antihistaminic properties and there are no higher dose restrictions to avoid QTc prolongation. In addition, removal of the potentially interfering R enantiomer makes the lowest dose of escitalopram more predictably efficacious. Escitalopram is therefore the SSRI for which pure SERT inhibition is most likely to explain almost all of its pharmacological actions. Escitalopram is considered perhaps the best-tolerated SSRI, with the fewest cytochrome P450 (CYP450)-mediated drug interactions.

Serotonin Partial Agonist Reuptake Inhibitors (SPARIs)

Vilazodone combines SERT inhibition with $5HT_{1A}$ partial agonism. For this reason, vilazodone is called a SPARI (serotonin partial agonist reuptake inhibitor) (Figure 7-22). The combination of serotonin reuptake inhibition with $5HT_{1A}$ partial agonism has long been known by clinicians to enhance the unipolar antidepressant properties and tolerability of SSRIs/SNRIs in some patients (e.g., adding the $5HT_{1A}$ partial agonist buspirone [Chapter 8 on anxiety]; the serotonin 1A/dopamine 2 partial agonists aripiprazole, brexpiprazole, or cariprazine [Chapter 5]; or the serotonin/dopamine antagonist with $5HT_{1A}$ partial agonist properties, quetiapine). With vilazodone this combination mechanism is achieved with only one drug, avoiding drug interactions and various off-target receptor actions that may be undesired with the other drugs listed.

In animal models, adding $5HT_{1A}$ partial agonism to SSRIs causes more immediate and robust elevations of brain 5HT levels than SSRIs do alone. This is thought to be due to the fact that $5HT_{1A}$ partial agonists are a type of "artificial serotonin," selective especially for presynaptic somatodendritic $5HT_{1A}$ autoreceptors, and that $5HT_{1A}$ partial agonist action occurs immediately after the drug is given (Figure 7-23). Thus, $5HT_{1A}$ immediate partial agonist actions are theoretically additive or synergistic with simultaneous SERT inhibition (Figure 7-23) since this leads to faster and more robust actions at $5HT_{1A}$ somatodendritic autoreceptors (Figure 7-24) than with SERT inhibition alone (Figure 7-12), including their downregulation (Figure 7-25). This hypothetically

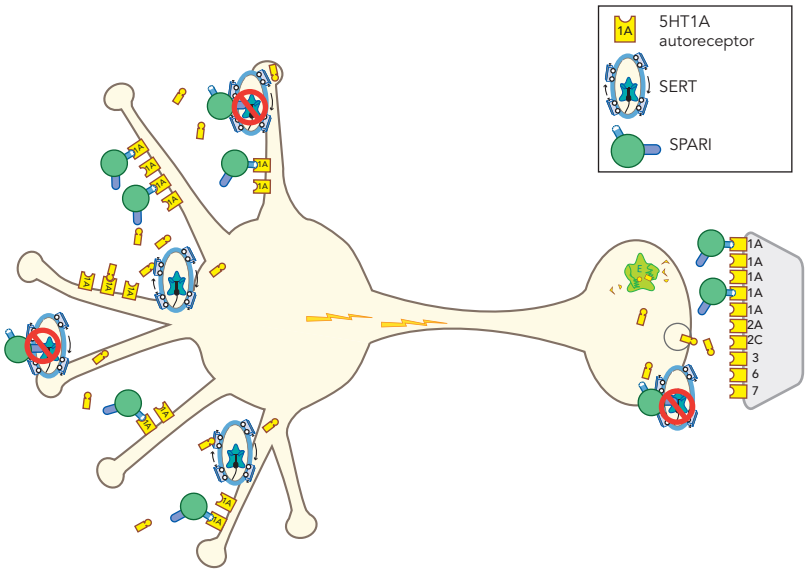


Figure 7-23 Mechanism of action of serotonin partial agonist reuptake inhibitors (SPARIs), part 1. When a SPARI is administered, about half of serotonin transporters (SERTs) and half of serotonin 1A ($5HT_{1A}$) receptors are occupied immediately.

SPARI action: first, about half of SERTs and half of 5HT1A receptors are occupied immediately

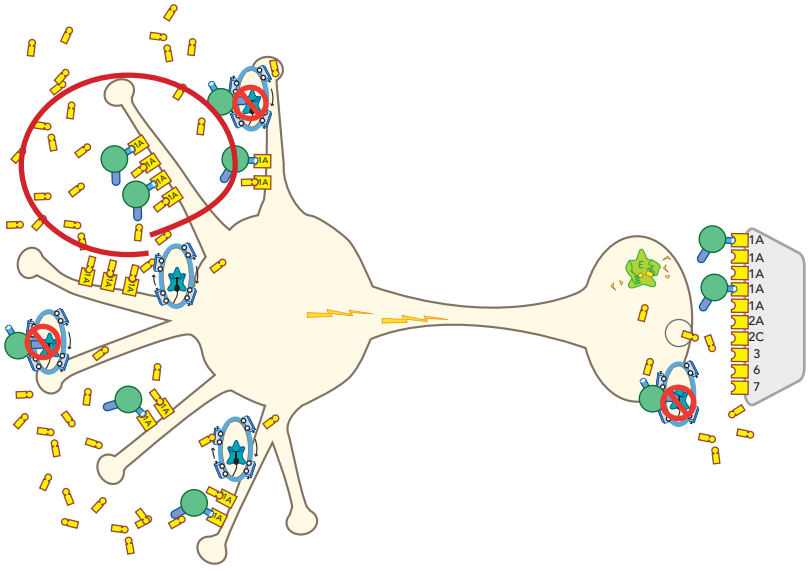


Figure 7-24 Mechanism of action of serotonin partial agonist reuptake inhibitors (SPARIs), part 2. Blockade of the serotonin transporter (SERT) causes serotonin to increase initially in the somatodendritic area of the serotonin neuron (left).

SPARI action: second, 5HT increases at 5HT1A somatodendritic receptors on the left

causes faster and more robust elevation of synaptic 5HT (Figure 7-26) than possible with SSRIs alone (Figure 7-14). In addition, $5HT_{1A}$ partial agonism with vilazodone's SPARI mechanism occurs immediately at postsynaptic $5HT_{1A}$ receptors (Figure 7-26), with actions at these receptors that are thus faster and with a different type of stimulation compared to the delayed full agonist actions of serotonin itself when increased by SERT inhibition alone (Figure 7-14). The downstream actions of $5HT_{1A}$ receptors that lead to enhanced dopamine release (Figure 7-27) may be hypothetically responsible for enhanced antidepressant and precognitive effects (see Chapter 5 and Figure 5-22). The addition of $5HT_{1A}$ partial agonist actions to SERT inhibition may also account for the observed reduction

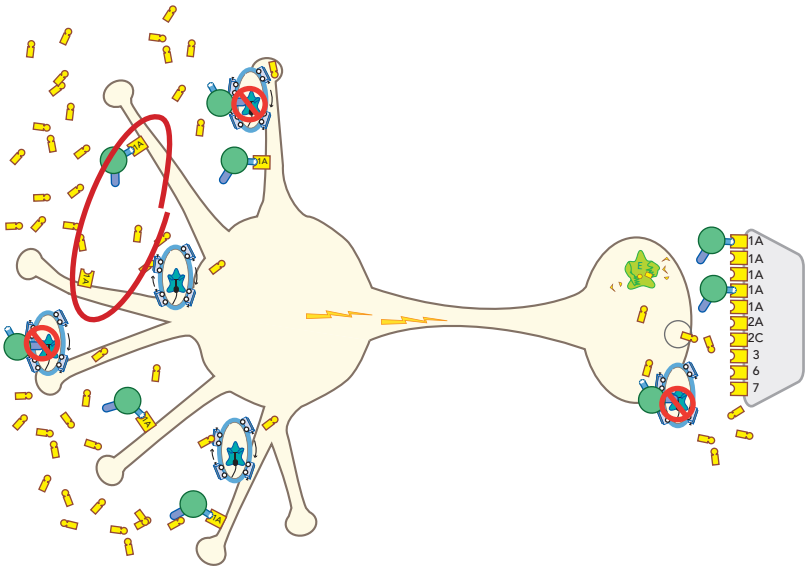


Figure 7-25 Mechanism of action of serotonin partial agonist reuptake inhibitors (SPARIs), part 3. The consequence of serotonin increasing in the somatodendritic area of the serotonin (5HT) neuron is that the somatodendritic $5HT_{1A}$ autoreceptors desensitize or downregulate (red circle).

SPARI action: third, 5HT actions on the left cause 5HT1A autoreceptors to desensitize/downregulate

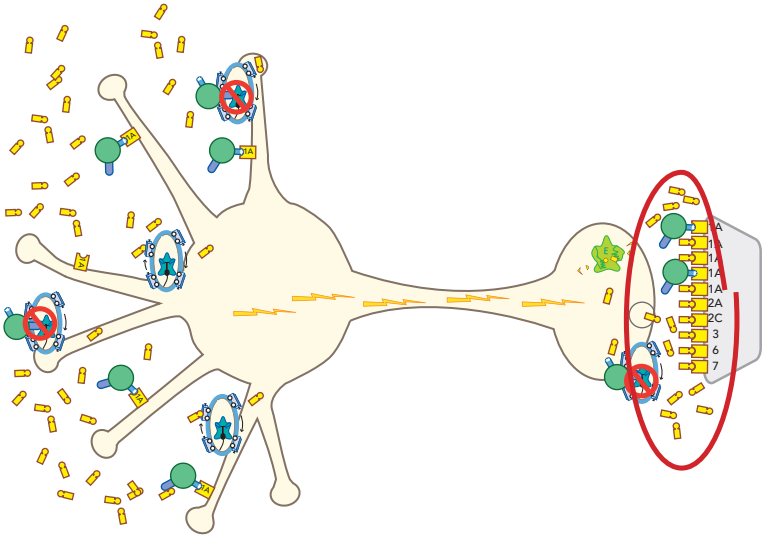


Figure 7-26 Mechanism of action of serotonin partial agonist reuptake inhibitors (SPARIs), part 4. Once the somatodendritic receptors downregulate, there is no longer inhibition of impulse flow in the serotonin (5HT) neuron. Thus, neuronal impulse flow is turned on. The consequence of this is release of 5HT in the axon terminal (red circle).

SPARI action: fourth, neuronal firing and serotonin release are disinhibited at the synapse on the right

in sexual dysfunction and the relative lack of weight gain seen in patients treated with vilazodone.

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

SNRIs combine the robust SERT inhibition of the SSRIs with various degrees of inhibition of the norepinephrine transporter (NET) (Figures 7-28 through 7-32).

Theoretically, there should be some therapeutic advantage of adding NET inhibition to SERT inhibition, since one mechanism may add efficacy to the other mechanism by widening the reach of these drugs to both the serotonin and the norepinephrine monoamine neurotransmitter systems throughout more brain regions (see Chapter 6 and Figures 6-38 and 6-40). A practical indication that

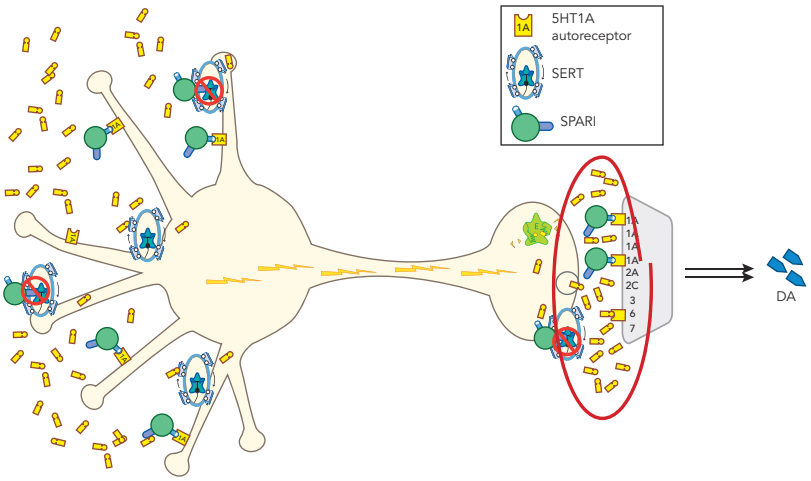


Figure 7-27 Mechanism of action of serotonin partial agonist reuptake inhibitors (SPARIs), part 5. Finally, once the SPARIs have blocked the serotonin transporter (SERT), increased somatodendritic serotonin (5HT), desensitized somatodendritic $5HT_{1A}$ autoreceptors, turned on neuronal impulse flow, and increased release of 5HT from axon terminals, the final step (shown here, red circle) may be the desensitization of postsynaptic 5HT receptors. This timeframe correlates with antidepressant action. In addition, the addition of $5HT_{1A}$ partial agonism may lead to downstream enhancement of dopamine (DA) release, which may mitigate sexual dysfunction.

SPARI action: finally, antidepressant actions begin, and downstream enhancement of DA release may mitigate sexual dysfunction

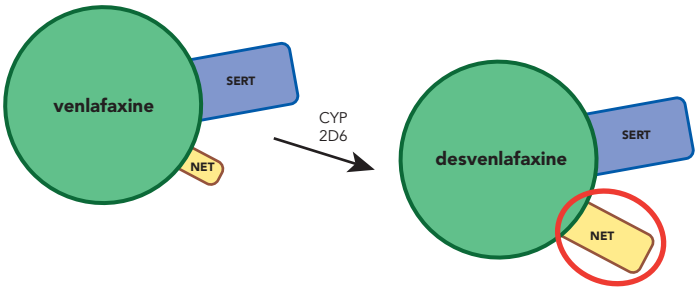


Figure 7-28 Venlafaxine and desvenlafaxine. Venlafaxine inhibits both the serotonin transporter (SERT) and the norepinephrine transporter (NET), thus combining two therapeutic mechanisms in one agent. Venlafaxine's serotonergic actions are present at low doses, while its noradrenergic actions are progressively enhanced as dose increases. Venlafaxine is converted to its active metabolite, desvenlafaxine, by CYP450 2D6. Like venlafaxine, desvenlafaxine inhibits reuptake of serotonin and norepinephrine, but its NET actions are greater relative to its SERT actions compared to venlafaxine. Venlafaxine administration usually results in plasma levels of venlafaxine that are about half those of desvenlafaxine; however, this can vary depending on genetic polymorphisms of CYP450 2D6 and if patients are taking drugs that are inhibitors or inducers of CYP450 2D6. Thus, the degree of NET inhibition with venlafaxine administration may be unpredictable. Desvenlafaxine has now been developed as a separate drug. It has relatively greater norepinephrine reuptake inhibition than venlafaxine but is still more potent at the SERT.

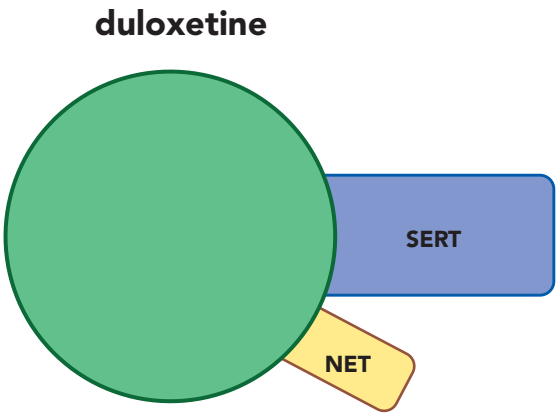


Figure 7-29 Duloxetine. Duloxetine inhibits both the serotonin transporter (SERT) and the norepinephrine transporter (NET). Its noradrenergic actions may contribute to efficacy for painful physical symptoms.

dual monoamine mechanisms may lead to more efficacy is the finding that the SNRI venlafaxine frequently seems to have greater unipolar antidepressant efficacy as the dose increases, theoretically due to recruiting more and more NET inhibition as the dose is raised (i.e., the noradrenergic "boost"). Clinicians and experts currently debate whether remission rates are higher with SNRIs compared to SSRIs or whether SNRIs are more helpful in depressed patients who fail to respond to SSRIs than are other options. One area where SNRIs have established clear efficacy but SSRIs have not is in the treatment of pain.

NET Inhibition Increases Dopamine in the Prefrontal Cortex

Although SNRIs are commonly called "dual action" serotonin–norepinephrine agents, they actually have

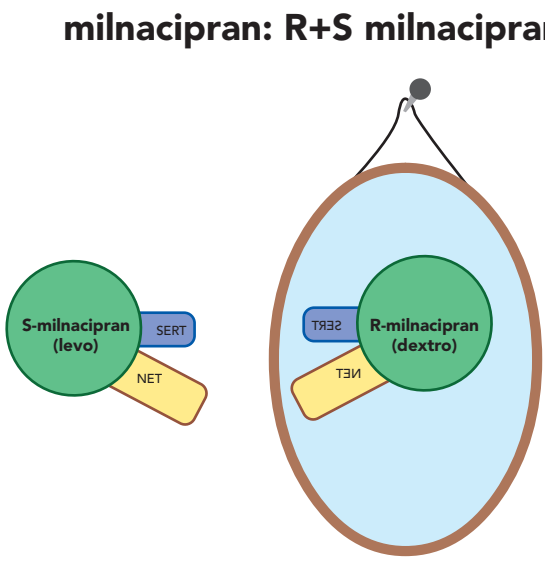


Figure 7-30 Milnacipran. Milnacipran inhibits both the serotonin transporter (SERT) and the norepinephrine transporter (NET) but is a more potent inhibitor of NET than SERT. Its robust NET inhibition may contribute to efficacy for painful physical symptoms. Milnacipran consists of two enantiomers: S (levo) and R (dextro), with S as the more active enantiomer.

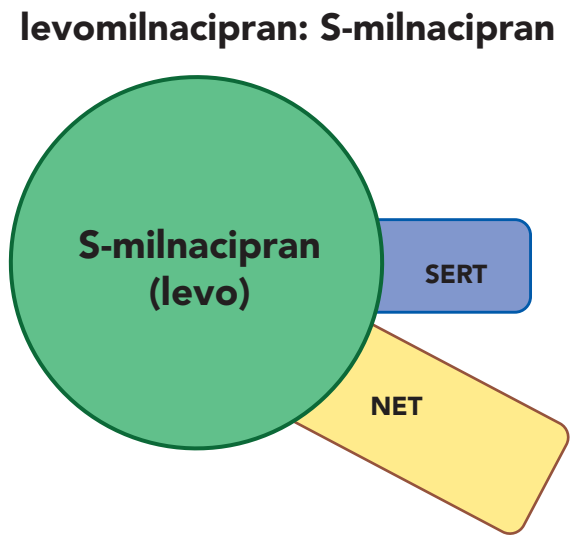


Figure 7-31 Levomilnacipran. The R and S enantiomers of milnacipran are mirror images of each other; the S enantiomer is the active enantiomer. The S enantiomer of milnacipran has been developed and marketed as levomilnacipran.

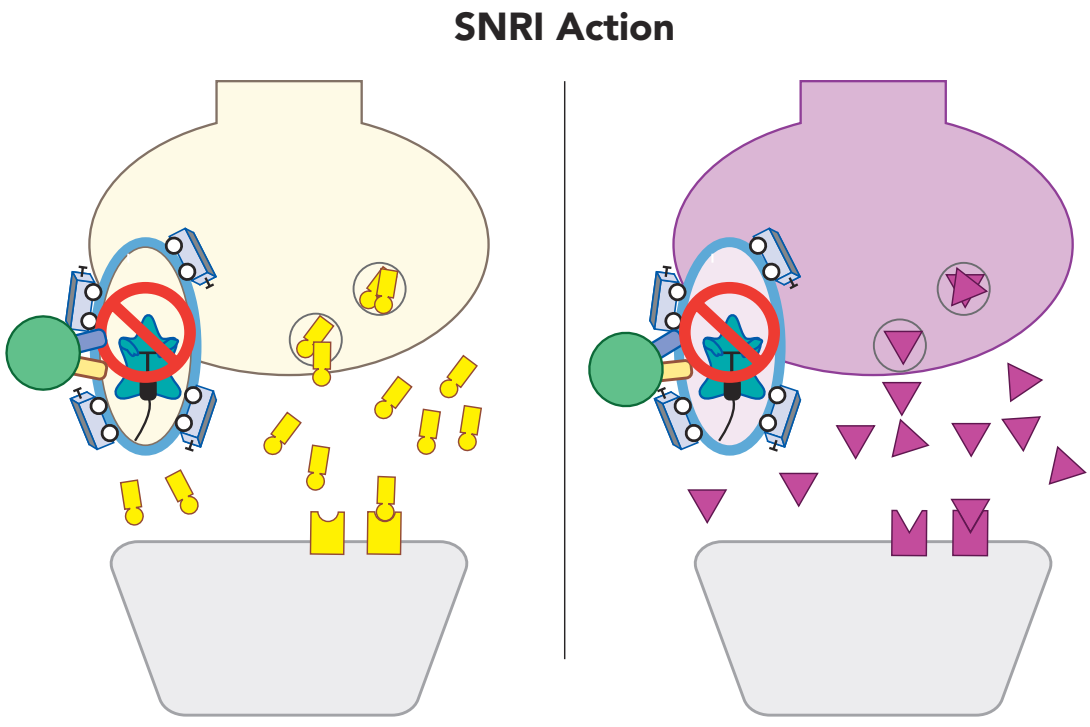


Figure 7-32 SNRI actions. The acute dual actions of the serotonin–norepinephrine reuptake inhibitors (SNRIs) are shown. Both the serotonin reuptake inhibitor portion of the SNRI molecule (left panel) and the norepinephrine reuptake inhibitor portion of the SNRI molecule (right panel) are inserted into their respective reuptake pumps. Consequently, both pumps are blocked, and synaptic serotonin and norepinephrine are increased.

a third action on dopamine (DA) in the prefrontal cortex, but not elsewhere in the brain. Thus, they are not "full" triple action agents since they do not inhibit the DA transporter (DAT) except at doses beyond the clinical range, but SNRIs can perhaps be considered to have "two-and-a-half actions," and not just two. That is, SNRIs not only boost serotonin and norepinephrine (NE) throughout the brain (Figure 7-32), but they also boost DA specifically in the prefrontal cortex (Figure 7-33). This third mechanism of boosting DA in an important area of the brain associated with several symptoms of depression should add another theoretical advantage to the pharmacology of SNRIs and to their efficacy in the treatment of major depression.

How does NET inhibition boost DA in the prefrontal cortex? The answer is illustrated in Figure 7-33. In the prefrontal cortex, SERTs and NETs are present in abundance on serotonin and NE nerve terminals, respectively, but there are very few DATs on DA nerve terminals in this part of the brain (Figure 7-33, see also Chapter 4 and Figure 4-9A). The consequence of this lack of DATs in the prefrontal cortex is that once DA is released there, it is free to cruise away from the synapse (Figure 7-33A). The diffusion radius of DA is thus wider (Figure 7-33A) than the diffusion radius of NE in the prefrontal cortex (Figure 7-33B) since there are NETs at the NE synapse (Figure 7-33B) but no DAT at the DA synapse (Figure 7-33A). This arrangement may enhance the regulatory importance of DA in the prefrontal cortex functioning, since DA in this part of the brain can interact with DA receptors not only at its own synapse, but at a distance, perhaps enhancing the ability of DA to regulate cognition in an entire area within its diffusion radius, not just at a single synapse.

Dopamine action is therefore not terminated by DAT in the prefrontal cortex to any significant extent, but by two other mechanisms. That is, DA diffuses away from the DA synapse until it either encounters the enzyme COMT (catechol-*O*-methyltransferase), which degrades it (see Chapter 4 and Figure 4-3) or until it encounters a NET, which transports it into the NE neuron (Figure 7-33A). NETs in fact have a greater affinity for DA than they do for NE, so they will pump DA as well as NE into NE nerve terminals, halting the action of either.

What is interesting is to see what happens when there is NET inhibition in the prefrontal cortex. As expected, NET inhibition enhances synaptic NE levels and increases the diffusion radius of NE (Figure 7-33B). Somewhat surprising may be that NET inhibition also enhances DA levels and increases DA's diffusion radius (Figure

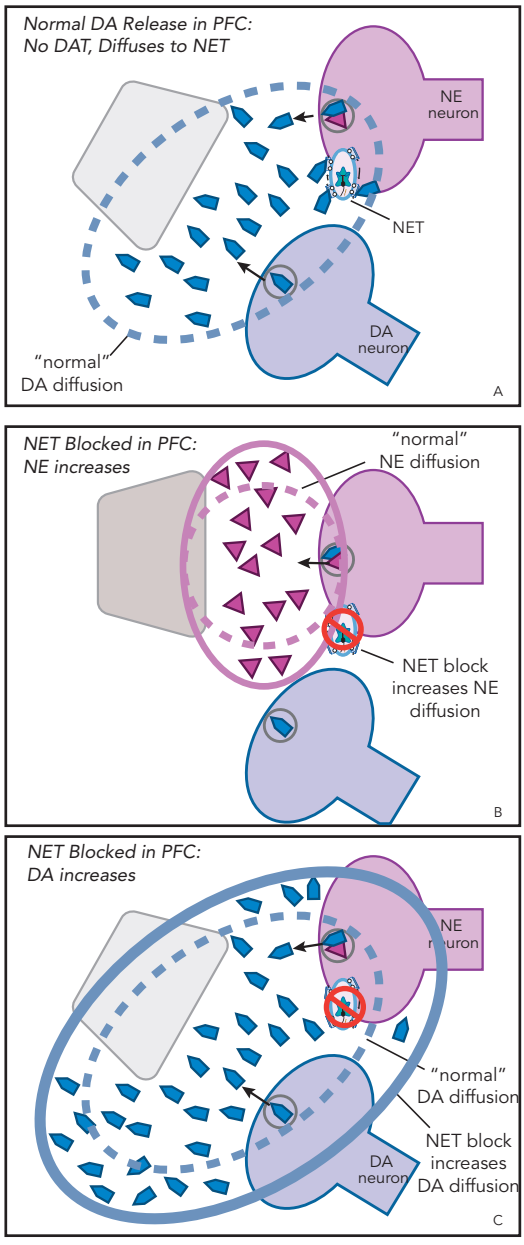


Figure 7-33 Norepinephrine transporter blockade and dopamine in the prefrontal cortex. (A) Although there are abundant serotonin transporters (SERTs) and norepinephrine transporters (NETs) in the prefrontal cortex (PFC), there are very few dopamine transporters (DATs). This means that dopamine (DA) can diffuse away from the synapse and therefore exert its actions within a larger radius. Dopamine's actions are terminated at norepinephrine (NE) axon terminals, because DA is taken up by NETs. (B) NET blockade in the PFC leads to an increase in synaptic NE, thus increasing NE's diffusion radius. (C) Because NET takes up DA as well as NE, NET blockade also leads to an increase in synaptic DA, further increasing its diffusion radius. Thus, agents that block NET increase NE throughout the brain and both NE and DA in the PFC.

7-33C). The bottom line is that NET inhibition increases both NE and DA in the prefrontal cortex. Thus, SNRIs have two-and-a-half mechanisms: boosting serotonin throughout the brain, boosting NE throughout the brain, and boosting DA in the prefrontal cortex (but not in other DA projection areas).

Venlafaxine

Depending upon the dose, venlafaxine has different degrees of inhibition of serotonin reuptake (most potent and robust even at low doses) versus NE reuptake (moderate potency and robust only at higher doses) (Figure 7-28). However, there are no significant actions on other receptors. It remains controversial whether venlafaxine or other SNRIs have greater efficacy in unipolar major depression than SSRIs, either in terms of enhanced remission rates, more robust sustained remission over long-term treatment, or greater efficacy for treatment-resistant unipolar depression, but this does seem plausible given two mechanisms and the boosting of two monoamines. Venlafaxine is approved and widely used for several anxiety disorders as well. Adding NET inhibition likely accounts for two side effects of venlafaxine in some patients: sweating and elevated blood pressure.

Venlafaxine is available as an extended-release formulation, which not only allows for once-daily administration but also significantly reduces side effects, especially nausea. In contrast to several other psychotropic drugs available in controlled-release formulations, extended-release venlafaxine is a considerable improvement over the immediate-release formulation, which has fallen into little or no use because of unacceptable nausea and other side effects, especially when immediate-release venlafaxine is started or when it is stopped. However, venlafaxine even in controlled-release formulation can cause withdrawal reactions, sometimes quite bothersome, especially after sudden discontinuation from high-dose long-term treatment. Nevertheless, the controlled-release formulation is highly preferred because of enhanced tolerability.

Desvenlafaxine

Venlafaxine is a substrate for CYP450 2D6, which converts it to an active metabolite desvenlafaxine (Figure 7-28). Desvenlafaxine has greater NET inhibition relative to SERT inhibition compared to venlafaxine. Normally, after venlafaxine administration, the plasma levels of venlafaxine are about half of those for desvenlafaxine. However, this is highly variable, depending upon whether the patient is taking another drug that is a CYP450 2D6 inhibitor, which shifts the plasma levels towards more venlafaxine and less desvenlafaxine, also reducing the relative amount of NET inhibition. Variability in plasma levels of venlafaxine versus desvenlafaxine is also due to genetic polymorphisms for CYP450 2D6, such that poor metabolizers will shift the ratio of these two drugs towards more parent venlafaxine and away from the active metabolite desvenlafaxine, and thus reduce the relative amount of NET inhibition. As a result of these considerations, it can be somewhat unpredictable how much NET inhibition a given dose of venlafaxine will have in a given patient at a given time, whereas this is more predictable for desvenlafaxine. Expert clinicians have learned to solve this problem with skilled dose titration of venlafaxine, but the development of desvenlafaxine as a separate drug may also solve this problem, with less need for dose titration and more consistent NET inhibition at a given dose across all patients.

Duloxetine

This SNRI, characterized pharmacologically by slightly more potent SERT than NET inhibition (Figure 7-29), has transformed how we think about depression and pain. Classic teaching was that depression caused pain that was psychic (as in "I feel your pain") and not somatic (as in "ouch"), and that psychic pain was secondary to emotional suffering in depression; therefore, it was thought, anything that made depression better would make psychic pain better nonspecifically. Somatic pain was thus not thought to be caused by depression, although depression could supposedly make it worse, and classically somatic pain was not treated with drugs for depression.

Studies with duloxetine have changed all this. Not only does this SNRI relieve unipolar depression in the absence of pain, but it also relieves pain in the absence of depression. All sorts of pain are improved by this SNRI, from diabetic peripheral neuropathic pain, to fibromyalgia, to chronic musculoskeletal pain such as that associated with osteoarthritis and low back problems, and more. These findings of the efficacy of duloxetine for multiple pain syndromes have also validated that painful physical (somatic) symptoms are a legitimate set of symptoms that accompany depression and are not just a form of emotional pain. The use of SNRIs such as duloxetine in pain syndromes is discussed in Chapter 9. So, duloxetine has established efficacy not only in unipolar depression and in chronic pain, but also in patients with chronic painful physical

symptoms of unipolar depression. Painful physical symptoms are frequently ignored or missed by patients and clinicians alike in the setting of unipolar major depression, and until recently, the link of these symptoms to major depression was not well appreciated, in part because painful physical symptoms are not included in the list of symptoms for the formal diagnostic criteria for depression (see Chapter 6 and Figure 6-1). Nevertheless, it is now widely appreciated that painful physical symptoms are frequently associated with a major depressive episode, and are also one of the leading residual symptoms after initial treatment with drugs for depression (Figure 7-5). It appears that the dual SNRI actions of duloxetine and other SNRIs are superior to the selective serotonergic actions of SSRIs for treatment of conditions such as neuropathic pain of diabetes and chronic painful physical symptoms associated with depression. The role of NET inhibition seems to be critical for the treatment not only of painful conditions without depression, but also for painful physical symptoms associated with depression. Duloxetine has also shown efficacy in the treatment of cognitive symptoms of depression that are prominent in geriatric depression, possibly exploiting the pro-noradrenergic and pro-dopaminergic consequences of NET inhibition in the prefrontal cortex (see Figure 7-33).

Duloxetine can be given once a day, but this is usually only a good idea after the patient has had a chance to become tolerant to it after initiating it at twice-daily dosing, especially during titration to higher doses. Duloxetine may have a lower incidence of hypertension and milder withdrawal reactions than venlafaxine.

Milnacipran

Milnacipran is the first SNRI marketed in Japan and many European countries such as France, where it is currently marketed as a drug for unipolar depression. In the US, milnacipran is not approved for unipolar depression, but is approved for fibromyalgia. Interestingly, it is the other way around in Europe: milnacipran is approved for unipolar depression but not approved for the treatment of fibromyalgia. Milnacipran is a bit different from other SNRIs in that it is a relatively more potent NET than SERT inhibitor (Figure 7-30), whereas the others are more potent SERT than NET inhibitors (Figures 7-28 and 7-29). This unique pharmacological profile may explain milnacipran's somewhat different clinical profile compared to other SNRIs. Since noradrenergic actions may be equally or more important for treatment of pain-related conditions compared to serotonergic actions, the robust NET inhibition of milnacipran suggests that it may be particularly useful in chronic pain related conditions, not just fibromyalgia where it is approved, but possibly as well for the painful physical symptoms associated with unipolar depression and chronic neuropathic pain.

Milnacipran's potent NET inhibition also suggests a potentially favorable pharmacological profile for the treatment of cognitive symptoms, including cognitive symptoms of unipolar depression as well as cognitive symptoms frequently associated with fibromyalgia, sometimes called "fibro-fog." Other clinical observations possibly linked to milnacipran's robust NET inhibition are that it can be more energizing and activating than other SNRIs. Common residual symptoms after treatment with an SSRI include not only cognitive symptoms, but also fatigue, lack of energy, and lack of interest, among other symptoms (Figure 7-5). NET inhibition may be related to observations that milnacipran may cause more sweating and urinary hesitancy than some other SNRIs. For patients with urinary hesitancy, generally due theoretically to robust pro-noradrenergic actions at bladder α_1 receptors, an α_1 antagonist can reduce these symptoms. Milnacipran must generally be given twice daily due to its shorter half-life.

Levomilnacipran

Milnacipran is actually a racemic mixture of two enantiomers (Figure 7-30). The S or levo enantiomer is the active enantiomer (Figure 7-31) and has been independently developed for unipolar major depressive disorder in the US, where it is mostly available. Like racemic milnacipran, levomilnacipran has greater NET inhibition than SERT inhibition and may target fatigue and lack of energy as potential clinical advantages. Also, it is dosed in a controlled-release formulation, so, unlike racemic milnacipran, can be given only once a day.

Norepinephrine–Dopamine Reuptake Inhibitors (NDRIs): Bupropion

For many years, the mechanism of action of bupropion has been unclear and still remains somewhat controversial. Bupropion itself only has weak reuptake blocking properties for dopamine (DAT inhibition), and for norepinephrine (NET inhibition) (Figures 7-34 and 7-35). No other specific or potent pharmacological actions have been consistently identified for this agent. Bupropion's actions both as a drug for unipolar depression and upon norepinephrine and dopamine neurotransmission, however, have always appeared to be more powerful than these weak properties could explain,

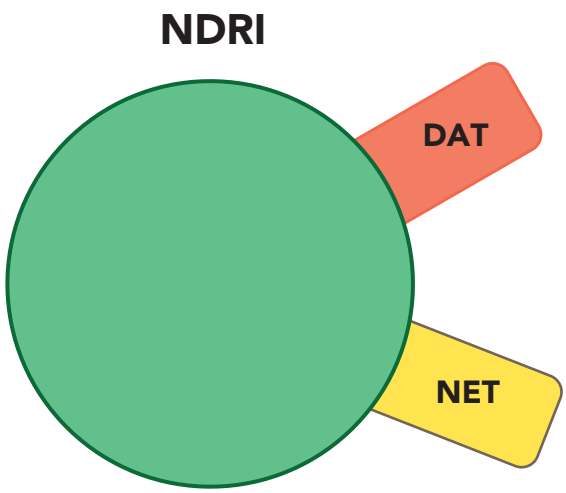


Figure 7-34 Norepinephrine–dopamine reuptake inhibitor (NDRI). The prototypical norepinephrine–dopamine reuptake inhibitor (NDRI) is bupropion. Bupropion has weak blocking properties for the dopamine transporter (DAT) and for the norepinephrine transporter (NET). Its antidepressant actions may be explained in part by the more potent inhibitory properties of its metabolites.

leading to proposals that bupropion acts rather vaguely as an adrenergic modulator of some type.

Bupropion is metabolized to a number of active metabolites, some of which are not only more potent NET inhibitors than bupropion itself and equally potent DAT inhibitors, but are also concentrated in the brain. In some ways, therefore, bupropion is both an active drug and a precursor for other active drugs (i.e., a prodrug for multiple active metabolites). The most potent of these is the + enantiomer of the 6-hydroxy metabolite of bupropion, also known as radafaxine.

Can the net effects of bupropion on NETs (Figure 7-36A and 7-36B) and DATs (Figure 7-36C) account for its clinical actions in depressed patients at therapeutic doses? If one believes that 90% transporter occupancy of DATs and NETs are required for drugs for antidepressant actions, the answer would be "no." Human positron emission tomography (PET) scans suggest that as little as 10–15% and perhaps no more than 20–30% of striatal DATs may be occupied at therapeutic doses of bupropion. NET occupancy would be expected to be in this same range. Is this enough to explain bupropion's antidepressant actions?

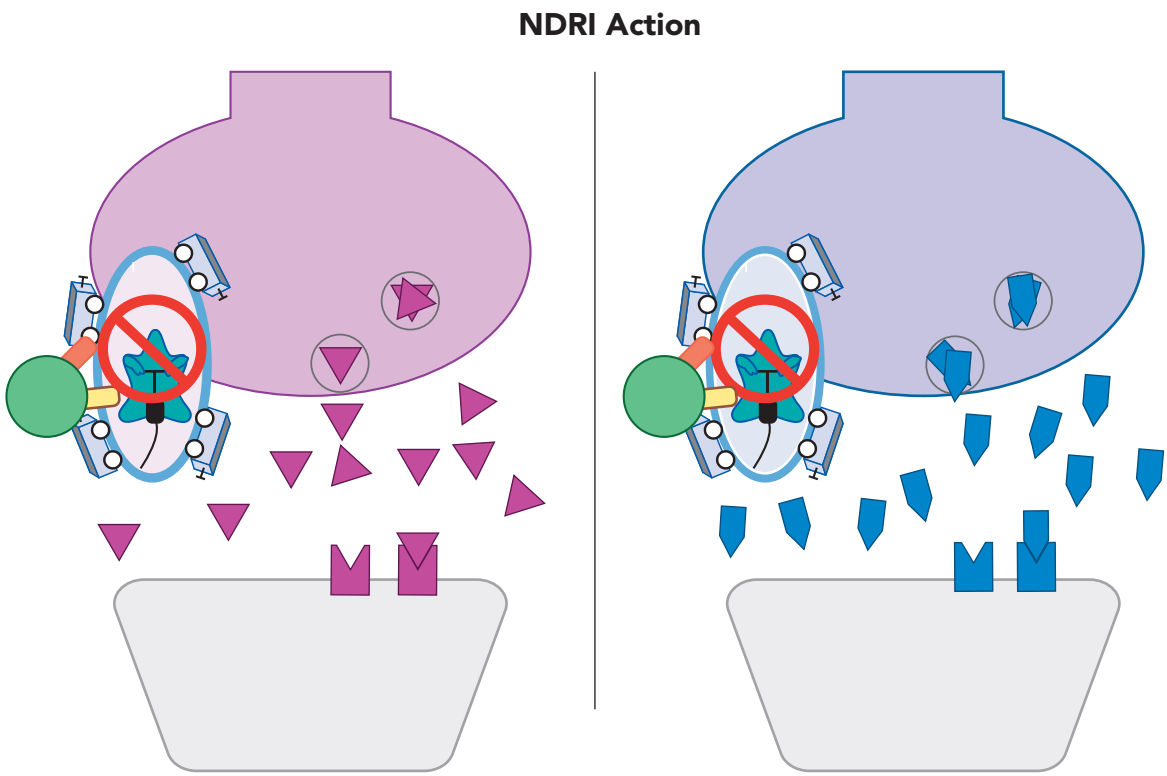


Figure 7-35 NDRI actions. The norepinephrine reuptake inhibitor portion of the NDRI molecule (left panel) and the dopamine reuptake inhibitor portion of the NDRI molecule (right panel) are inserted into their respective reuptake pumps. Consequently, both pumps are blocked, and synaptic norepinephrine and dopamine are increased.

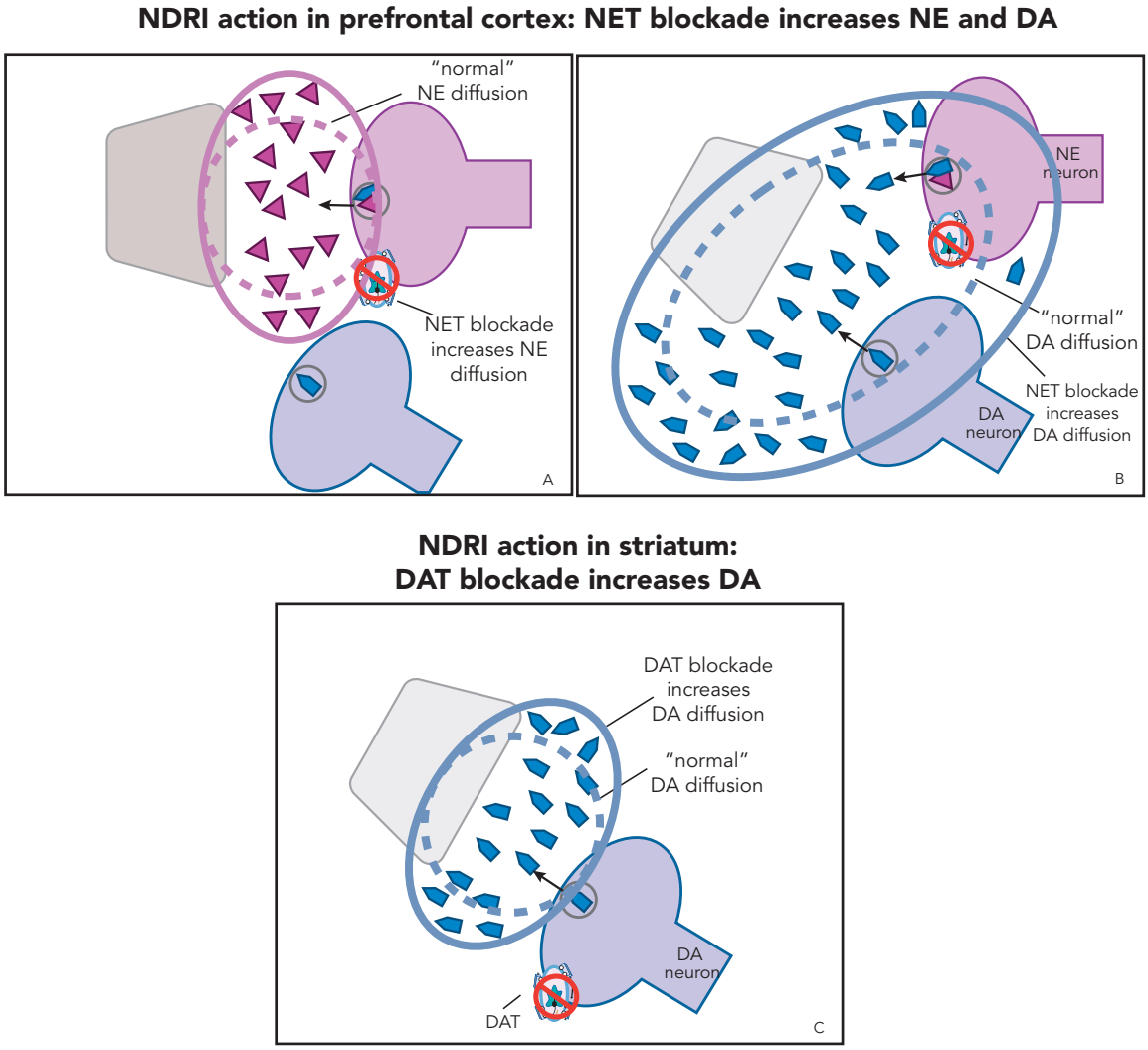


Figure 7-36 **NDRI actions in prefrontal cortex and striatum.** Norepinephrine–dopamine reuptake inhibitors (NDRIs) block the transporters for both norepinephrine (NETs) and dopamine (DATs). (A) NET blockade in the prefrontal cortex leads to an increase in synaptic norepinephrine (NE), thus increasing NE's diffusion radius. (B) Because the prefrontal cortex lacks DATs, and NETs transport dopamine (DA) as well as NE, NET blockade also leads to an increase in synaptic DA in the prefrontal cortex, further increasing DA's diffusion radius. Thus, despite the absence of DAT in the prefrontal cortex, NDRIs still increase DA there. (C) DAT is present in the striatum, and thus DAT inhibition increases DA diffusion there.

Whereas it is clear from many research studies that SSRIs must be dosed to occupy a substantial fraction of SERTs, perhaps up to 80% or 90% of these transporters, in order to be effective drugs for depressions, this is far less clear for NET or DAT occupancy, particularly in the case of drugs with an additional pharmacological mechanism that may be synergistic with NET or DAT inhibition. That is, when most SNRIs are given in doses that occupy 80–90% of SERTs, substantially fewer NETs are occupied, yet there is evidence of both additional therapeutic actions and NE-mediated side effects of these agents with perhaps as little as 50% NET occupancy.

Furthermore, there appears to be such a thing as "too much DAT occupancy." That is, when 50% or more of DATs are occupied rapidly and briefly, this can lead to unwanted clinical actions, such as euphoria and reinforcement (see discussion of the mysterious DATs in Chapter 11 on attention deficit hyperactivity disorder [ADHD] treatment). In fact, rapid, short-lasting, and high degrees of DAT occupancy are the pharmacological characteristics of abusable stimulants such as cocaine (discussed in Chapter 13 on drug abuse and reward). When 50% or more of DATs are occupied more slowly and in a more long-lasting manner, especially with

controlled-release formulations, DAT inhibitors are less abusable and more useful for ADHD (see Chapter 11). The issue to be considered here is whether a low level of slow-onset and long-lasting DAT occupancy is the desirable solution for the DAT mechanism to be useful as a drug for unipolar depression: thus, not too much or too fast DAT inhibition and therefore abusable; not too little DAT inhibition and therefore ineffective; but just enough DAT inhibition with slow enough onset and long enough duration of action to make it an effective drug for unipolar depression.

The fact that bupropion is not known to be particularly abusable, is not a scheduled substance, yet is proven effective for treating nicotine addiction, is consistent with the possibility that it is occupying DATs in the striatum and nucleus accumbens in a manner sufficient to mitigate craving but not sufficient to cause abuse (Figure 7-36C). This use of bupropion for smoking cessation is discussed further in Chapter 13 on drug abuse and reward. Perhaps this low level of DAT occupancy (Figure 7-36C) is also how bupropion works in unipolar depression, combined with an equally low action on NETs (Figure 7-36A and 7-36B).

Bupropion was originally marketed only in the US as an immediate-release dosage formulation for three-times-daily administration as a drug for unipolar depression. Development of a twice-daily formulation (bupropion SR) and then a once-daily formulation (bupropion XL) have not only reduced the frequency of seizures at peak plasma drug levels, but have also increased convenience and enhanced compliance as well. Thus, the use of immediate-release bupropion is all but abandoned in favor of once-daily administration.

Bupropion is generally activating or even stimulating. Bupropion does not appear to cause the bothersome sexual dysfunction that frequently occurs with many drugs for unipolar depression that act by SERT inhibition, probably because bupropion lacks a significant serotonergic component to its mechanism of action. Thus, bupropion has proven to be a useful drug for unipolar depression not only for patients who cannot tolerate the serotonergic side effects of SSRIs, but also for patients whose depression does not respond to serotonergic boosting by SSRIs. Consistent with its pharmacological profile, bupropion is especially targeted at the symptoms of the "dopamine deficiency syndrome" and "reduced positive affect" (see Figure 6-41), including improvement in the symptoms of loss of happiness, joy, interest, pleasure, energy, enthusiasm, alertness, and self-confidence. Almost every active clinician knows that patients who have residual symptoms of reduced positive affect following treatment with an SSRI or an SNRI, or who develop these symptoms as a side effect of an SSRI or SNRI, frequently benefit from switching to bupropion or from augmenting their SSRI or SNRI treatment with bupropion. The combination of bupropion with an SSRI or an SNRI has a theoretical rationale as a strategy for covering the entire symptom portfolio from symptoms of reduced positive affect to symptoms of increased negative affect (Figure 6-41). Bupropion combined with the μ-opioid antagonist naltrexone is approved for the treatment of obesity and mentioned in Chapter 13 on impulsivity/compulsivity syndromes. Bupropion combined with the NMDA (*N*-methyl-D-aspartate) antagonist dextromethorphan is in late-stage clinical trials both for depression (mentioned below) and for agitation in Alzheimer disease (discussed in Chapter 12 on dementia).

Agomelatine

Agomelatine (Figure 7-37) is approved to treat unipolar depression in many countries outside of the US. It has agonist actions at melatonin 1 (MT_1) and melatonin 2 (MT_2) receptors and antagonist actions at $5HT_{2C}$ receptors (Figure 7-37). As discussed above in the section

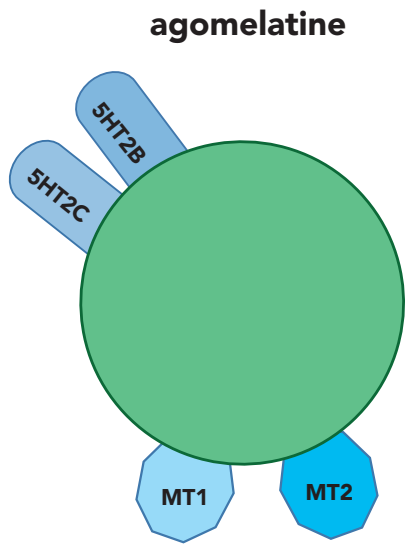


Figure 7-37 Agomelatine. Endogenous melatonin is secreted by the pineal gland and mainly acts in the suprachiasmatic nucleus to regulate circadian rhythms. There are three types of receptors for melatonin: 1 and 2 (MT_1 and MT_2), which are both involved in sleep, and 3, which is actually the enzyme NRH–quinine oxidoreductase 2 and not thought to be involved in sleep physiology. Agomelatine is not only a melatonin 1 and 2 receptor agonist, but is also a $5HT_{2C}$ and $5HT_{2B}$ receptor antagonist, and is available to treat depression in countries outside of the US.

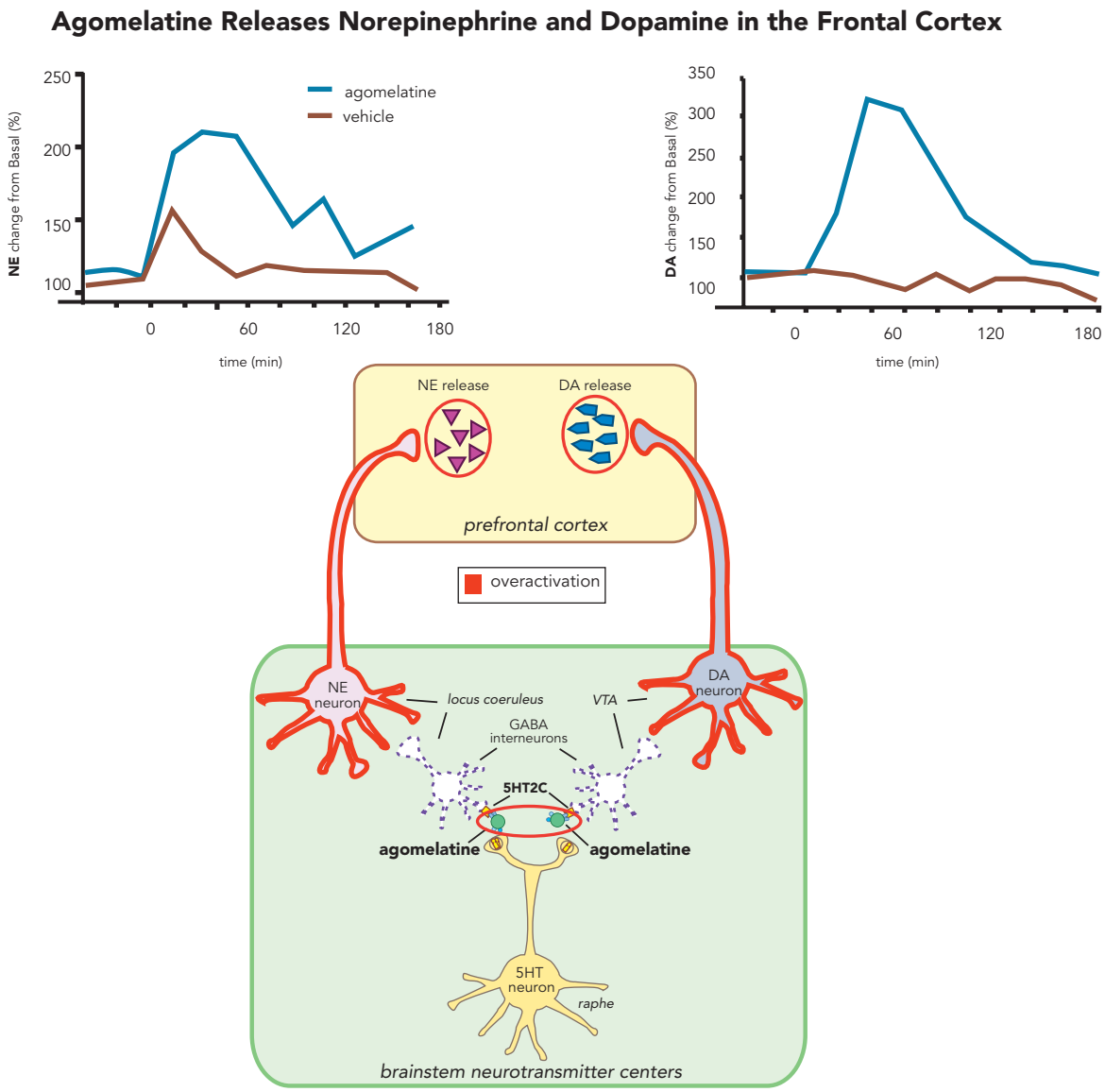


Figure 7-38 **Agomelatine releases norepinephrine and dopamine in the prefrontal cortex.** Normally, serotonin binding at $5HT_{2C}$ receptors on γ-aminobutyric acid (GABA) interneurons in the brainstem inhibits norepinephrine (NE) and dopamine (DA) release in the prefrontal cortex. When a $5HT_{2C}$ antagonist such as agomelatine binds to $5HT_{2C}$ receptors on GABA interneurons (bottom red circle), it prevents serotonin (5HT) from binding there and thus prevents inhibition of NE and DA release in the prefrontal cortex; in other words, it disinhibits their release (top red circles).

on fluoxetine, $5HT_{2C}$ antagonist actions are a property of several drugs used to treat unipolar depression (agomelatine, fluoxetine, trazodone, mirtazapine, some tricyclic antidepressants) and bipolar depression (olanzapine and quetiapine). $5HT_{2C}$ receptors are located in the midbrain raphe and prefrontal cortex where they regulate the release of dopamine and norepinephrine, an action thought to improve depressive symptoms (see Figure 7-38). $5HT_{2C}$ receptors are also localized in the suprachiasmatic nucleus (SCN) of the hypothalamus, the brain's "pacemaker," where they interact with melatonin receptors also located there (Figure 7-39). Light is detected by the retina during the day, and this information travels to the SCN via the retinohypothalamic tract (Figure 7-39; see also Chapter 6 and Figures 6-36A and 6-36B), which normally synchronizes many circadian rhythms downstream from the SCN. For example, both melatonin receptors and

$5HT_{2C}$ receptors fluctuate in a circadian manner in the SCN, with high receptor expression at night/dark and low receptor expression in the day/light. That makes sense since melatonin is only secreted at night in the dark (see Chapter 6 and Figures 6-35 and 6-36B). In some patients with unipolar depression, however, circadian rhythms are "out of synch," including low melatonin secretion at night among numerous other changes. Theoretically, agomelatine, by stimulating melatonin receptors in the SCN and simultaneously blocking $5HT_{2C}$ receptors there as well, appears to resynchronize circadian rhythms, reverse the phase delay of depression, and thereby exert an antidepressant effect (Figure 7-39).

Mirtazapine

Mirtazapine (Figure 7-40) is marketed worldwide and, unlike almost every other drug for unipolar depression, it does not block any monoamine transporter. Instead, mirtazapine is a multifunctional drug with five principal mechanisms of action: $5HT_{2A}$, $5HT_{2C}$, $5HT_3$, α_2-adrenergic,

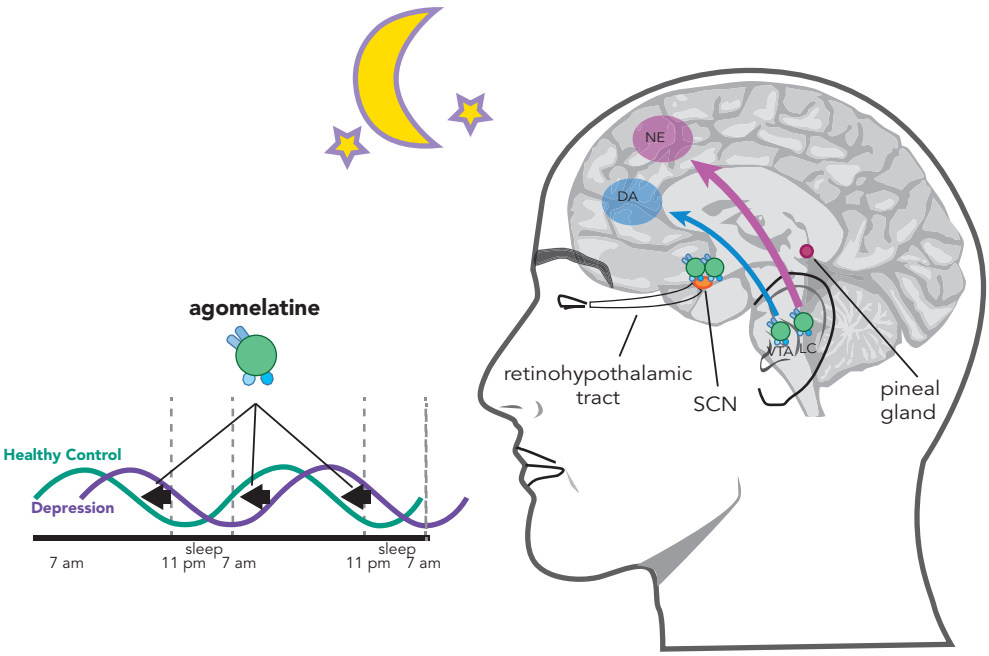


Figure 7-39 Agomelatine may resynchronize circadian rhythms. Agomelatine, which acts as an agonist at melatonin 1 and 2 receptors, may resynchronize circadian rhythms by acting as "substitute melatonin." Thus, even in the absence of melatonin production in the pineal gland, agomelatine can stimulate melatonin 1 and 2 receptors in the suprachiasmatic nucleus (SCN) to reset circadian rhythms. $5HT_{2C}$ receptors are also present in the SCN and blocked by agomelatine. In addition, by blocking $5HT_{2C}$ receptors in the ventral tegmental area (VTA) and locus coeruleus (LC), agomelatine promotes dopamine (DA) and norepinephrine (NE) release in the prefrontal cortex.

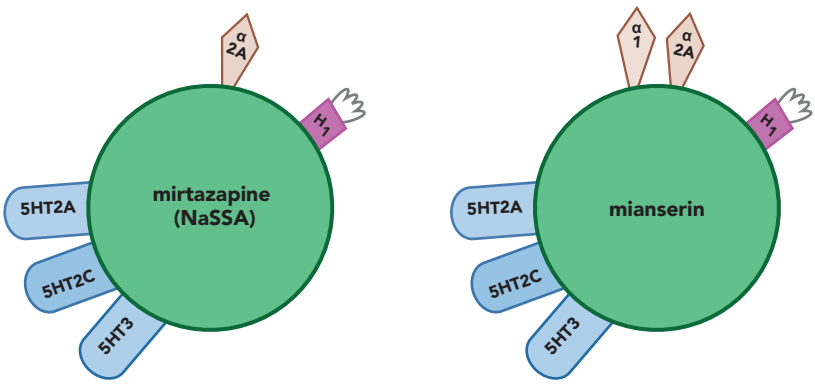


Figure 7-40 Mirtazapine and mianserin. Mirtazapine's primary therapeutic action is α_2 antagonism. It also blocks three serotonin (5HT) receptors: $5HT_{2A}$, $5HT_{2C}$, and $5HT_3$. Finally, it blocks histamine 1 (H_1) receptors. Mianserin has a similar binding profile to mirtazapine, the only difference being additional effects at α_1 receptors. NaSSA: noradrenergic and specific serotonergic antidepressant.

and H_1 histamine antagonism. Two other α_2 antagonists are marketed as drugs for depression in some countries (but not the US), namely mianserin (worldwide except US) and setiptiline (Japan). Unlike mirtazapine, mianserin also has potent α_1 antagonist properties, which tend to mitigate its ability to enhance serotonergic neurotransmission so that this drug enhances predominantly noradrenergic neurotransmission, yet with associated $5HT_{2A}$, $5HT_{2C}$, $5HT_3$, and H_1 antagonist properties (Figure 7-40).

Clinical consequences of blocking H_1 receptors have been discussed in Chapter 5 and illustrated in Figure 5-13A, showing that H_1 antagonist actions are associated with sedation and weight gain. $5HT_{2A}$ antagonist properties also have been discussed in Chapter 5 and illustrated in Figures 5-16 and 5-17, showing increases in downstream release of dopamine in the prefrontal cortex, potentially associated with antidepressant actions. $5HT_{2A}$ antagonism also improves sleep, especially slow-wave sleep, which can be helpful in many depressed patients. $5HT_{2C}$ antagonist actions were just explained in the preceding section and illustrated in Figure 7-38, showing enhanced release of norepinephrine and dopamine in the prefrontal cortex, which would theoretically improve depression. Here we explain the other actions of mirtazapine, notably α_2 antagonist actions and $5HT_3$ antagonist actions. Some other drugs for unipolar depression also have potent α_2 antagonist actions (Figure 5-35), including brexpiprazole (Figure 5-57) and quetiapine (Figure 5-45). Some other drugs for bipolar depression also have α_2 antagonist actions, including quetiapine (Figure 5-45) and lurasidone (Figure 5-53). Another agent for treatment of unipolar depression that has potent $5HT_3$ antagonist properties is vortioxetine, discussed below.

Alpha-2 Antagonist Action

Alpha-2 antagonism is another way to enhance the release of monoamines and exert an antidepressant action in unipolar depression. Recall that norepinephrine turns off its own release by interacting with presynaptic α_2 autoreceptors on noradrenergic neurons (discussed in Chapter 6 and illustrated in Figures 6-14 through 6-16; see also Figure 7-41A and B on the right). Therefore, when an α_2 antagonist is administered, norepinephrine can no longer turn off its own release and noradrenergic neurons are thus disinhibited from their axon terminals, such as those in the raphe and in the cortex as shown in Figure 7-41C on the right.

The general principle of serotonin turning off serotonin release at serotonin $5HT_{1B}$ autoreceptors (Figure 4-41 and Figure 7-41A compared to 7-41B on the left) has already been discussed and is illustrated again here. However, there are also α_2 "hetero" receptors on serotonin neurons (Figure 7-41A, B, C on the left). There are many cases where neurotransmitter release is controlled not only by their "own" autoreceptor, but also by presynaptic receptors for "another" neurotransmitter at heteroreceptors (Figure 7-41A; see also Figure 4-45 and discussion of presynaptic $5HT_{1B}$ heteroreceptors on norepinephrine, dopamine, histamine, and acetylcholine neurons). The same phenomenon is shown in Figure 7-41B where not only is serotonin turning off serotonin release at its own $5HT_{1B}$ presynaptic autoreceptor on the left hand part of the serotonin neuron, but also norepinephrine migrating from a norepinephrine terminal is turning off serotonin release via an α_2 presynaptic heteroreceptor on the right hand part of the serotonin neuron. Norepinephrine is also turning off its own release via an α_2 presynaptic receptor (Figure 7-41B on the right at the norepinephrine neuron). This sets up the situation whereby an α_2 antagonist can have a dual effect, facilitating the release of both norepinephrine and serotonin (Figure 7-41C). Not only does α_2 antagonism disinhibit norepinephrine release (Figure 7-41C on the right), it also disinhibits serotonin release (Figure 7-41C on the left). Thus, α_2 antagonism causes dual 5HT–NE action. This is something like the same net outcome as an SNRI but by an entirely different mechanism. Rather than blocking serotonin and norepinephrine presynaptic transporters, α_2 antagonism "cuts the brake cable" of noradrenergic inhibition (NE stepping on the brake to prevent 5HT and NE release shown in Figure 7-41B is blocked in Figure 7-41C).

These two mechanisms, monoamine transport blockade and α_2 antagonism, are synergistic, so that blocking them simultaneously gives a much more powerful disinhibitory signal to these two neurotransmitters than if only one mechanism is blocked. For this reason, the α_2 antagonist mirtazapine is often combined with SNRIs for treatment of cases that do not respond to an SNRI alone. This combination of mirtazapine with an SNRI is sometimes called "California rocket fuel" because of the potentially powerful drugs for depression blasting the patient out of the depths of depression.

$5HT_3$ Antagonist Action

The $5HT_3$ receptors best known to clinicians are perhaps those localized in the chemoreceptor trigger zone of the brainstem, where they mediate nausea and vomiting, especially in response to cancer chemotherapy, and

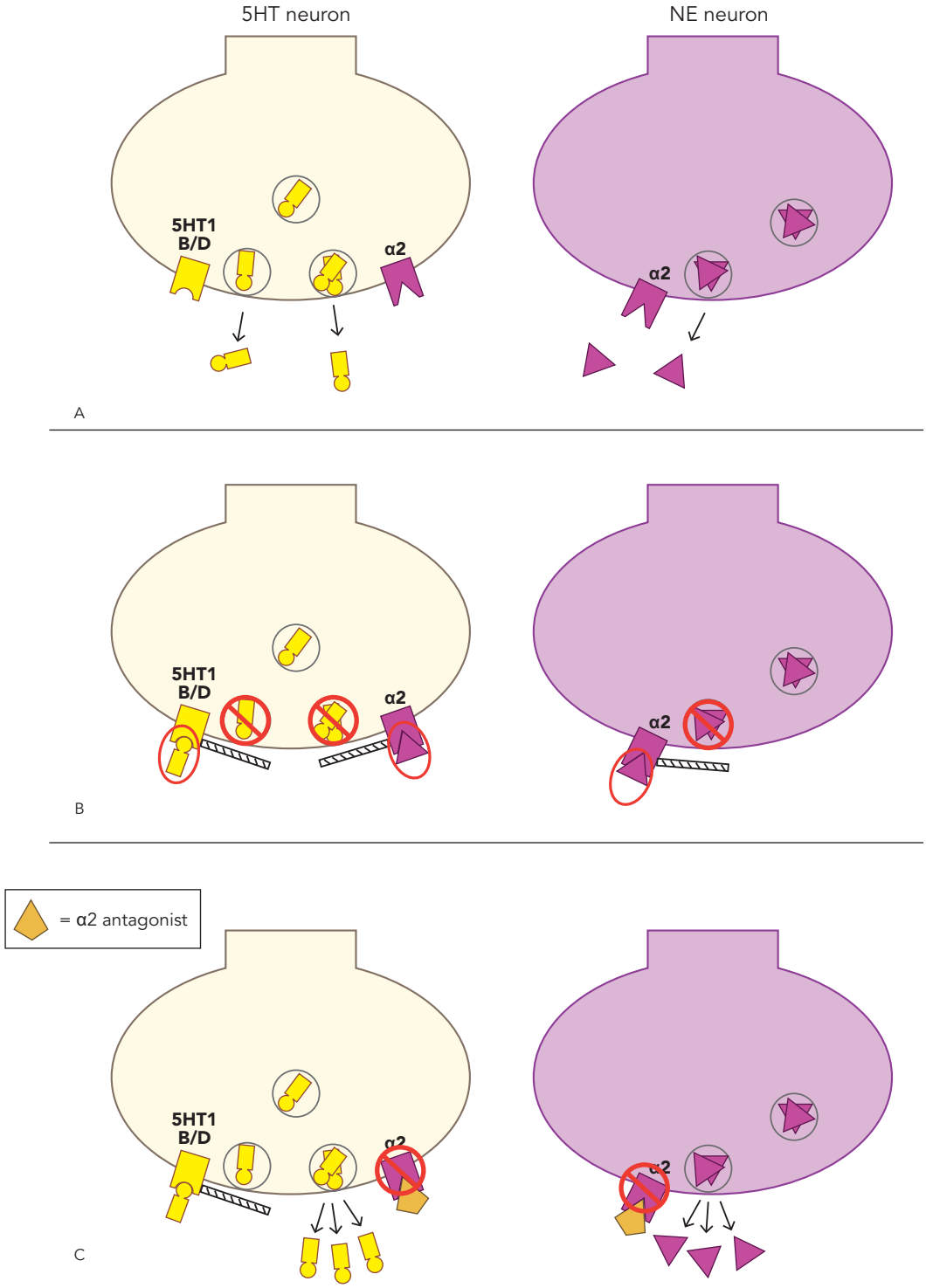


Figure 7-41 Alpha-2 antagonism increases serotonin and norepinephrine release in raphe and cortex. (A) On the left, a serotonergic neuron is shown with $5HT_{1B/D}$ autoreceptors and α_2-adrenergic heteroreceptors. On the right, a noradrenergic neuron is shown with presynaptic α_2 autoreceptors. (B) $5HT_{1B/D}$ autoreceptors and α_2-adrenergic heteroreceptors on serotonergic neurons both function as "brakes" to shut off serotonin release when bound by their respective neurotransmitters (left). Likewise, when norepinephrine binds to α_2 autoreceptors on the norepinephrine neuron, this shuts off further norepinephrine release (right). (C) Alpha-2 antagonists "cut the serotonin brake cable" when they block α_2 presynaptic heteroreceptors, thus leading to enhanced serotonin release (left). Alpha-2 antagonists also "cut the norepinephrine brake cable" by blocking presynaptic α_2 autoreceptors, leading to enhanced norepinephrine release (right).

also those localized in the gastrointestinal tract itself, where they mediate nausea, vomiting, and diarrhea/bowel motility when stimulated by serotonin, including when stimulated by serotonin that is a side effect of peripherally increased serotonin by SSRIs/SNRIs. Blocking these $5HT_3$ receptors can therefore protect against chemotherapy-induced nausea and vomiting as well as against serotonin-induced gastrointestinal side effects that can accompany agents that increase serotonin.

More important to the mechanism of action of central $5HT_3$ antagonists such as mirtazapine and vortioxetine in the treatment of unipolar depression are the $5HT_3$ receptors in the brain that regulate the release of various neurotransmitters downstream in some brain circuits that mediate the symptoms of depression. $5HT_3$ receptors in the brain are usually localized on GABA (γ-aminobutyric acid) interneurons, and they are always excitatory. This means that when serotonin stimulates a $5HT_3$ receptor, it causes GABA to inhibit whatever neuron is downstream from it. This was shown for $5HT_3$–GABA interactions at glutamate neurons (Figure 4-49) and at acetylcholine and norepinephrine neurons (Figure 4-48). $5HT_3$ antagonism is a powerful disinhibitor of glutamate release (Figure 7-42) and of acetylcholine and norepinephrine (Figure 7-43), actions that theoretically release neurotransmitters downstream to have antidepressant action.

Serotonin Antagonist/Reuptake Inhibitors (SARIs)

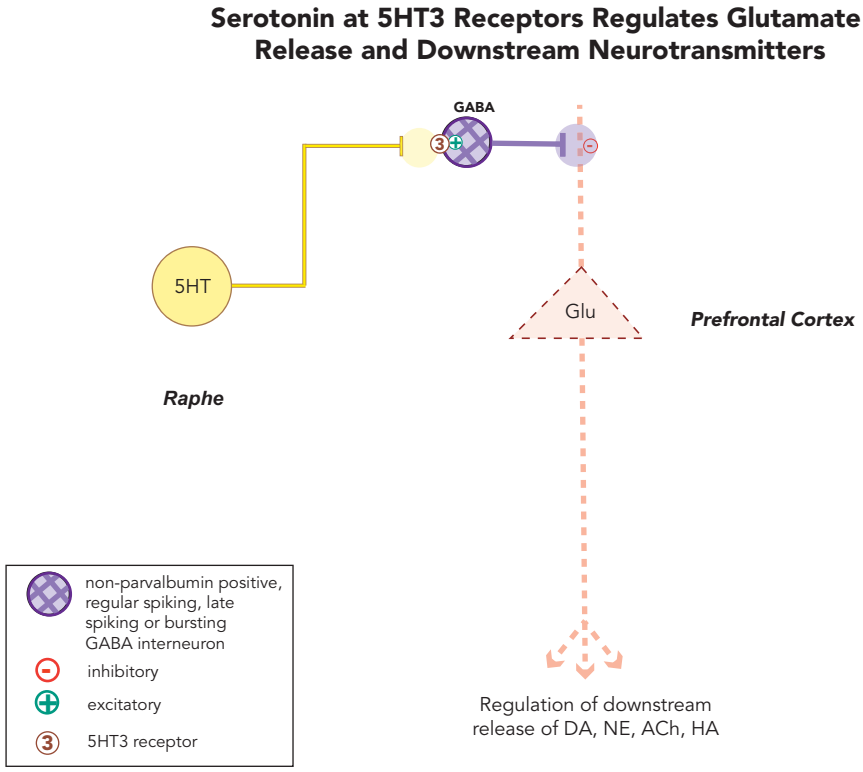
The prototype drug that blocks serotonin 2A and 2C receptors as well as serotonin reuptake is trazodone, classified as a serotonin antagonist/reuptake inhibitor (SARI) (Figure 7-44). Nefazodone is another SARI with robust $5HT_{2A}$ antagonist actions and weaker $5HT_{2C}$ antagonism and SERT inhibition, but is no longer commonly used because of rare liver toxicity (Figure 7-44). Trazodone is a very interesting agent, since it acts like two different drugs, depending upon the dose and the formulation. We discussed a very similar situation in Chapter 5 for quetiapine (Figure 5-46).

A more complete picture of trazodone's binding properties has emerged from recent studies (Figures 7-44 and 7-45) and reflects that it is a serotonin antagonist not just at $5HT_{2A}$ and $5HT_{2C}$ receptors, but also at $5HT_{1D}$, $5HT_{2B}$, and $5HT_7$ receptors. In addition, trazodone has potent antagonist properties at α_{1B}, α_{1A}, α_{2C}, and α_{2B} receptors, H_1 histamine receptors, and agonist actions at $5HT_{1A}$ receptors (Figure 7-45). Because of these various pharmacological actions occur with varying potencies, it means that trazodone will act predominantly via its highest-affinity receptor interactions at low doses, and will recruit its lower-affinity receptor actions at higher doses.

Different Drug at Different Doses and at Different Delivery Rates?

Trazodone is famous for its effectiveness and utility at low doses as a hypnotic (Figure 7-46). That is, doses of trazodone lower than those effective for antidepressant action are quite frequently used for insomnia. Hypnotic doses engage the receptors for which trazodone has the highest affinity and, amongst these, blockade is hypothetically linked to hypnotic actions (i.e., $5HT_{2A}$, α_1 subtypes, and H_1). Blocking $5HT_{2A}$ receptors enhances slow-wave sleep, and blocking α_1 subtypes and H_1 receptors interferes with monoamine arousal mechanisms (discussed in Chapter 5 and illustrated in Figures 5-13 and 5-14). The best way to deliver a hypnotic is with a standard oral formulation that is immediate in onset, peaks quickly, and is out of the system by morning. Since insomnia is one of the most frequent residual symptoms of depression after treatment with an SSRI/SNRI (discussed earlier in this chapter and illustrated in Figure 7-5), addition of a hypnotic is often necessary in treating patients with a major depressive episode. Not only can addition of a hypnotic potentially relieve the insomnia itself, it may also increase remission rates due to improvement of other symptoms such as loss of energy and depressed mood (Figure 7-5). Thus, the ability of low doses of trazodone to improve sleep in depressed patients has led to its popular use at low doses as an augmenting option for residual insomnia that persists after treatment with SSRIs/SNRIs.

The original oral formulation of trazodone used for depression was short in duration, required multiple daily doses higher than hypnotic doses (Figure 7-47), and was associated with peak dose sedation after daytime doses, not an ideal profile for a drug for unipolar depression. Although trazodone's antidepressant actions at higher doses are undisputed as well as its lack of causing sexual dysfunction or weight gain, the presence of daytime sedation makes using trazodone at antidepressant doses in the standard oral formulation difficult in clinical practice. However, a once-daily controlled-release formulation with higher doses of trazodone is available for use in depression, which blunts peak plasma drug levels to reduce daytime sedation. These higher doses recruit additional known antidepressant receptor actions, including serotonin reuptake inhibition (Figures 7-10



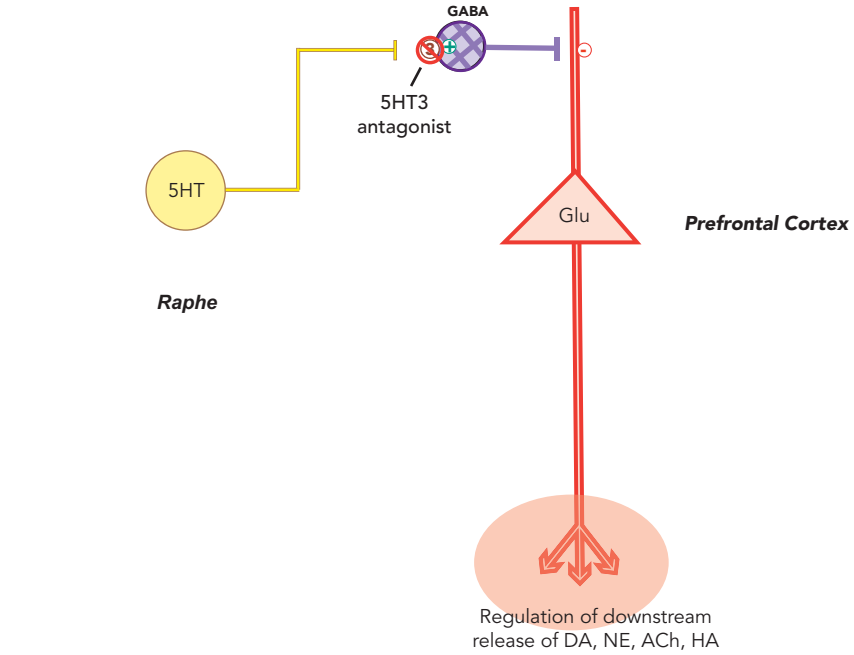
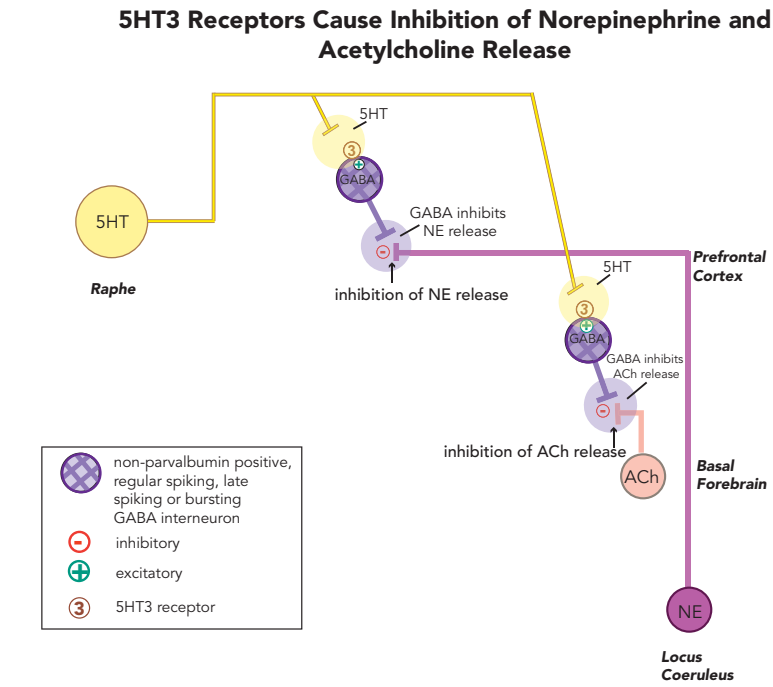


Figure 7-42 **5HT$_3$ receptors regulate glutamate and downstream neurotransmitters.** Serotonin (5HT) binding at 5HT$_3$ receptors on GABA interneurons is stimulatory; thus, it increases GABA release. GABA, in turn, inhibits glutamate pyramidal neurons, reducing glutamate output. Decreased release of excitatory glutamate means that there may be a resultant decrease in downstream release of neurotransmitters, since pyramidal neurons synapse with the neurons of most other neurotransmitters. Antagonism at the 5HT$_3$ receptor removes GABA inhibition and thus disinhibits pyramidal neurons. The increase in glutamate neurotransmission may in turn increase the downstream release of neurotransmitters.



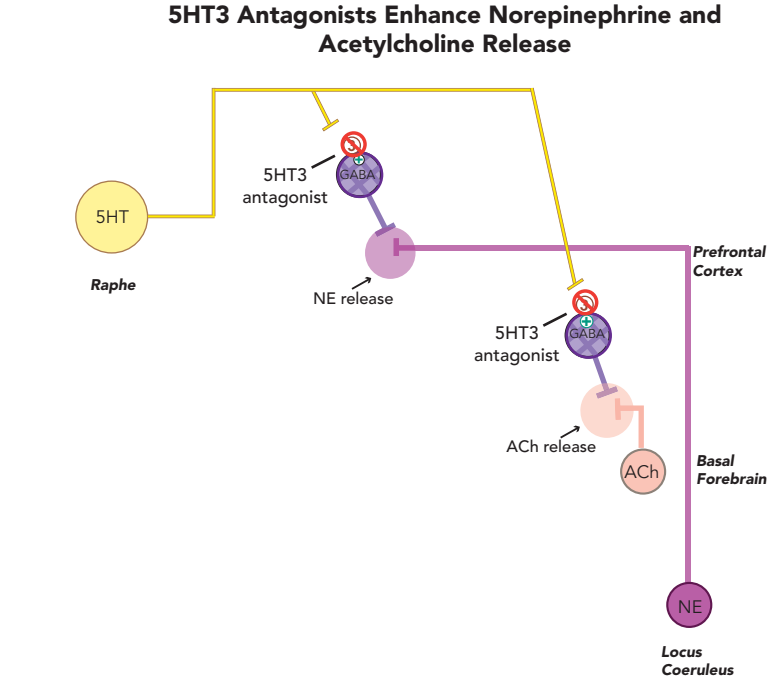


Figure 7-43 **5HT$_3$ receptors regulate norepinephrine and acetylcholine release.** When serotonin (5HT) is released, it binds to 5HT$_3$ receptors on GABAergic neurons, which release GABA onto noradrenergic and cholinergic neurons, thus reducing release of norepinephrine (NE) and acetylcholine (ACh), respectively. Antagonism at the 5HT$_3$ receptor removes GABA inhibition and disinhibits noradrenergic and cholinergic neurons, leading to release of norepinephrine and acetylcholine.

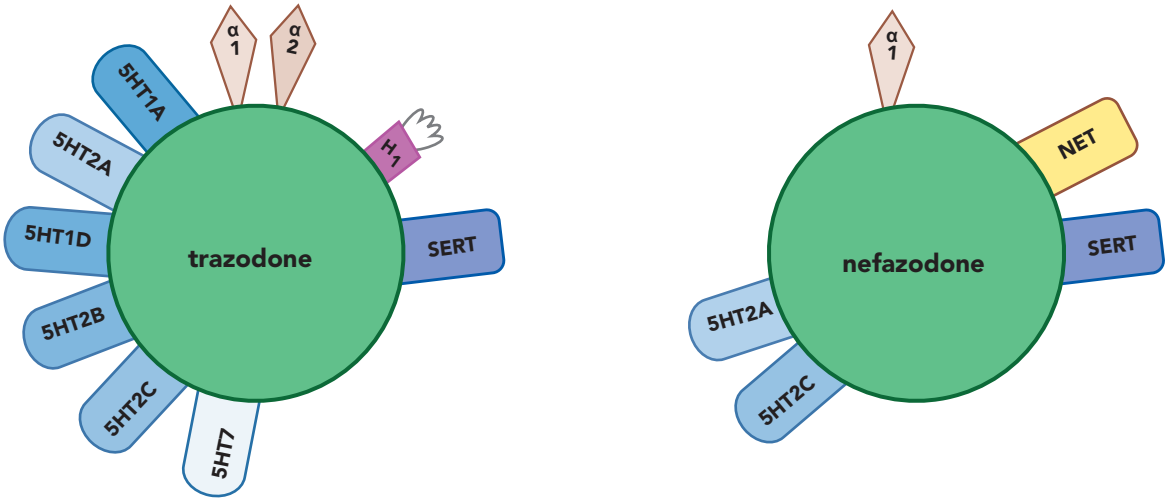


Figure 7-44 Serotonin antagonist/reuptake inhibitors (SARIs). Shown here are icons for two serotonin antagonist/reuptake inhibitors (SARIs): trazodone and nefazodone. These agents have a dual action, but the two mechanisms are different from the dual action of the serotonin–norepinephrine reuptake inhibitors (SNRIs). The SARIs act by potent blockade of serotonin 2A ($5HT_{2A}$) receptors as well as dose-dependent blockade of serotonin 2C ($5HT_{2C}$) receptors and the serotonin transporter (SERT). SARIs also block α_1-adrenergic receptors. Trazodone has the unique properties of histamine 1 (H_1) receptor antagonism and antagonism at multiple additional serotonin receptors.

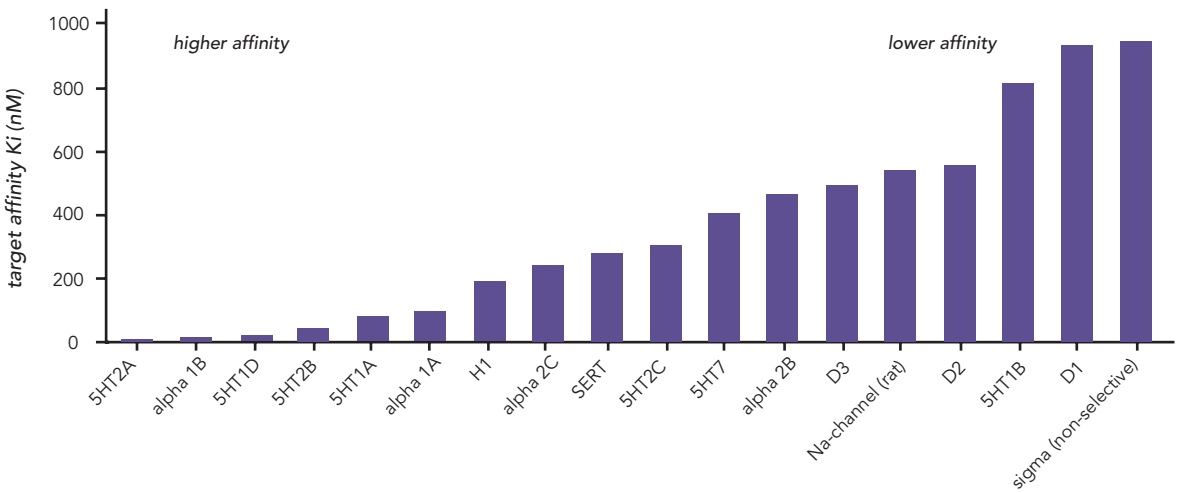


Figure 7-45 Trazodone affinity for different receptors. Trazodone has binding affinity for numerous receptor subtypes, but the potency varies. Thus, at low doses, trazodone may act predominantly via its highest-affinity receptor actions, with other properties becoming relevant only at higher doses.

through 7-15) and antagonist action at $5HT_{1D}$, $5HT_{2C}$, $5HT_7$, and α_2 receptors, as well as $5HT_{1A}$ agonist actions. The bottom line is that there are numerous potential mechanisms to cause monoamine neurotransmitter release and antidepressant actions at higher doses. Furthermore, with first-dose hypnotic actions, trazodone can exert its antidepressant actions with rapid onset and enhanced tolerability for some side effects compared to SSRIs/SNRIs. That is, SSRIs/SNRIs raise serotonin levels to act at all serotonin receptors, stimulating $5HT_{1A}$ receptors for therapeutic actions while concomitantly stimulating $5HT_{2A}$ receptors and $5HT_{2C}$ receptors that theoretically cause the side effects of SSRIs including sexual dysfunction, insomnia, and activation/anxiety (Figure 7-48A). However, trazodone blocks the actions of serotonin at $5HT_{2A}$ and $5HT_{2C}$ receptors, accounting for its profile of lack of sexual dysfunction and reduction of anxiety and insomnia.

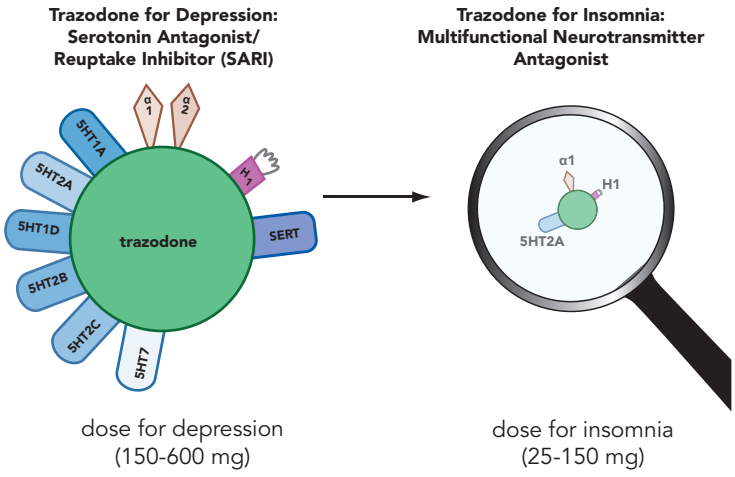


Figure 7-46 Trazodone at different doses. (Left) High doses that recruit saturation of the serotonin transporter (i.e., 150–600 mg) are required for trazodone to have therapeutic actions in depression. At this high dose, trazodone is a multifunctional serotonergic agent with antagonist actions at $5HT_{2A}$ and $5HT_{2C}$ receptors as well as additional serotonin receptors. Trazodone is also an α_1 and histamine 1 (H_1) antagonist at these doses. (Right) At lower doses of trazodone (i.e., 25–150 mg), it does not saturate the serotonin transporter; it does, however, retain antagonist actions at $5HT_{2A}$, α_1, and H_1 receptors, with corresponding efficacy for insomnia.

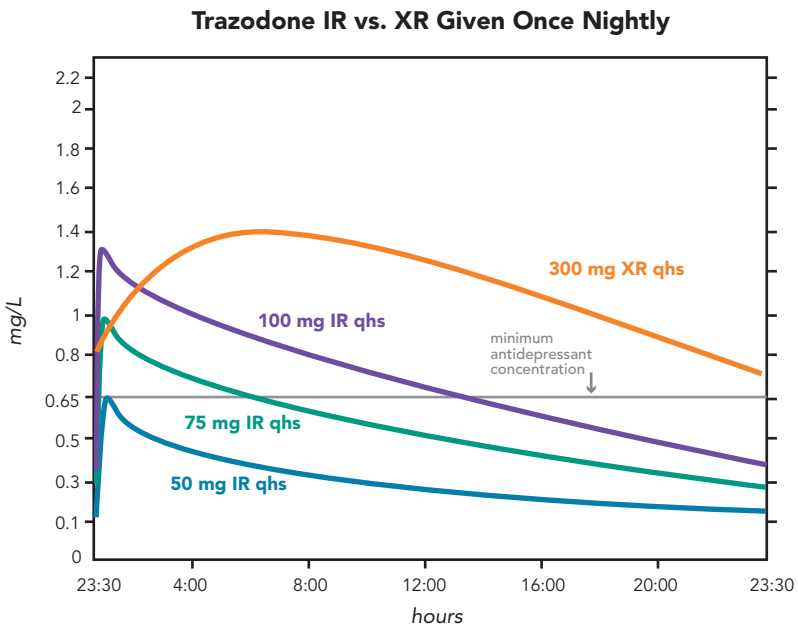


Figure 7-47 Trazodone IR versus XR given once nightly. Shown here are steady-state estimates of the plasma trazodone levels from the hypnotic dosing of 50, 75, or 100 mg once nightly of trazodone immediate release (IR). Peak drug concentrations are reached rapidly with a similarly rapid fall off overnight. The minimum levels estimated for antidepressant actions of trazodone are reached transiently, if at all, by hypnotic dosing. By contrast, 300 mg of trazodone extended release (XR) given once nightly generates plasma levels that rise slowly and never fall below minimum antidepressant concentrations. Peak levels of trazodone XR at 300 mg are about the same as the peak levels of trazodone IR at 100 mg.

Vortioxetine

Vortioxetine is a drug approved for treating unipolar depression and which causes SERT inhibition as well as having antagonist actions at $5HT_3$ and $5HT_7$ receptors, with agonist actions at $5HT_{1A}$ receptors and weak partial agonist to antagonist actions at $5HT_{1B/D}$ receptors (Figure 7-49). This unique blend of pharmacological actions leads to downstream release of many different neurotransmitters as will be explained here, and these actions hypothetically lead to antidepressant effects in unipolar depression, characterized by robust pro-cognitive actions, especially improving processing speed. The importance of cognitive symptoms in unipolar depression is discussed in Chapter 6 as the possible clinical consequence of loss of neurotrophic factors, synapses, and neurons (Figures 6-27 through 6-31).

What is cognitive processing speed and what could be the mechanism by which vortioxetine improves this more than other antidepressants? "Cognition" is not a single, simple brain function and "cognitive dysfunction" is not a single, simple symptom. Cognitive impairment that can be measured as part of the symptom profile

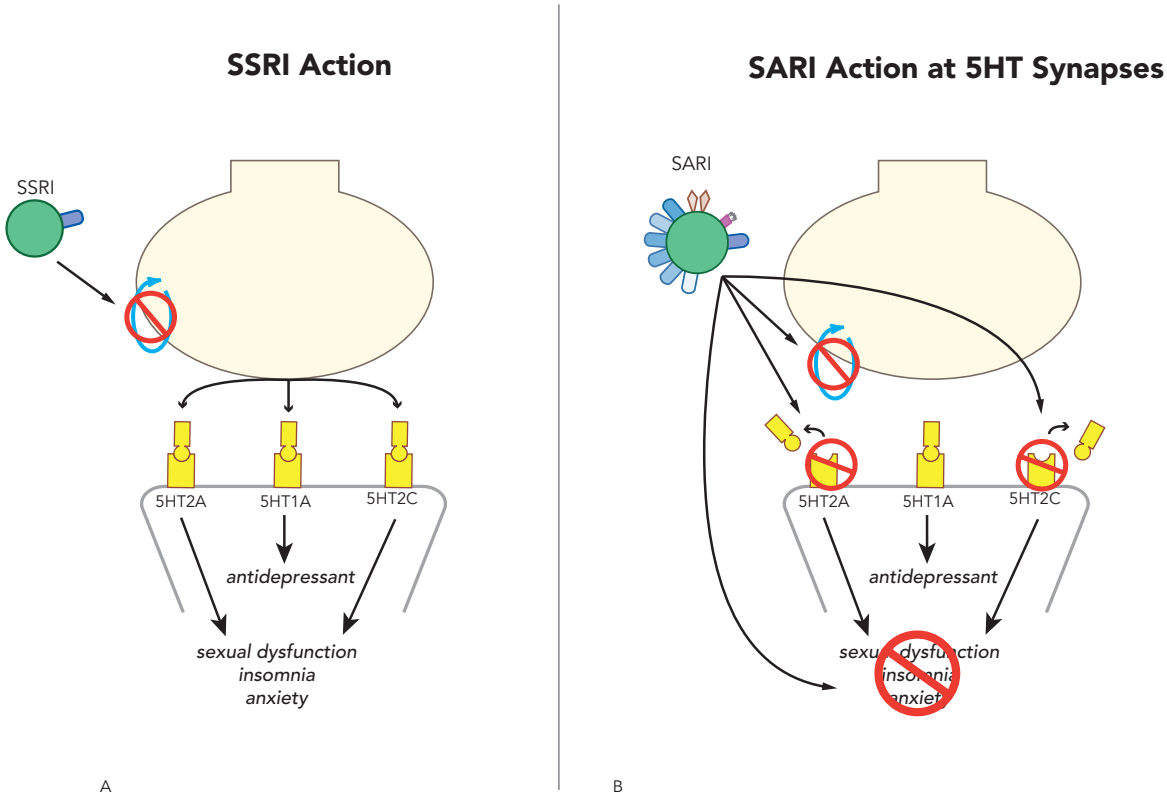


Figure 7-48 SSRI vs. SARI. (A) Inhibition of the serotonin transporter (SERT) by a selective serotonin reuptake inhibitor (SSRI) at the presynaptic neuron increases serotonin at all receptors, with $5HT_{1A}$-mediated antidepressant actions but also $5HT_{2A}$- and $5HT_{2C}$-mediated sexual dysfunction, insomnia, and anxiety. (B) SERT inhibition by a serotonin 2A antagonist/reuptake inhibitor (SARI) at the presynaptic neuron increases serotonin at $5HT_{1A}$ receptors, where it leads to antidepressant actions. However, SARI action also blocks serotonin actions at $5HT_{2A}$ and $5HT_{2C}$ receptors, thus failing to cause sexual dysfunction, insomnia, or anxiety. In fact, these blocking actions at $5HT_{2A}$ and $5HT_{2C}$ receptors can improve insomnia and anxiety, and theoretically can exert antidepressant actions of their own.

of a psychiatric disorder, and that can be targeted for improvement with drug treatment, is the type of cognition most relevant to psychopharmacology. Intellectual impairments as measured by IQ are not particularly amenable to improvement with drug treatment and, other than with schizophrenia, are not generally associated with psychiatric disorders treated in psychopharmacology. On the other hand, "problems concentrating" and "difficulty paying attention" are seen in many psychiatric disorders and are treatable in a range of conditions, including mood disorders (Chapter 6), anxiety disorders (Chapter 8), schizophrenia and psychotic disorders (Chapter 4), ADHD (Chapter 11), sleep disorders (Chapter 10), and beyond. Such cognitive symptoms are a great example of a domain of psychopathology that cuts across many, many psychiatric disorders and implies that the same circuits and neuronal networks are impaired across all these various disorders. It also implies that the same treatments may work to improve cognition across all these various disorders. "Memory difficulties" are the hallmark of dementia and discussed in Chapter 12. "Memory difficulties" in mood disorders are discussed in Chapter 6 and may be a component of chronic depression and PTSD, when loss of synapses and neurons in a major node in the neuronal network of memory, namely the hippocampus, occurs. If early loss of neurotrophic factors in mood disorders hypothetically causes potentially reversible loss of synapses, it is important to treat cognitive symptoms in depression soon after they emerge so effective treatments for depression can trigger the release of growth factors and restore synaptogenesis (Figures 6-27 through 6-31), before neurons are lost and the changes become irreversible. Thus, recognizing and targeting cognitive symptoms is becoming more important as new treatments emerge.

But how can we recognize and monitor cognitive symptoms in psychopharmacology? A simple if

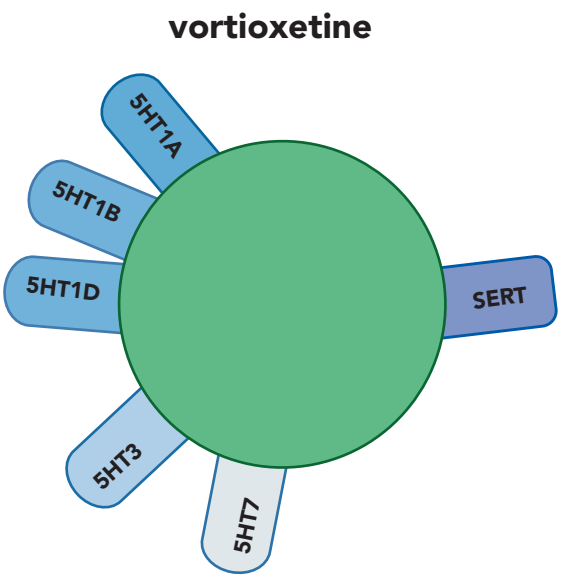


Figure 7-49 Vortioxetine. Vortioxetine is a serotonin reuptake inhibitor and also has actions at several serotonin receptors, including $5HT_{1A}$, $5HT_{1B}$, $5HT_{1D}$, $5HT_3$, and $5HT_7$.

somewhat whimsical way to categorize cognitive dysfunction and to understand the role of improving individual domains of cognition applicable to psychopharmacology is illustrated in Figure 7-50 as the "Fab Four" of cognition. Remember the original Fab Four, the Beatles? Each musician can represent one of the Fab Four of cognition as well. John, arguably the leader, wanted all the attention, so he represents "attention," which some also refer to as concentration. Paul, perhaps the brains of the operation and the writer of many of the songs, is "executive function," also called "problem solving." The quiet culture carrier of the group, George, represents memory, of which there are many kinds, short-term, long-term, verbal, and more. And finally, the drummer, Ringo, represents processing speed, or pace. You can imagine if any of these four is out of synch with the other three, the music would be a disaster. All four can potentially be compromised in psychiatric disorders. It turns out that for depression, a test that measures a bit of all these dimensions of cognition, but arguably most prominently measures processing speed, is the DSST (digital symbol substitution test). When processing speed is slowed, just like an offbeat drummer in a band, overall cognitive functioning can also feel like a disaster for a depressed patient, lagging in cognitive performance, with mental effort now becoming exhausting and work productivity greatly reduced, all causing great frustration. This simple, quick DSST can be useful in

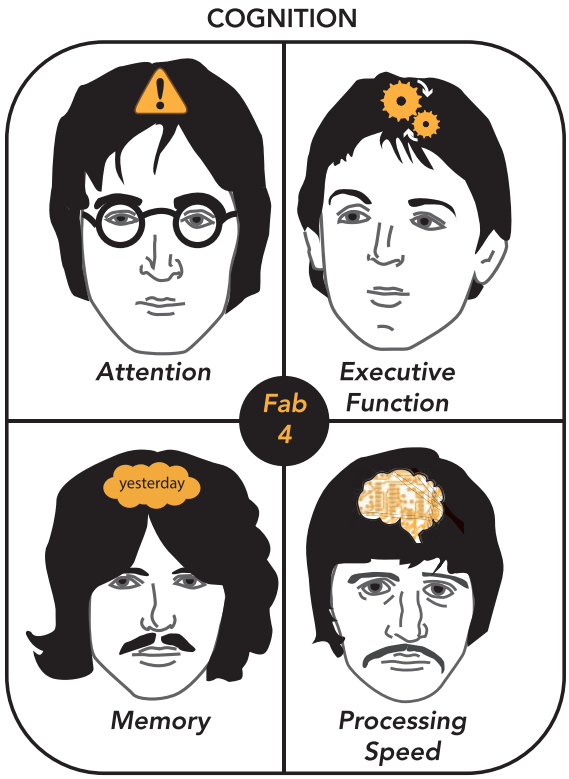


Figure 7-50 The "Fab Four" of cognition. Cognition is not a single, simple brain function. Rather, there are four major cognitive domains, represented here by the four members of the Beatles: attention or concentration (John), executive function or problem solving (Paul), memory (George), and processing speed (Ringo). All four domains work in concert to keep cognition playing at its best; if any one of these domains dysfunctions, then cognitive impairment can occur.

calibrating the objective decline in cognitive performance of patients with subjective cognitive complaints, and in tracking their improvement on treatment. Vortioxetine improves cognition better than other antidepressants in unipolar major depression, as demonstrated by superior performance on the DSST measuring processing speed. How does vortioxetine work as an antidepressant and specifically how does it exert its superior pro-cognitive effects?

SERT Inhibition and $5HT_{1A}$ Agonism

To begin, vortioxetine is a SERT inhibitor and a $5HT_{1A}$ agonist, thus combining the actions already discussed for SSRIs (Figures 7-10 through 7-15) and for combining SERT inhibition with $5HT_{1A}$ agonists (see Chapter 5 and Figures 7-23 through 7-27). These mechanisms alone are sufficient for antidepressant action since they raise both serotonin levels (SERT inhibition) and the pro-

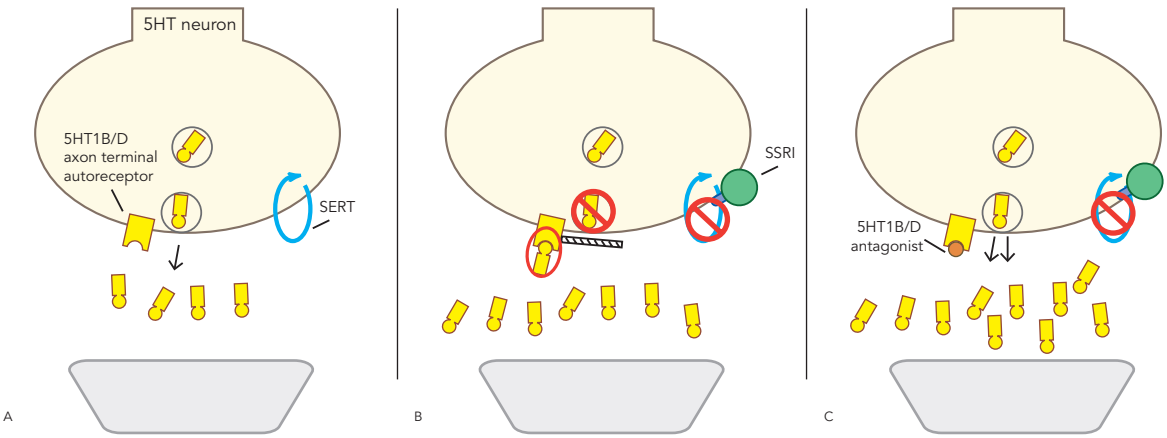


Figure 7-51 SERT inhibition and $5HT_{1B/D}$ presynaptic antagonism. (A) $5HT_{1B/D}$ autoreceptors and serotonin transporters (SERTs) are both present on the axon terminal of a serotonin (5HT) neuron. (B) When SERT is inhibited, synaptic availability of serotonin is increased. However, serotonin binding at the $5HT_{1B/D}$ receptor prevents further serotonin release. (C) When both SERTs and the $5HT_{1B/D}$ receptors are blocked, increased synaptic serotonin via SERT inhibition is combined with ongoing serotonin release via $5HT_{1B/D}$ antagonism, further increasing the availability of serotonin in the synapse.

cognitive neurotransmitter dopamine, acetylcholine, and norepinephrine levels ($5HT_{1A}$ agonism) (see also discussion in Chapter 4, Figure 4-44).

SERT Inhibition and $5HT_{1B/D}$ Presynaptic Antagonism

An additional receptor action that theoretically raises serotonin levels even further than by SERT inhibition alone is inhibition of the $5HT_{1B/D}$ presynaptic autoreceptor (Figure 7-51). That is, when SERT is inhibited, the amount of synaptic serotonin that accumulates is blunted because the build-up of serotonin stimulates presynaptic $5HT_{1B/D}$ autoreceptors, and this turns off further serotonin release (compare Figure 7-51A and B). However, when $5HT_{1B/D}$ presynaptic autoreceptors are simultaneously inhibited, negative feedback to serotonin release cannot occur, so serotonin release increases even more (Figure 7-51C).

$5HT_{1B}$ Partial Agonism/Antagonism at Heteroreceptors

Another putative mechanism of antidepressant and pro-cognitive actions of vortioxetine is antagonist/partial agonist actions on $5HT_{1B}$ receptors located on presynaptic nerve terminals of acetylcholine, dopamine, histamine, and norepinephrine neurons in the prefrontal cortex. These receptors were discussed earlier in Chapter 4 and illustrated in Figure 4-45, showing how serotonin acting at these receptors inhibits the release of acetylcholine, histamine, dopamine, and norepinephrine. These receptors are shown again in Figure 7-52A and when they are blocked by a $5HT_{1B}$ partial agonist/antagonist, this enhances the release of the antidepressant and pro-cognitive neurotransmitters dopamine, norepinephrine, histamine, and acetylcholine (Figure 7-52B).

SERT Inhibition and $5HT_3$ Antagonism

Another mechanism whereby $5HT_3$ antagonists enhance the release of the pro-cognitive neurotransmitters acetylcholine, dopamine, and norepinephrine is illustrated in the earlier discussion of $5HT_3$- antagonism (Figure 7-43) and is one of the most potent of vortioxetine's several pharmacological actions.

SERT Inhibition and $5HT_7$ Antagonism

Serotonin inhibits its own release by actions at $5HT_7$ receptors (compare Figures 7-53A and 7-53B). Thus, antagonism at $5HT_7$ receptors enhances serotonin release, especially in the presence of SERT inhibition (Figure 7-53C). Blocking 5HT7 receptors on GABA neurons in the brainstem raphe prevents the downstream inhibition of serotonin release by GABA, especially in the presence of SERT inhibition, and leads instead to increased downstream release of serotonin (Figure 7-53C).

$5HT_7$ receptors also regulate glutamate release downstream in the prefrontal cortex (Figure 7-54A). Blocking these $5HT_7$ receptors on GABA interneurons enhances the release of glutamate and of downstream monoamine neurotransmitters (compare Figures 7-54A and 7-54B), which may have both antidepressant and pro-cognitive actions. Indeed, in experimental animals, selective $5HT_7$ antagonists do have pro-cognitive and antidepressant actions. Also, numerous agents with

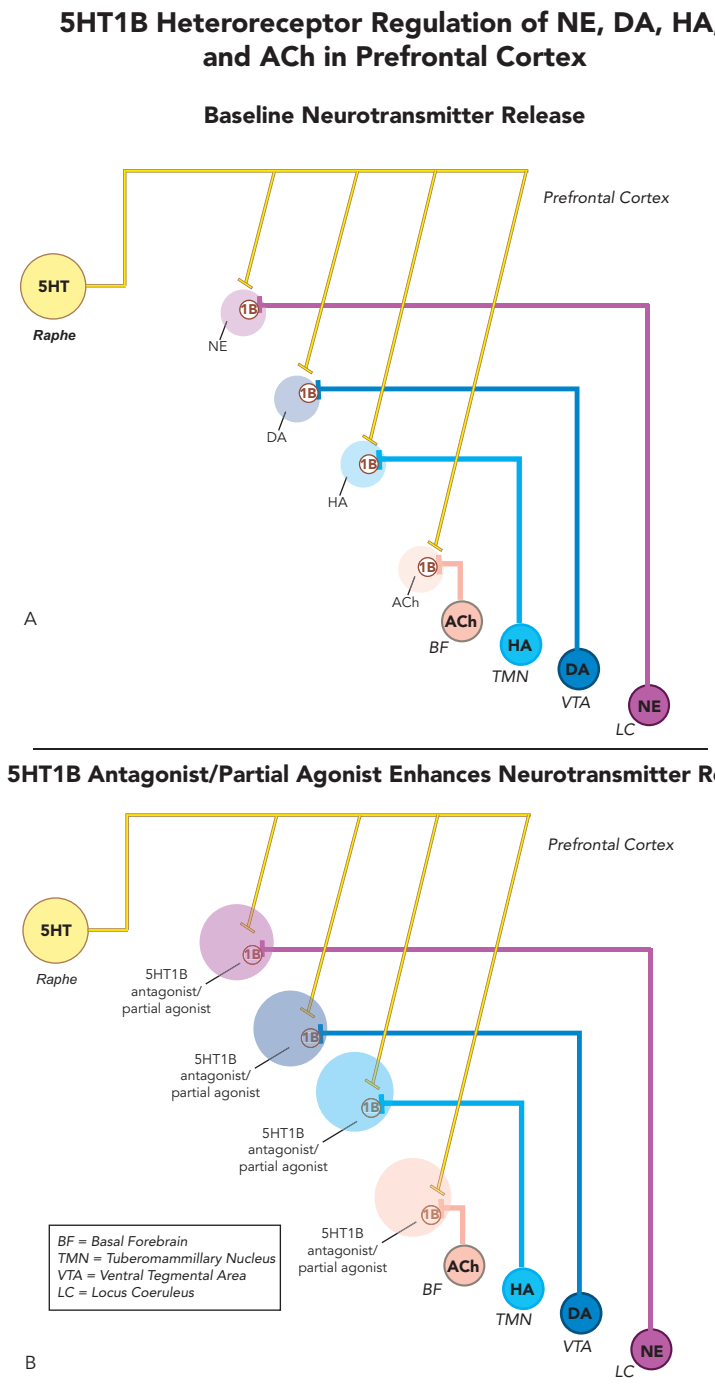


Figure 7-52 **$5HT_{1B}$ heteroreceptors regulate neurotransmitter release.** (A) $5HT_{1B}$ receptors on the presynaptic nerve terminals of norepinephrine (NE), dopamine (DA), acetylcholine (ACh), and histamine (HA) neurons can theoretically regulate the release of these neurotransmitters. Serotonin (5HT) acting at these receptors would be inhibitory. (B) Antagonism or partial agonism of $5HT_{1B}$ heteroreceptors on ACh, HA, DA, and NE neurons would prevent serotonin from exerting its inhibitory effects, thus potentially increasing the release of these neurotransmitters.

$5HT_7$ antagonism are effective drugs for depression and possibly for improving cognition, including not only vortioxetine, but also trazodone (Figures 7-44 and 7-45), quetiapine, brexpiprazole, aripiprazole, and lurasidone (see Chapter 5 and Figure 5-39).

Putting it all together, vortioxetine's pharmacological mechanism of action is multimodal, with numerous synergistic mechanisms not only leading to the release of serotonin and to potentiating the release of serotonin (i.e., via SERT, $5HT_{1B/D}$ presynaptic, and $5HT_7$ blockade), but

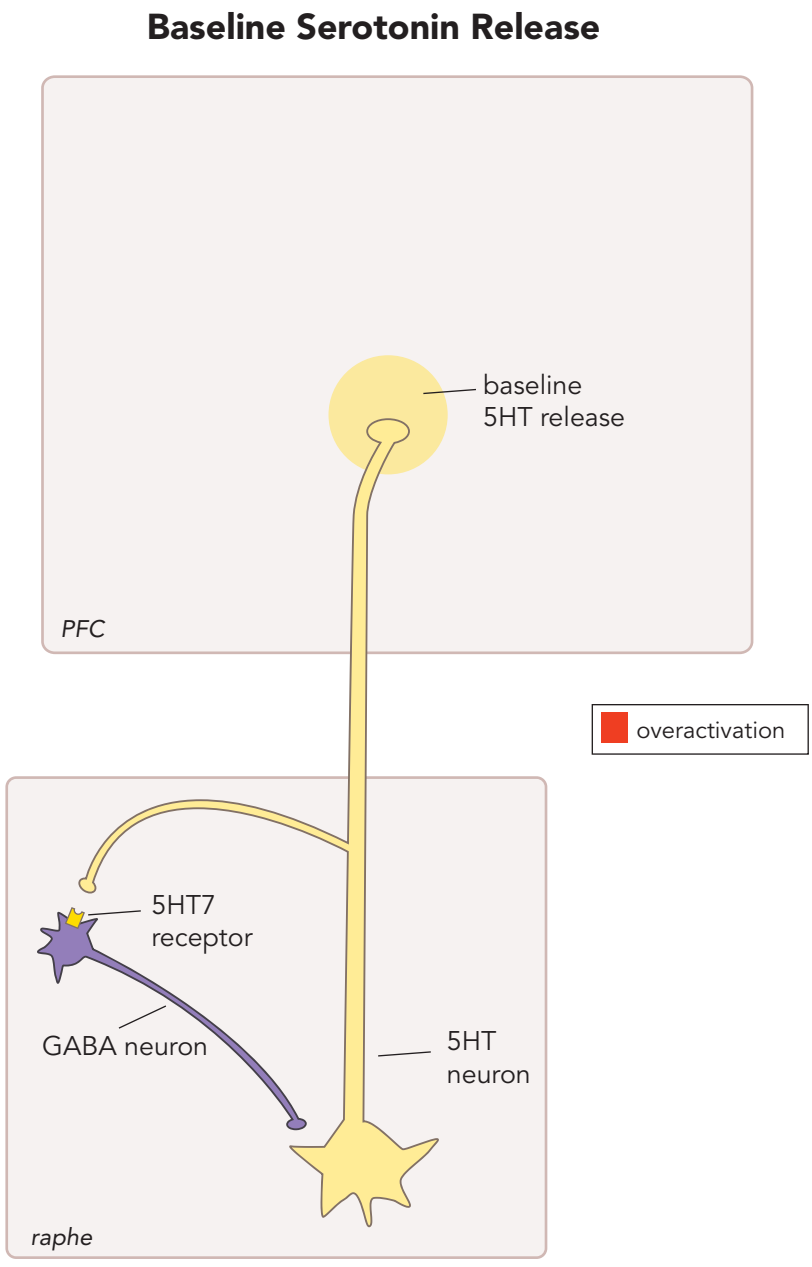


Figure 7-53A **5HT$_7$ receptors regulate serotonin release, part 1.** 5HT$_7$ receptors are located on GABA interneurons in the raphe nucleus. At baseline, when these receptors are not bound, serotonin is released into the prefrontal cortex.

also leading to the release of four further antidepressant and pro-cognitive neurotransmitters, namely dopamine, norepinephrine, acetylcholine, and histamine (i.e., via 5HT$_{1A}$ agonism, 5HT$_{1B}$ heteroreceptor partial agonism/antagonism, and 5HT$_3$ antagonism). This unique combination of mechanisms may account for the unique pro-cognitive actions of vortioxetine in unipolar major depression.

Neuroactive Steroids

Another rapid-onset mood treatment is the neuroactive steroid brexanolone, a cyclodextrin-based intravenous formulation of the naturally occurring neuroactive steroid allopregnanolone (Figure 7-55). Administered by a 60-hour intravenous infusion for postpartum depression, brexanolone has a rapid-onset and sustained antidepressant effect. As briefly mentioned in Chapter 6,

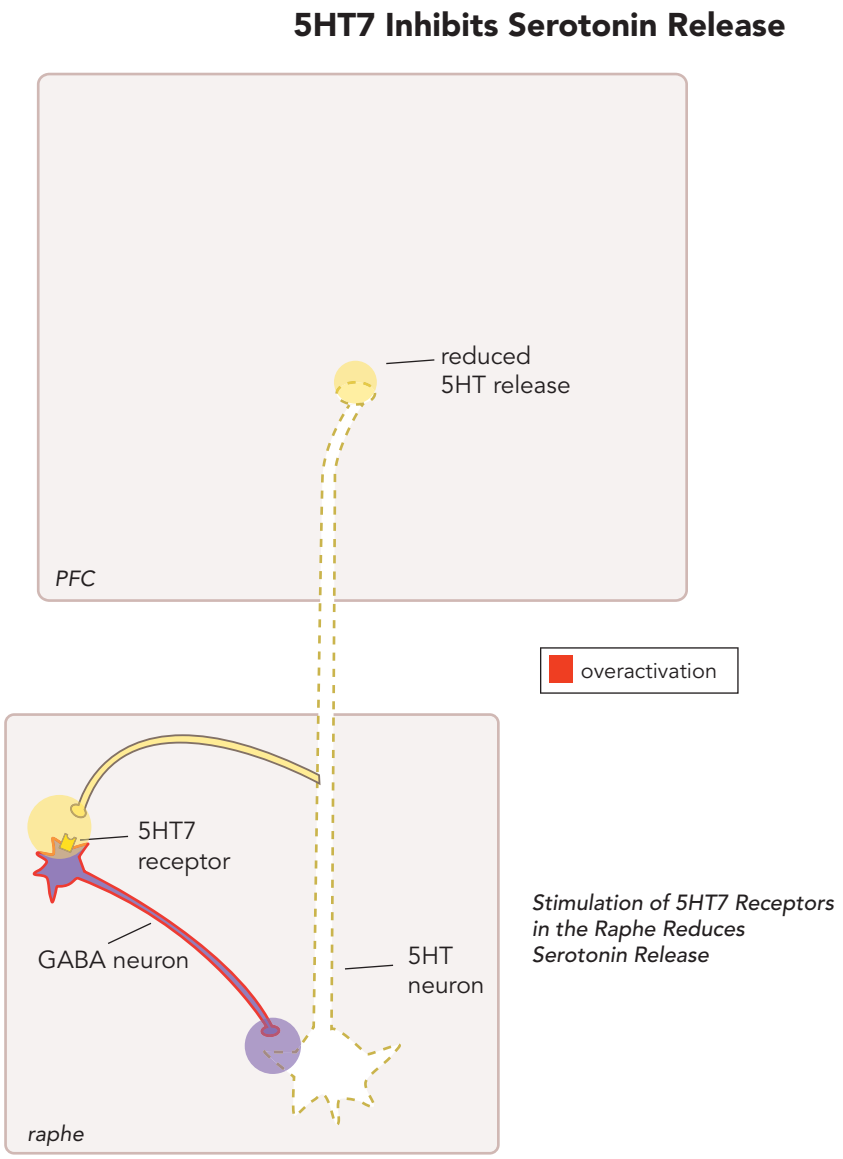


Figure 7-53B **5HT$_7$ receptors regulate serotonin release, part 2.** When serotonin binds to 5HT$_7$ receptors on GABA interneurons in the raphe nucleus, this stimulates GABA release. GABA in turn inhibits serotonin release in the prefrontal cortex.

Stimulation of 5HT7 Receptors in the Raphe Reduces Serotonin Release

pregnant women have high circulating and presumably brain levels of naturally occurring allopregnanolone. After delivery of the baby, there is a precipitous decline in circulating and presumably brain levels of neuroactive steroids, hypothetically triggering the sudden onset of a major depressive episode in vulnerable women. Rapidly restoring neuroactive steroid levels over a 60-hour period of continuous intravenous infusion with brexanolone rapidly reverses depression, and the 60-hour duration of administration seems to provide the time necessary for postpartum patients to accommodate to their lower levels of neuroactive steroids without relapsing, following the infusion.

Neuroactive steroids bind to GABA$_A$ receptors at a specific allosteric site called the neuroactive steroid site, which enhances the inhibitory action of GABA at GABA$_A$ receptors (Figure 7-56; see also discussion in Chapter 6 and Figures 6-20 and 6-21). Neuroactive steroids target the benzodiazepine-sensitive GABA$_A$ receptors, just like benzodiazepines (Figure 7-56A) but also the benzodiazepine-insensitive GABA$_A$ receptors, unlike benzodiazepines (Figure 7-56B).

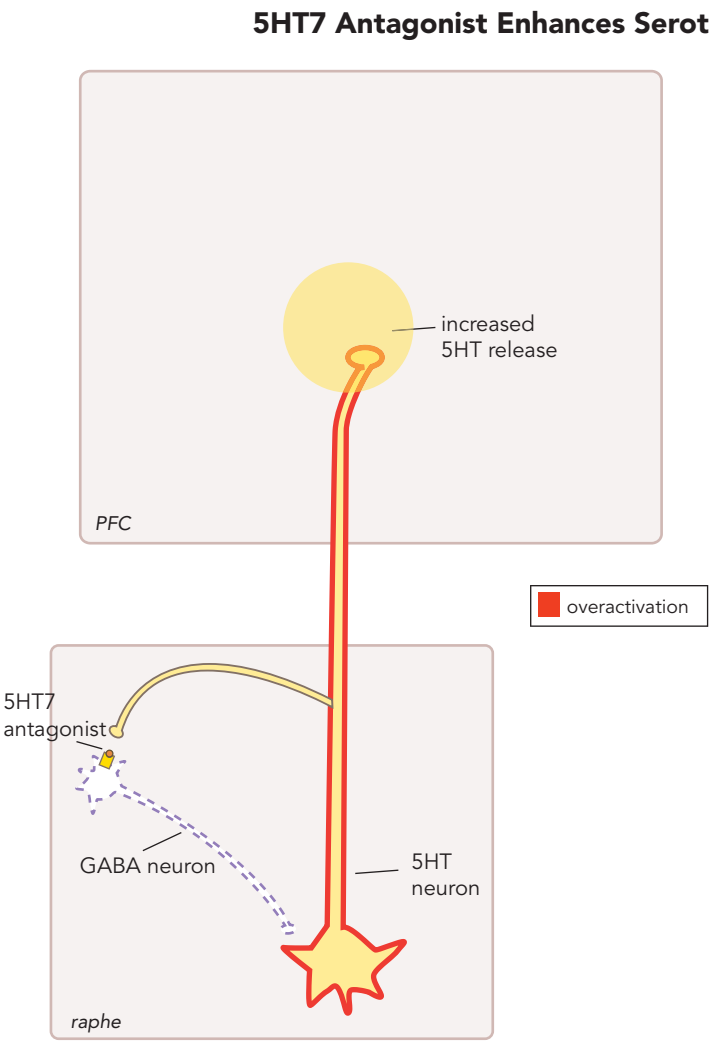


Figure 7-53C **5HT$_7$ receptors regulate serotonin release, part 3.** Antagonism at 5HT$_7$ receptors on GABA interneurons in the raphe nucleus turns off GABA release. This prevents the downstream inhibition of serotonin release by GABA, thus increasing serotonin in the prefrontal cortex.

Certain general anesthetics (e.g., propofol, etomidate, alphaxolone, alfadalone) also bind at the same sites as neuroactive steroids, but are dosed much higher. Since benzodiazepines do not have antidepressant actions, it is the targeting of the benzodiazepine-insensitive GABA$_A$ receptors (Figure 7-56B) that is thought to be the primary mechanism of antidepressant action of neuroactive steroids.

The benzodiazepine-insensitive GABA$_A$ receptors are extrasynaptic and mediate tonic inhibition (see discussion in Chapter 6 and Figure 6-20). The way in which engaging their allosteric neuroactive steroid sites results in a rapid and possibly enduring treatment for major depression is unknown. Hints as to why boosting GABA action may be effective for a novel approach to the treatment of depression come from observations that GABA levels are reduced in the plasma, spinal fluid, and brains of depressed patients; GABA interneurons are reduced in brains of depressed patients; and mRNA levels for the specific GABA$_A$ receptor subunits that encode the benzodiazepine-insensitive GABA$_A$ receptor subtypes are also deficient in brains of depressed patients who died by suicide. Perhaps neuroactive steroids compensate for these GABA-related defects and this is how they mediate their rapid-onset antidepressant actions.

SAGE-217 (Figure 7-57) is a synthetic orally active allopregnanolone analogue in clinical testing as a rapid-onset antidepressant for major depressive disorder, with some promising preliminary results.

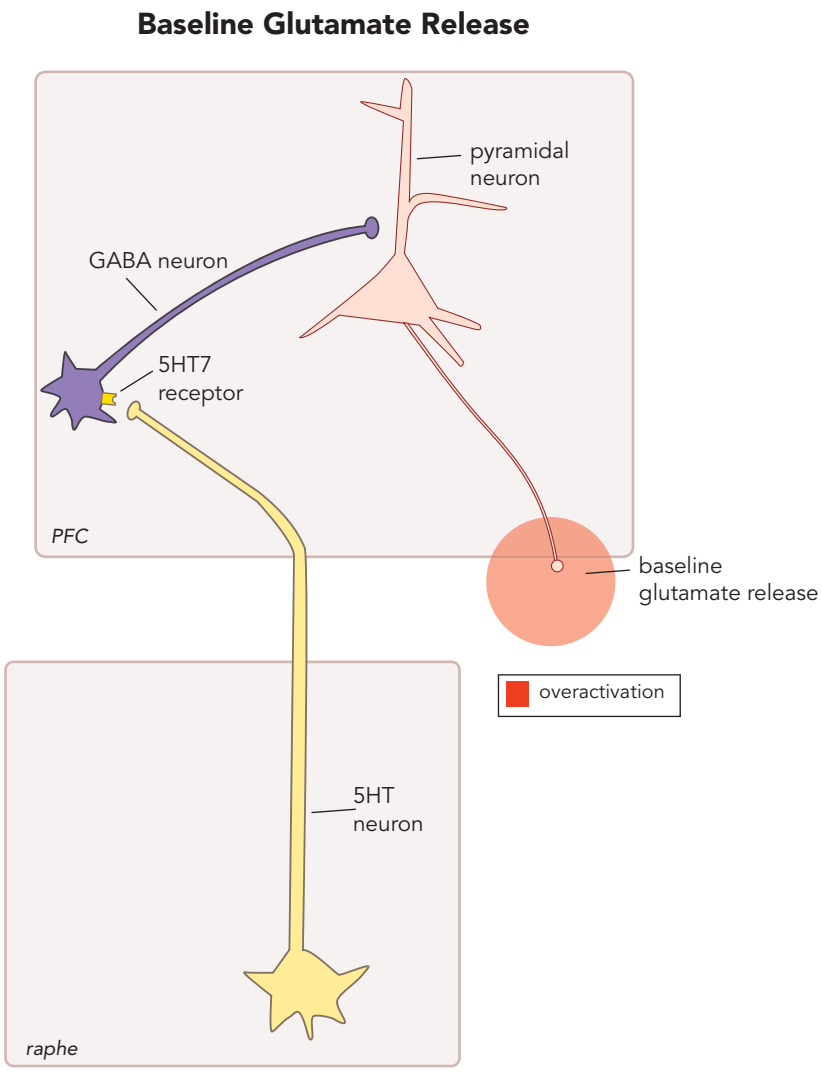


Figure 7-54A **5HT$_7$ receptors regulate glutamate release, part 1.** 5HT$_7$ receptors are located on GABA interneurons in the prefrontal cortex, which themselves synapse with glutamate neurons. At baseline, when these receptors are not bound, glutamate is released.

TREATMENT RESISTANCE IN UNIPOLAR DEPRESSION

Choosing Treatment for Treatment Resistance in Depression on the Basis of Genetic Testing

Genetic testing has the potential of assisting the selection of psychotropic drug treatment for depression, especially when several first-line treatments have failed to work or to be tolerated. Genotyping has already entered other specialties in medicine, and is poised to enter mental health practice. In the not-too-distant future, experts foresee that most patients will have their entire genomes entered as part of their permanent electronic medical records. In the meantime, it is possible to obtain from various laboratories genetic variants for a number of genes that regulate drug metabolism (pharmacokinetic genes) and that hypothetically regulate efficacy and side effects of drugs in depression (pharmacodynamic genes). For example, several genetic forms of numerous cytochrome P450 (CYP450) drug metabolizing enzymes can be obtained to predict high or low levels of drug, and therefore lack of efficacy (low drug levels) or side effects (high drug levels). These findings can also be coupled with phenotyping, namely obtaining the actual plasma drug level itself. CYP450 genotypes and the actual plasma drug levels together can thus potentially help explain side effects and lack of therapeutic effects in some patients.

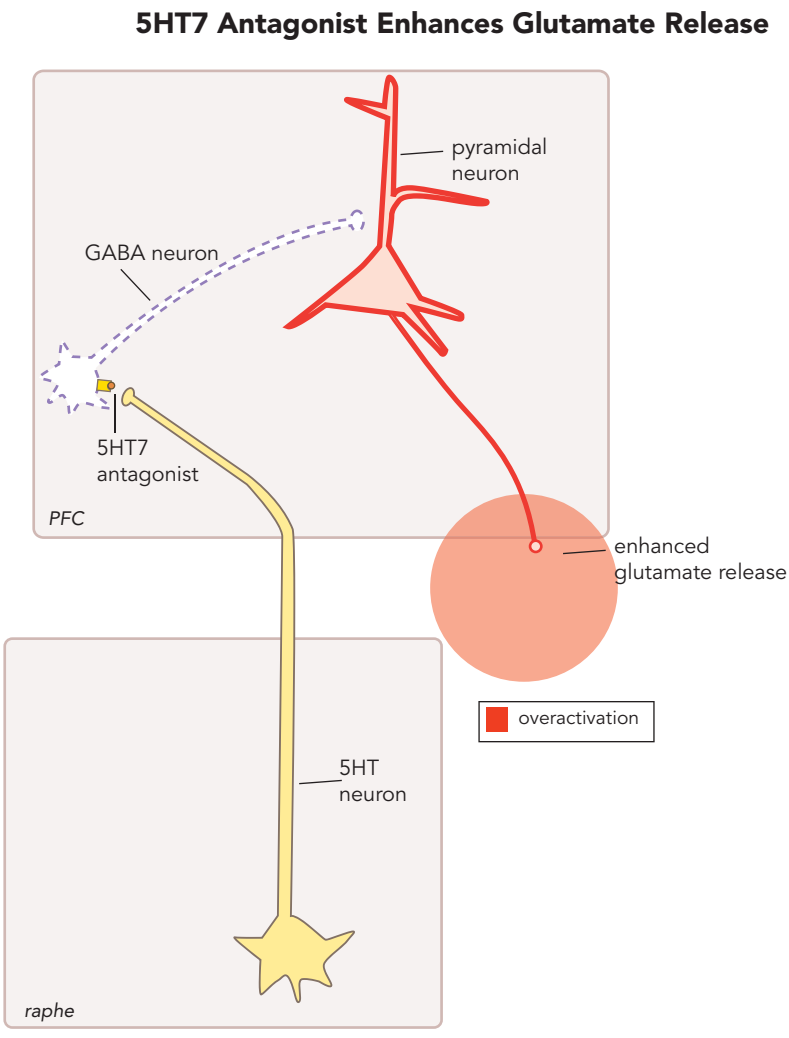


Figure 7-54B **5HT$_7$ receptors regulate glutamate release, part 2.** Antagonism at 5HT$_7$ receptors on GABA interneurons in the prefrontal cortex turns off GABA release. This prevents inhibition of glutamate release by GABA, thus increasing glutamate downstream.

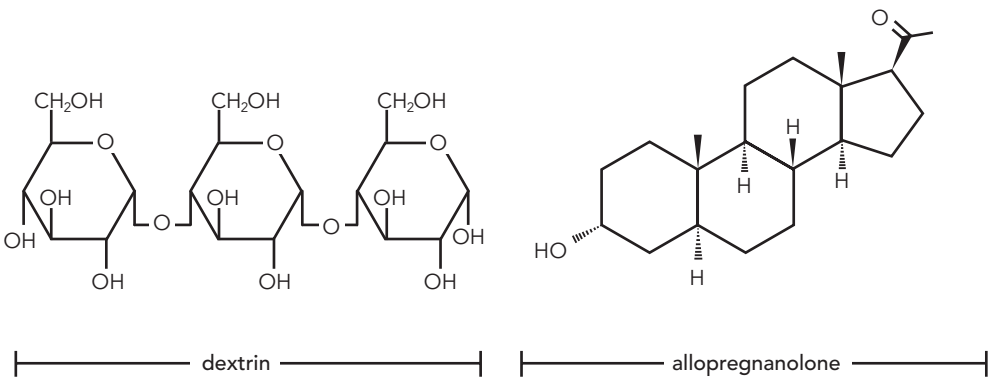


Figure 7-55 **Brexanolone.** Brexanolone is a cyclodextrin-based intravenous formulation of the naturally occurring neuroactive steroid allopregnanolone.

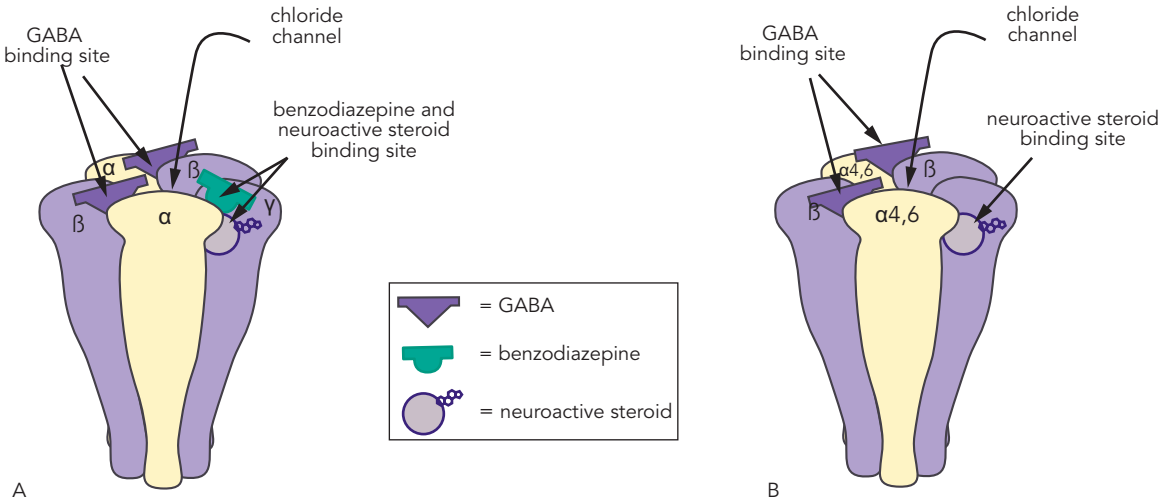


Figure 7-56 Neuroactive steroid binding site on $GABA_A$ neurons. Neuroactive steroids bind to $GABA_A$ receptors at a specific allosteric site called the neuroactive steroid site to enhance the inhibitory action of GABA at these receptors. Neuroactive steroids bind to both benzodiazepine-sensitive (A) and benzodiazepine-insensitive (B) $GABA_A$ receptors.

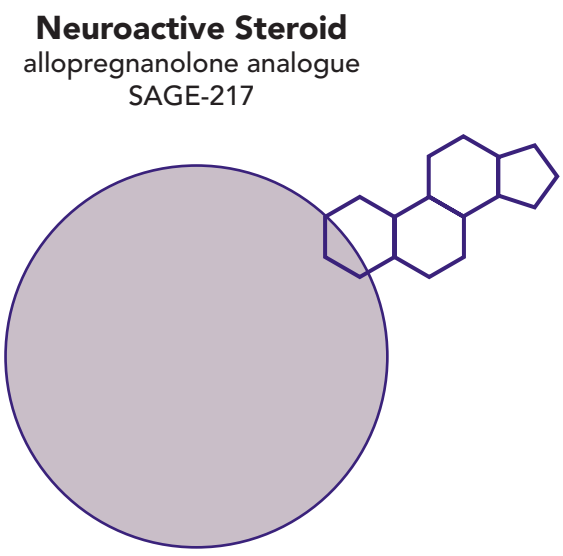


Figure 7-57 SAGE-217. SAGE-217 is a synthetic orally active allopregnanolone analogue in clinical testing as a rapid onset antidepressant for major depressive disorder.

Treatment responses are not "all or none" phenomena, and genetic markers in psychopharmacology will, in all likelihood, explain a greater or lesser likelihood of response, nonresponse, or side effects, but will not tell a clinician with certainty what drug to prescribe for a specific individual to guarantee a clinical response or avoid a side effect. So far, and for the foreseeable future, in the practice of psychopharmacology, the information obtained from pharmacogenomics will likely tell whether the patient is "biased" towards responding or not, tolerating or not, and, along with past treatment response, help the clinician make a future treatment recommendation that has a higher chance of success but is not guaranteed to be effective and tolerated. Some call this process the "weight of the evidence" and others "equipoise," where the genetic information will enrich the prescribing decision, but not necessarily dictate a single compelling choice. Genetic testing makes the prescriber think about, and develop feasible neurobiologically based hypotheses for, the next choices in treatment, rather than mere random selection from amongst treatments that have not yet been attempted.

Augmenting Strategies for Unipolar Depression

As discussed above and illustrated in Figures 7-4 and 7-6, there are diminishing returns of efficacy for unipolar depression, the more drugs for depression that are tried. This has led to earlier use of antidepressant combinations for patients who do not respond well to a single agent, in an attempt to add together synergistic mechanisms that could help the patient attain remission.

Serotonin/Dopamine Antagonists/Partial Agonists as Augmenting Agents for Treatment-Resistant Unipolar Depression

Serotonin/dopamine blocking agents originally developed for psychosis are now some of the most common adjunctive treatments to SSRIs/SNRIs in patients with unipolar depression who fail to respond adequately to one

or more trials of the various first-line monoamine agents discussed so far in this chapter.

Olanzapine–Fluoxetine Combination

Dopamine 2 (D_2) antagonist actions likely account for olanzapine's approval in schizophrenia, bipolar mania, and bipolar maintenance. $5HT_{2A}$ antagonist actions likely account for some of olanzapine's ability to improve symptoms of depression ($5HT_{2A}$ actions on mood are discussed in Chapter 5 and illustrated in Figure 5-17C). However, the fact that olanzapine works much better for unipolar (or bipolar) depression when combined with fluoxetine suggests that not only are serotonin reuptake blocking properties a component of the antidepressant effect of olanzapine–fluoxetine combination therapy, but also $5HT_{2C}$ antagonist actions (Figure 7-38). Both olanzapine and fluoxetine are $5HT_{2C}$ antagonists, and, in combination, the net $5HT_{2C}$ antagonism is greater than with either drug alone. So, this olanzapine–fluoxetine combination for depression could be considered a potent SERT/$5HT_{2C}$ inhibitor. Although highly efficacious for treatment-resistant unipolar depression (Table 7-1), the combination of olanzapine with fluoxetine is often associated with unacceptable weight gain and metabolic disturbances. Olanzapine–fluoxetine combination is also approved for bipolar depression and is discussed in the section on bipolar depression below.

Quetiapine

Quetiapine (see Chapter 5 and Figure 5-45) is approved for schizophrenia, acute bipolar mania, and bipolar maintenance, likely due to its D_2 antagonist actions. Its efficacy as an augmenting agent to SSRIs/SNRIs for depression is likely linked to the combined actions of quetiapine and its active metabolite norquetiapine at both $5HT_{2C}$ receptors (Figure 7-38) and at the norepinephrine transporter (NET) (Figure 5-34; also described in Chapter 5 and illustrated in Figure 5-45). In addition, quetiapine acts at other candidate receptors for antidepressant efficacy including as an antagonist at $5HT_{2A}$ (Chapter 5 and Figure 5-17C), $5HT_7$ (Figure 7-53C) and α_{2A} receptors (Figure 5-35), as well as an agonist at $5HT_{1A}$ receptors (Chapter 5 and Figure 5-22). All of these receptor actions are hypothetically associated with antidepressant efficacy and, added together, could make a theoretically powerful synergy of antidepressant mechanisms (Table 7-1). However, quetiapine can cause a great deal of sedation and moderate weight gain and metabolic disturbance due to its other receptor actions. Quetiapine is also approved for bipolar depression and discussed in the section on bipolar depression below.

Aripiprazole

This D_2/$5HT_{1A}$ partial agonist (Chapter 5 and Figure 5-56) is approved for schizophrenia, acute bipolar mania, and bipolar maintenance and is one of the most extensively prescribed augmenting agents to SSRIs/SNRIs in unipolar major depression (in the US) (Table 7-1). It likely acts in schizophrenia and bipolar mania as a D_2 partial agonist, whereas its prominent $5HT_{1A}$ partial agonist actions (Chapter 5 and Figure 5-22) likely contribute to its antidepressant actions. Secondary properties with potential antidepressant action may also be contributory including D_3, $5HT_7$, $5HT_{2C}$, and α_2

Table 7-1 Serotonin/dopamine blockers for bipolar spectrum

	Evidence of efficacy in mixed features	FDA-approved for bipolar depression	FDA-approved for bipolar mania	FDA-approved for bipolar maintenance	FDA-approved for major depressive disorder
Aripiprazole			Yes	Yes	Yes (adjunct)
Asenapine	Yes, MMX		Yes	Yes	
Brexpiprazole					Yes (adjunct)
Cariprazine	Yes, MMX, DMX	Yes	Yes		
Lurasidone	Yes, DMX*	Yes			
Olanzapine	Yes, MMX	Yes (with fluoxetine)	Yes	Yes	Yes (with fluoxetine)
Quetiapine	Yes, MMX	Yes	Yes	Yes	Yes (adjunct)
Risperidone			Yes	Yes	
Ziprasidone	Yes, MMX		Yes	Yes	

MMX, mania with mixed features; DMX, depression with mixed features.
*unipolar and bipolar depression.

antagonist actions. Aripiprazole is generally well tolerated with little weight gain but some patients experience akathisia. Aripiprazole is not approved for the treatment of bipolar depression.

Brexpiprazole

Another D_2/$5HT_{1A}$ partial agonist (see Chapter 5 and Figure 5-57) is approved for schizophrenia and also for adjunctive treatment in unipolar depression (Table 7-1). Brexpiprazole is not approved for the treatment of bipolar depression. As mentioned earlier in discussion of brexpiprazole for psychosis in Chapter 5, there is some indication of reduced akathisia with brexpiprazole compared to aripiprazole, but this has not been proven in head-to-head trials. Reduced akathisia would be consistent with the binding profile of enhanced $5HT_{2A}$ (Chapter 5, Figure 5-17B), $5HT_{1A}$ (Chapter 5, Figure 5-22A), and α_1 (Figure 7-58A) binding of brexpiprazole compared to aripiprazole (compare the binding strips of aripiprazole in Figure 5-56 and brexpiprazole in Figure 5-57). As can be seen in these figures, brexpiprazole also has more potent α_2 antagonist, $5HT_7$ antagonist, and D_3 partial agonist binding than aripiprazole. These various differences in receptor binding profiles could theoretically contribute to different mechanisms of therapeutic action and side effects for brexpiprazole compared to aripiprazole.

Alpha-1 antagonist actions have been discussed in Chapter 5 and illustrated in Figure 5-13B showing how α_1 antagonism, particularly in the thalamus, could contribute to sedation when coupled with simultaneous blockade of muscarinic cholinergic and histamine receptors in the reticular activating arousal system (Chapter 5, Figures 5-13A and 5-8). However, particularly

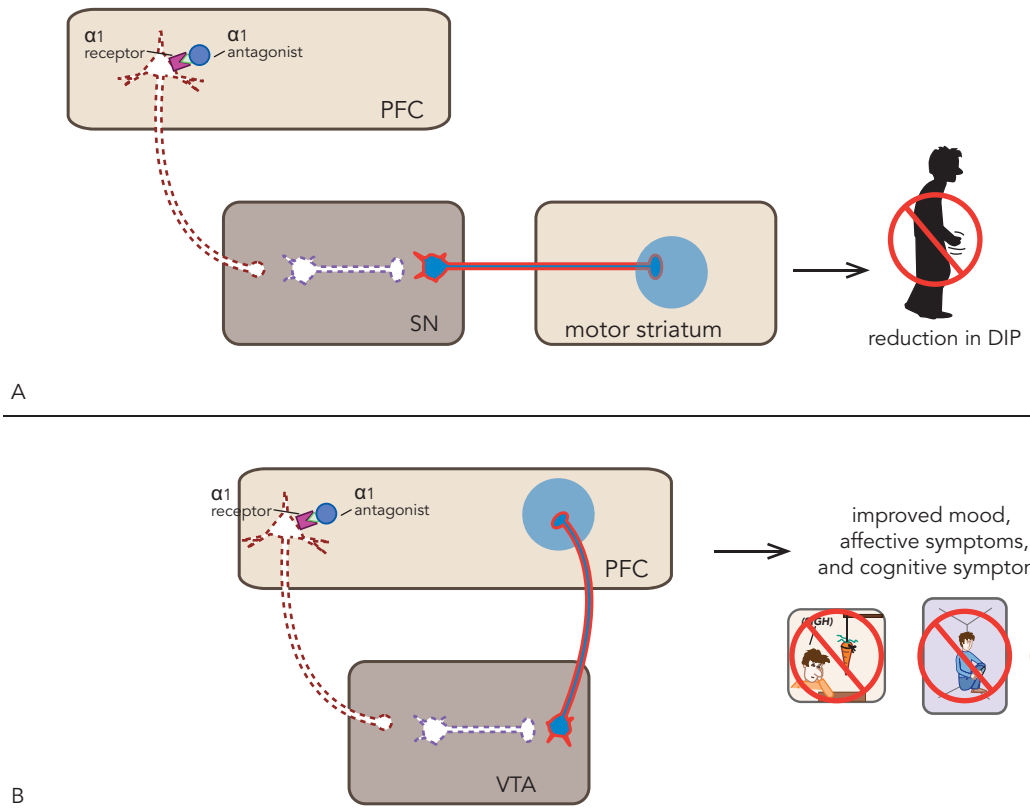


Figure 7-58 Alpha-1 antagonism and downstream dopamine release. Alpha-1 antagonism can modulate downstream dopamine release via two key pathways. (A) Alpha-1 antagonism decreases glutamatergic output in the substantia nigra (SN), leading to reduced activity of the GABA interneuron and therefore disinhibition of the nigrostriatal dopamine pathway. The increased dopamine release in the motor striatum can reduce motor side effects caused by D_2 antagonism because there is more dopamine to compete with the D_2 antagonist. (B) Alpha-1 antagonism reduces glutamatergic output in the ventral tegmental area (VTA), leading to reduced activity of the GABA interneuron and therefore disinhibition of the mesocortical dopamine pathway. Increased dopamine release in the prefrontal cortex (PFC) can potentially improve mood and reduce affective and cognitive symptoms.

without simultaneous muscarinic and histaminic antagonism, α_1 antagonist action in the prefrontal cortex could hypothetically also contribute both to the reduced motor side effects and to the known antidepressant effects seen with potent α_1 antagonists, particularly those with simultaneous $5HT_{2A}$ antagonist properties. Alpha-1 antagonist actions of brexpiprazole could also potentially contribute to its evidence of efficacy for agitation in Alzheimer disease and in PTSD (as augmentation of sertraline).

How does this happen and what circuits regulate α_1 antagonist action? The answer is that the reader is already familiar with the circuitry to explain the actions of α_1 antagonists, since it is the same circuitry already discussed for $5HT_{2A}$ receptors and illustrated in Chapter 5 in Figures 5-16 and 5-17. It is now known that α_1 receptors (illustrated here in Figure 7-58) are colocalized on the same pyramidal neurons with $5HT_{2A}$ receptors (discussed in Chapter 5 and illustrated in Figures 5-16 and 5-17). Since both α_1 receptors and $5HT_{2A}$ receptors are excitatory and postsynaptic, norepinephrine and serotonin acting together exert a more powerful excitatory control of prefrontal cortex function through their simultaneous action than either neurotransmitter acting alone.

Furthermore, the actions of an α_1 antagonist would be expected to have the same functional effects as a $5HT_{2A}$ antagonist, the two actions acting together to have a more powerful downstream inhibitory control of the prefrontal cortex output than blockade of either receptor alone. Figure 7-58A shows the α_1 receptors on those specific pyramidal neurons projecting to the substantia nigra (same pyramidal neurons and circuitry as shown in Chapter 5, Figure 5-17B). When this glutamatergic neuron is inhibited by an α_1 antagonist, its innervation of the substantia nigra reduces GABA tone there, allowing disinhibition of dopamine release into the motor striatum and reduction of drug-induced parkinsonism (Figure 7-58A; just as shown in Chapter 5 and Figure 5-17B). Thus, drug-induced parkinsonism caused by D_2 blockers will be maximally reduced by those D_2 blockers that have both $5HT_{2A}$ and α_1 antagonist actions. Indeed, the lowest frequency and severity of drug-induced parkinsonism induced by dopamine blockers is for those that also have robust α_1 and $5HT_{2A}$ antagonist actions, namely, brexpiprazole, quetiapine, clozapine, and iloperidone.

Synergy of α_1 antagonism with $5HT_{2A}$ antagonism can theoretically also enhance antidepressant action, this time in the circuit of pyramidal neurons innervating the ventral tegmental area dopamine neurons that project to the prefrontal cortex (Figure 7-58B and Chapter 5, Figure 5-17C). What this means is that α_1 antagonists would theoretically have the same effect as $5HT_{2A}$ antagonists in this circuit, and the two working together would exert a more powerful control of the prefrontal cortex and its downstream projections, to further facilitate dopamine release in the prefrontal cortex and to cause antidepressant action. In fact, this synergy is likely to be an important component of the mechanism of antidepressant action for those agents that are both α_1 and $5HT_{2A}$ antagonists, including brexpiprazole, quetiapine, and trazodone. The enhancement of dopamine release in the prefrontal cortex by simultaneous α_1 and $5HT_{2A}$ blockade may theoretically contribute as well to improving "top-down" control of agitation in Alzheimer disease and PTSD symptoms, which are seen in ongoing studies of brexpiprazole.

Cariprazine

Carpirazine (Chapter 5 and Figure 5-58) is a $D_3/D_2/5HT_{1A}$ partial agonist as well as a $5HT_{2A}/\alpha_1/\alpha_2$ antagonist, approved for the treatment of acute bipolar mania and bipolar depression; it also has evidence of efficacy as an adjunct to SSRI/SNRIs in unipolar depression (Table 7-1). Cariprazine's antidepressant mechanism of action is discussed below in the section on treating bipolar depression.

Ketamine

Observations that the intravenous infusion of subanesthetic doses of ketamine could rapidly improve depression in patients inadequately responsive to monoamine-targeting drugs has set forth a bit of a revolution in the treatment of depression. Ketamine is an approved anesthetic but used off-label for treatment-resistant depression. Whereas serotonin/dopamine blockers tend to be used after just one or two failures of an SSRI/SNRI, ketamine tends to be given to patients with multiple failures on various drugs for depression. Intravenous ketamine is a racemic mixture of R- and S-ketamine, each with overlapping binding properties at the NMDA subtype of glutamate receptor, its putative mechanism of antidepressant action, and at the σ_1 receptor (Figure 7-59). Actions at other sites, including μ-opioid and other neurotransmitter sites, are proposed but disputed, especially the possibility that ketamine's antidepressant actions may be linked in some way to μ-opioid as well as NMDA action. Thus, a debate exists as to how ketamine exerts its rapid-onset antidepressant effects, but NMDA antagonism – specifically at the

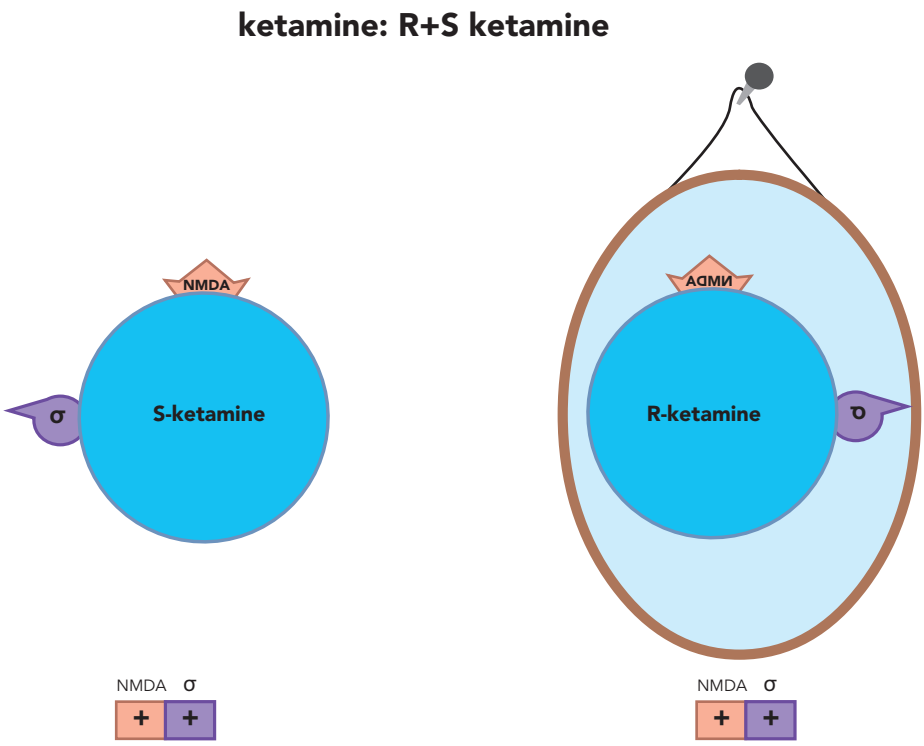


Figure 7-59 Ketamine. Ketamine is used off-label and is being studied for its potential therapeutic utility in treatment-resistant depression. Ketamine is an NMDA (*N*-methyl-D-aspartate) receptor antagonist, with additional weak actions at σ_1 receptors, the norepinephrine transporter (NET), μ-opioid receptors, and the serotonin transporter (SERT). Ketamine consists of two enantiomers, R and S.

open-channel phencyclidine (PCP) site (see discussion in Chapter 4 and Figure 4-30) – is the leading hypothesized target for explaining ketamine's antidepressant effects. What is unique about ketamine infusions is the rapid, almost immediate onset of antidepressant effects, sometimes accompanied by specific anti-suicidal ideation effects, in patients who seem to have "nonmonoaminergic" depressions since they have failed numerous standard monoamine-targeted antidepressant therapies. Unfortunately, the antidepressant effects of ketamine are usually not long lasting, but generally fade over a few days. In some cases, the antidepressant effects can be re-triggered by repeated infusions over time, or enhanced by monoaminergic antidepressant treatments following infusions.

Most interesting perhaps is the possibility that ketamine causes immediate improvement in neuronal plasticity as its downstream mechanism of immediately improving depression. Loss of neurotrophic factors in depression is discussed in Chapter 6 and illustrated in Figures 6-27 through 6-33). Recall that the neurotrophic hypothesis of depression and antidepressant response is based on evidence that deficiencies in neurotrophic factors such as BDNF (brain-derived neurotrophic factor) and possibly other growth factors such as VEGF (vascular endothelial growth factor) occur with chronic stress and major depression and that when monoaminergic drugs for depression are effective, they restore these growth factors, but with a delay of weeks after drug administration. On the other hand, when monoaminergic drugs for depression are not effective, it is assumed that for unknown reasons monoamines cannot restore the necessary growth factors. Loss of BDNF and VEGF are both linked to neuronal atrophy in brain regions such as the prefrontal cortex and hippocampus in chronic stress models in animals as well as in unipolar major depressive disorder. Chronic stress and depression are also thought to decrease the receptors for BDNF and VEGF, namely TRKB (tyrosine kinase 2) and FLK1 (fetal liver kinase 1), respectively. Ketamine increases both of these growth factors.

So, how does ketamine induce its rapid antidepressant response and rapid reversal of synaptic atrophy in depression? This is thought to occur because ketamine

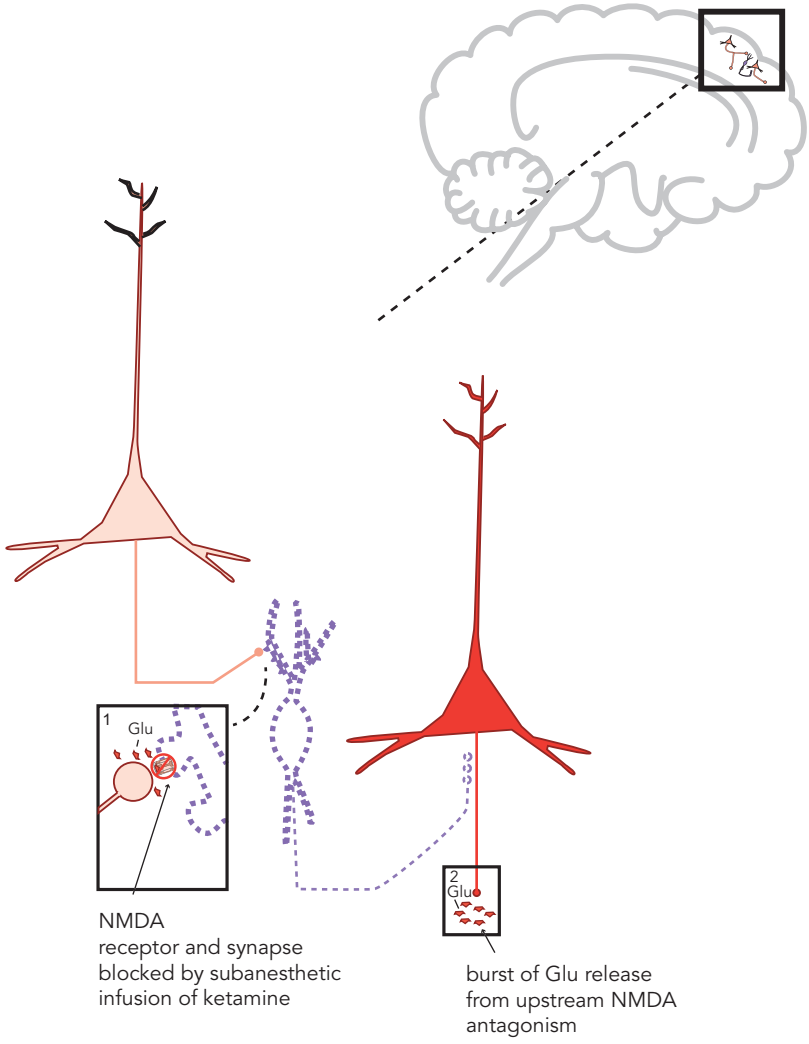
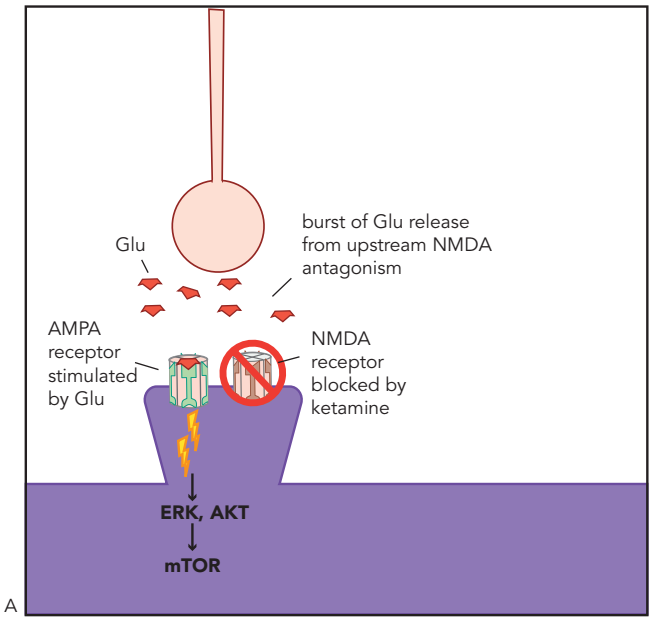


Figure 7-60 Mechanism of action of ketamine. Shown here are two cortical glutamatergic pyramidal neurons and a GABAergic interneuron. (1) If an *N*-methyl-D-aspartate (NMDA) receptor on a GABAergic interneuron is blocked by ketamine, this prevents the excitatory actions of glutamate (Glu) there. Thus, the GABA neuron is inactivated and does not release GABA (indicated by the dotted outline of the neuron). (2) GABA binding at the second cortical glutamatergic pyramidal neuron normally inhibits glutamate release; thus, the absence of GABA there means that the neuron is disinhibited and glutamate release is increased.

causes an immediate burst of downstream glutamate release after blocking NMDA receptors (discussed in Chapter 4 and illustrated in Figure 4-33; see also Figure 7-60). Ketamine's actions at NMDA receptors are not unlike what is hypothesized to occur due to neurodevelopmental abnormalities at NMDA synapses in schizophrenia (also discussed in Chapter 4 and illustrated in Figures 4-29B and 4-31 through 4-33). This is not surprising given that ketamine can produce a schizophrenia-like syndrome in humans especially at high doses and acute drug administration (Figure 4-33). However, when infused over time and at subanesthetic doses in the study of depressed patients, ketamine does not induce psychosis, but is thought to produce downstream release in glutamate (Figure 7-60). Glutamate that is released in this burst stimulates AMPA receptors while ketamine is blocking NMDA receptors (Figures 7-61 and 7-62). One hypothesis for why ketamine has antidepressant actions proposes that this stimulation of AMPA receptors first activates the ERK, AKT signal transduction cascade (Figures 7-61A). This then triggers the mTOR (mammalian target of rapamycin) pathway (Figures 7-61) and that causes the expression of synaptic proteins, leading to an increased density of dendritic spines (Figures 7-61B). Dendritic spine proliferation indicating new synaptogenesis can be seen within minutes to hours after ketamine is administered in animals. Hypothetically, it is this increase in dendritic spines and synaptogenesis that causes the rapid-onset antidepressant effect. Another hypothesis for why ketamine has antidepressant actions proposes that the stimulation of AMPA receptors from the burst



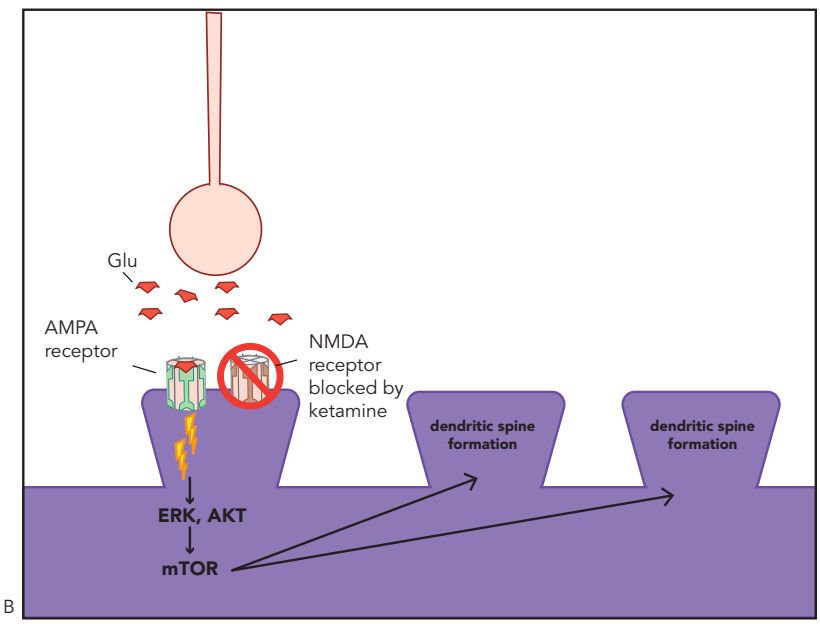


Figure 7-61 Ketamine, AMPA receptors, and mTOR. Glutamate activity heavily modulates synaptic potentiation; this is specifically modulated through NMDA (*N*-methyl-D-aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid) receptors. Ketamine is an NMDA receptor antagonist; however, its rapid antidepressant effects may also be related to indirect effects on AMPA receptor signaling. (A) One hypothesis is that blockade of the NMDA receptor leads to rapid activation of AMPA, which triggers the ERK, AKT signal transduction cascade, which then triggers the mammalian target of rapamycin (mTOR) pathway. (B) This in turn would lead to rapid AMPA-mediated synaptic potentiation and increase in dendritic spine formation. Traditional antidepressants also cause synaptic potentiation; however, they do so via downstream changes in intracellular signaling. This may therefore explain the difference in onset of antidepressant action between ketamine and traditional antidepressants.

of glutamate release (Figure 7-62A) activates another signal transduction pathway, namely voltage-sensitive calcium channels, which allow calcium influx that in turn activates BDNF and VEGF release to induce synaptic formation (Figure 7-62B). Thus, ketamine hypothetically reverses the atrophy caused by depression, and does this within minutes.

Esketamine

The S enantiomer of ketamine is approved for treatment-resistant depression in an intranasal formulation for administration, and is called esketamine (Figure 7-63). The exact pharmacology of R- versus S-ketamine and their active metabolites is still being determined in terms of neurotrophic actions. However, esketamine is indeed

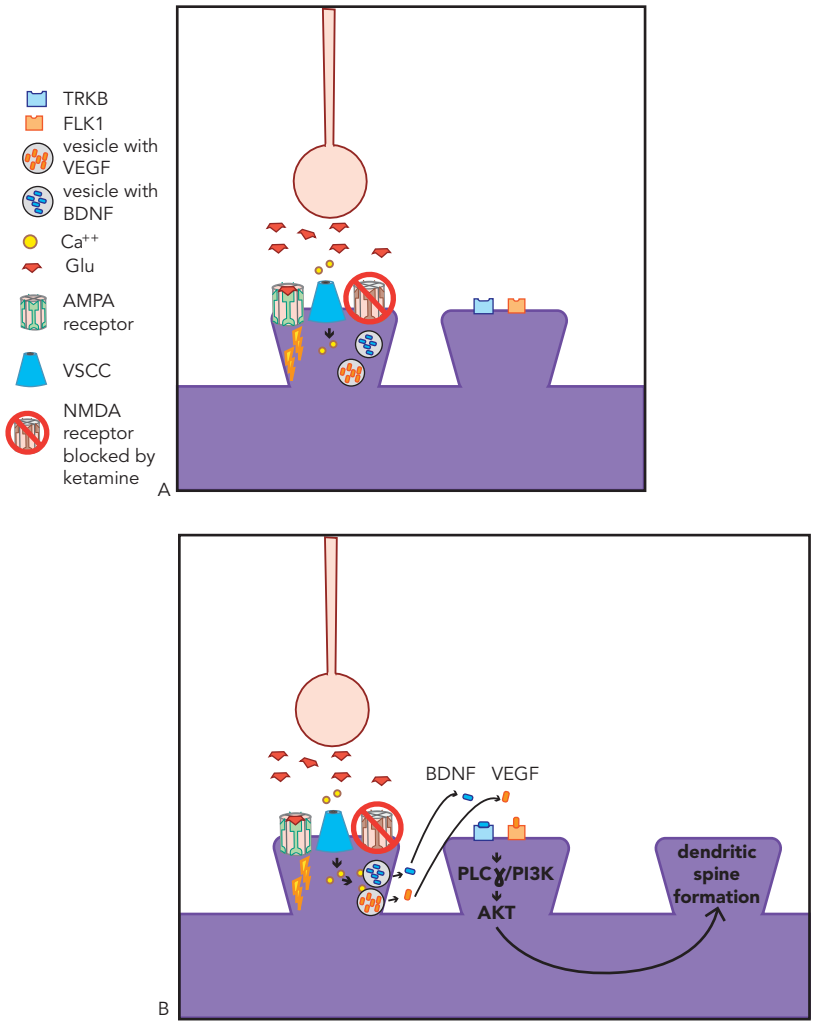


Figure 7-62 Ketamine, AMPA receptors, and BDNF/VEGF release. Glutamate activity heavily modulates synaptic potentiation; this is specifically modulated through NMDA (*N*-methyl-D-aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid) receptors. Ketamine is an NMDA receptor antagonist; however, its rapid antidepressant effects may also be related to indirect effects on AMPA receptor signaling. (A) A second hypothesis is that blockade of the NMDA receptor leads to rapid activation of AMPA, which activates voltage-sensitive calcium channels (VSCCs) to allow calcium influx. (B) This in turn would lead to activation of brain-derived neurotrophic factor (BDNF) and VEGF (vascular endothelial growth factor) release, which bind to TRKB and FLK1 receptors, respectively, triggering cascades that induce dendritic spine formation.

active as an acute rapid-onset antidepressant, and it is administered intranasally and rapidly, so that longer intravenous infusions are not necessary. After twice-weekly initiation, esketamine can be given intranasally in weekly or biweekly dosing as an augmenting agent to standard drugs for depression. A long-term study for up to a year of esketamine nasal spray plus a switch to an oral monoamine antidepressant not previously tried, showed sustained improvements in depression and acceptable safety.

Other Drug Combinations for Treatment-Resistant Depression

Other options to augment monoamine treatments for unipolar depression include agents that do not have robust antidepressant actions as monotherapies but can improve the action of the monoamine treatments (e.g., lithium, buspirone, and thyroid), as well as the very popular and often effective strategy of combining two monoamine drugs, each approved for unipolar depression, to create pharmacological synergy. However, none of these strategies are specifically approved.

Lithium

Lithium is discussed below as a treatment for mania, but has been used as well for unipolar depressed patients who fail to respond to treatment. Lithium augmentation of monoamine reuptake inhibitors, particularly the classic tricyclic antidepressants also discussed below, has been used in the past to boost treatment response in unipolar depression. As augmentation for treatment-resistant unipolar depression, lithium is administered in doses lower than those used for mania, but it has fallen out of favor in recent years.

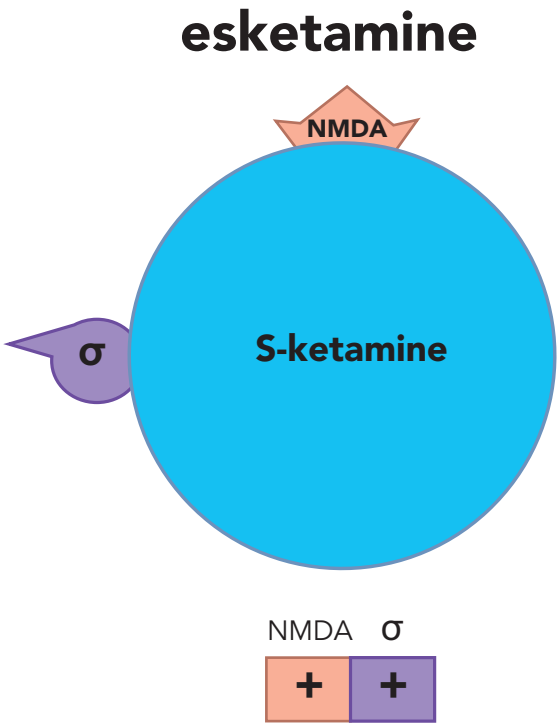


Figure 7-63 Esketamine. The R and S enantiomers of ketamine are mirror images of each other; the exact pharmacology of the R and S enantiomers and their active metabolites is still being determined. The S enantiomer of ketamine has been developed and marketed as esketamine.

Buspirone

Buspirone is a $5HT_{1A}$ partial agonist, so putting it together with an SSRI/SNRI is very much similar to the use of vilazodone (Figure 7-22 through Figure 7-27) or vortioxetine (Figure 7-49) discussed above. Indeed, most of the serotonin/dopamine agents used to augment monoamine antidepressants have $5HT_{1A}$ properties (e.g., quetiapine, aripiprazole, brexpiprazole, and cariprazine). Administering drugs that have $5HT_{1A}$ agonist actions is a favored approach for augmenting SSRI/SNRIs, but using buspirone for this is less common today than using other agents with $5HT_{1A}$ properties.

Thyroid Hormones

Thyroid hormones act by binding to nuclear ligand receptors to form a nuclear ligand-activated transcription factor. Abnormalities in thyroid hormone levels have long been associated with depression, and various forms and doses of thyroid hormones have for many years been utilized as augmenting agents to drugs for depression either to boost their efficacy in patients with inadequate response or to speed up their onset of action. Thyroid's known abilities to regulate neuronal organization, arborization, and synapse formation may have the downstream consequence of boosting monoamine neurotransmitters, and this may account for how thyroid hormones enhance antidepressant action in some patients. Augmentation of treatments for either unipolar or bipolar depression with thyroid hormones has also fallen out of favor in recent years.

Triple-Action Combo: SSRI/SNRI + NDRI

If boosting one neurotransmitter is good, and two is better, maybe three boosted neurotransmitters is best (Figures 7-64). Triple action (i.e, serotonin, dopamine, and norepinephrine) drugs for depression therapy with modulation of all three monoamines would be predicted to occur by combining either an SSRI with an NDRI or combining an SNRI with an NDRI, providing even more noradrenergic and dopaminergic action (Figure 7-64). These are perhaps some of the most popular combinations of two drugs for depression utilized in the US.

California Rocket Fuel: SNRI plus Mirtazapine

This potentially powerful combination exploits the pharmacological synergy attained by adding the enhanced serotonin and norepinephrine release from inhibition of both serotonin and norepinephrine reuptake by an SNRI to the disinhibition of both serotonin and norepinephrine release by the α_2 antagonist actions of mirtazapine (Figure 7-65). It is even possible that additional pro-dopaminergic actions result from the combination of norepinephrine reuptake blockade in the prefrontal cortex due to SNRIs with $5HT_{2C}$ actions of mirtazapine disinhibiting dopamine release. This combination can provide very powerful antidepressant action for some patients with unipolar major depressive episodes.

Arousal Combos

The frequent complaints of residual fatigue; loss of energy, motivation, and sex drive; and problems concentrating/problems with alertness may be approached by combining either a stimulant (dopamine transport inhibitor or DAT inhibitor) with an SNRI, or modafinil (another DAT inhibitor) with an SNRI (Figure 7-66), to recruit triple monoamine action and especially enhancement of dopamine.

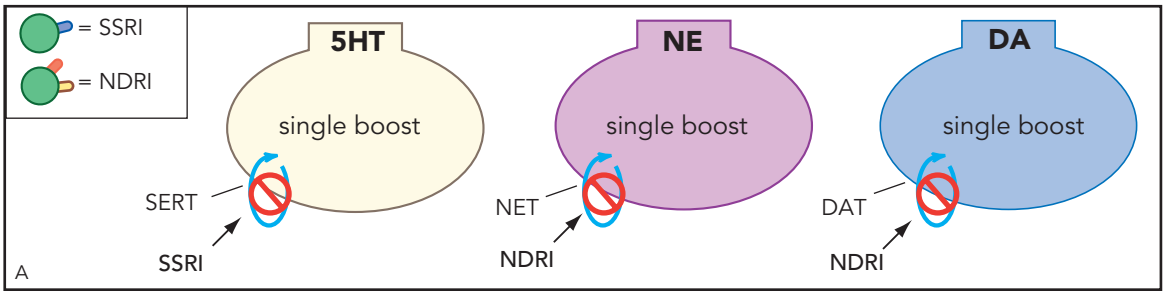
Second-Line Monotherapies Used for Treatment-Resistant Depression

Tricyclic Antidepressants

The tricyclic antidepressants (TCAs) (Table 7-2; Figure 7-67) were so-named because their chemical

Triple-Action Combos

SSRI + NDRI



SNRI + NDRI

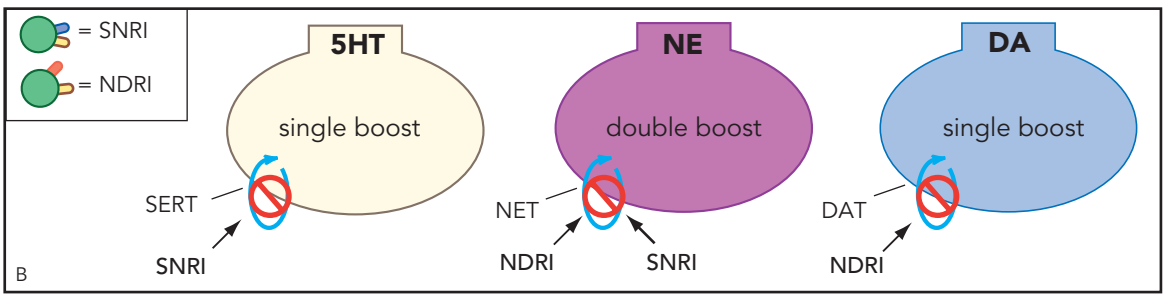


Figure 7-64 Triple-action combo: SSRI/SNRI plus NDRI. (A) Selective serotonin reuptake inhibitor (SSRI) plus a norepinephrine–dopamine reuptake inhibitor (NDRI) leads to a single boost for serotonin (5HT), norepinephrine (NE), and dopamine (DA). (B) Serotonin–norepinephrine reuptake inhibitor (SNRI) plus a norepinephrine–dopamine reuptake inhibitor (NDRI) leads to a single boost for serotonin (5HT), a double boost for norepinephrine (NE), and a single boost for dopamine (DA).

California Rocket Fuel

SNRI + mirtazapine

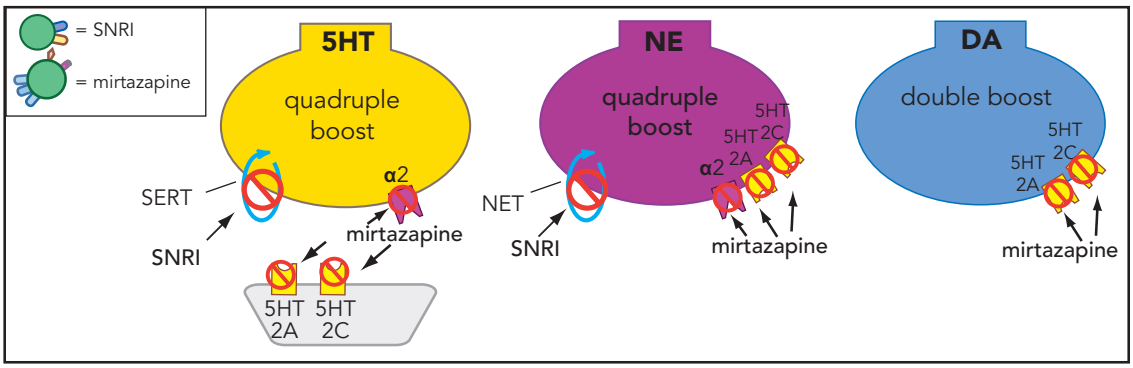


Figure 7-65 California rocket fuel: SNRI plus mirtazapine. Combining a serotonin–norepinephrine reuptake inhibitor (SNRI) with mirtazapine is a combination that has a great degree of theoretical synergy: serotonin (5HT) is quadruple-boosted (with reuptake blockade, α_2 antagonism, $5HT_{2A}$ antagonism, and $5HT_{2C}$ antagonism), norepinephrine (NE) is quadruple-boosted (with reuptake blockade, α_2 antagonism, $5HT_{2A}$ antagonism, and $5HT_{2C}$ antagonism), and there may even be a double boost of dopamine (DA) (with $5HT_{2A}$ and $5HT_{2C}$ antagonism).

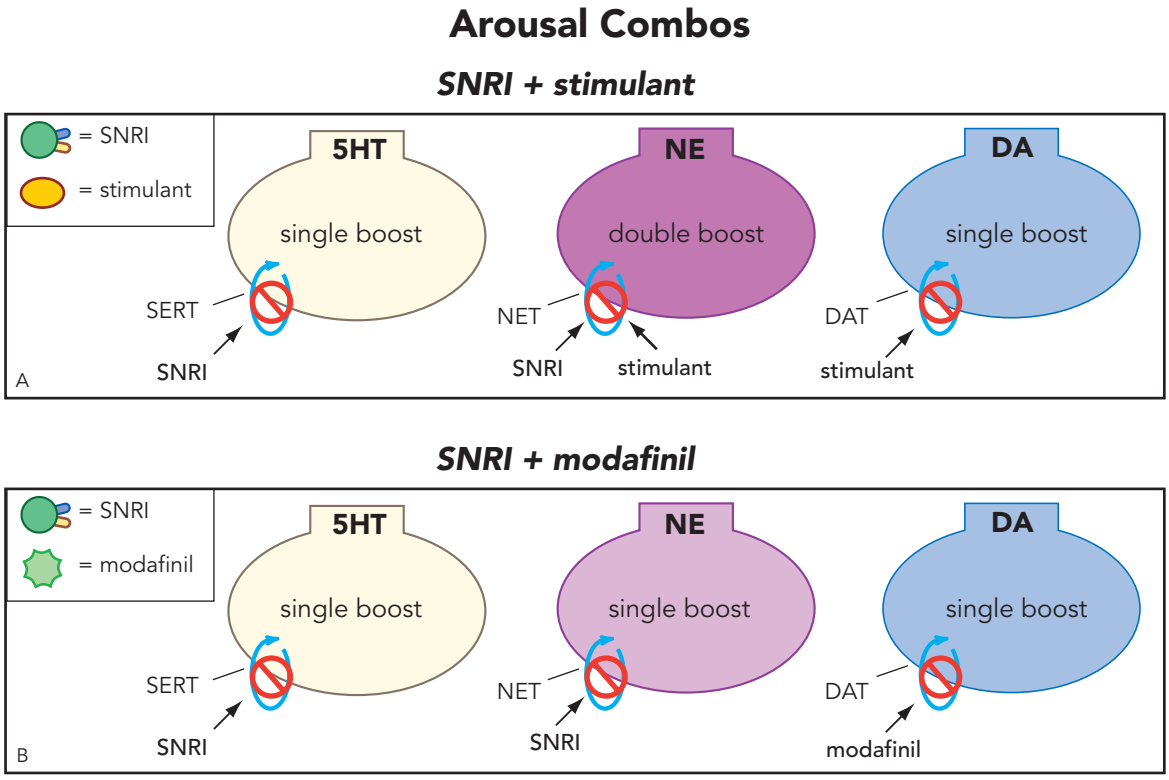


Figure 7-66 Arousal combo: SNRI plus stimulant/modafinil. (A) Serotonin (5HT) and dopamine (DA) are single-boosted and norepinephrine (NE) is double-boosted when a serotonin–norepinephrine reuptake inhibitor (SNRI) is combined with a stimulant. (B) Serotonin (5HT) and norepinephrine (NE) are single-boosted by the serotonin–norepinephrine reuptake inhibitor (SNRI) while dopamine (DA) is single-boosted by modafinil.

Table 7-2 Some tricyclic antidepressants still in use

Generic name	Trade name
Clomipramine	Anafranil
Imipramine	Tofranil
Amitriptyline	Elavil; Endep; Tryptizol; Laroxyl
Nortriptyline	Pamelor; Aventyl
Protriptyline	Vivactil
Maprotiline	Ludiomil
Amoxapine	Asendin
Doxepin	Sinequan; Adapin
Desipramine	Norpramin; Pertofran
Trimipramine	Surmontil
Dothiepin	Prothiaden
Lofepramine	Deprimyl; Gamanil
Tianeptine	Coaxil; Stablon

structure contains three rings. The TCAs were synthesized about the same time that other three-ringed phenothiazine molecules were shown to be effective tranquilizers for schizophrenia (i.e., the early D_2 antagonist drugs such as chlorpromazine) but were a disappointment when tested as drugs for psychosis. However, during testing for schizophrenia, they were serendipitously discovered to be effective in unipolar depression. Tricyclic antidepressants are not merely drugs for depression since one of them (clomipramine) has anti-obsessive–compulsive disorder; many of them have anti-panic effects at antidepressant doses and efficacy for neuropathic and low back pain at low doses.

Long after their antidepressant properties were observed, the TCAs were discovered to block the reuptake pumps for norepinephrine (i.e., NET), or for both norepinephrine and serotonin (i.e., SERT) (see Figure 7-67A). Some tricyclics have equal or greater potency for SERT inhibition (e.g., clomipramine); others are more selective for NET inhibition (e.g., desipramine, maprotiline,

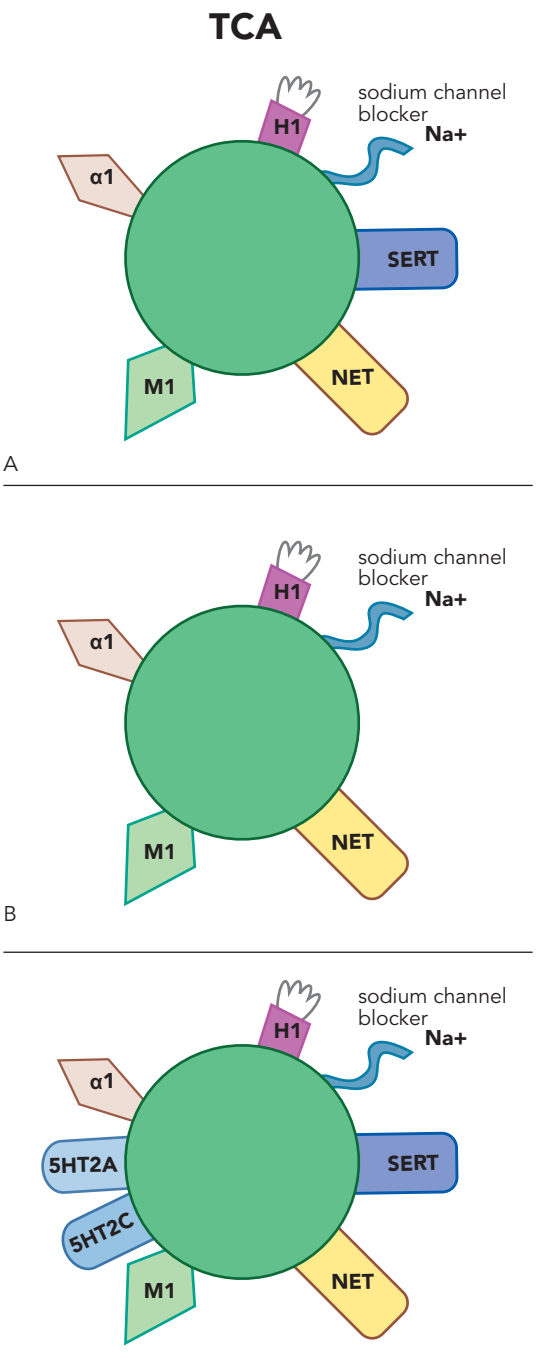


Figure 7-67 **Icons of tricyclic antidepressants (TCAs).** All tricyclic antidepressants block reuptake of norepinephrine and are antagonists at histamine 1 (H_1), α_1-adrenergic, and muscarinic cholinergic receptors; they also block voltage-sensitive sodium channels (A, B, and C). Some TCAs are also potent inhibitors of the serotonin reuptake pump (A, C), and some may additionally be antagonists at serotonin 2A and 2C receptors (C).

nortriptyline, protriptyline) (Figure 7-67B). Most, however, block both serotonin and norepinephrine reuptake to some extent (Figure 7-67A). In addition, some TCAs have antagonist actions at $5HT_{2A}$ and $5HT_{2C}$ receptors, which could contribute to the therapeutic profile of those tricyclics that have such pharmacological actions (Figure 7-67C).

The major limitation to the TCAs has never been their efficacy: these are quite effective agents. The problem with drugs in this class is the fact that all of them share at least four other unwanted pharmacological actions, namely, blockade of muscarinic cholinergic receptors, H_1 histamine receptors, α_1-adrenergic receptors, and voltage-sensitive sodium channels (Figure 7-67). As already discussed, blockade of H_1 receptors causes sedation and may cause weight gain (see Chapter 5 and Figure 5-13A). Blockade of muscarinic cholinergic receptors, also known as anticholinergic actions, causes dry mouth, blurred vision, urinary retention, and constipation (Figure 5-8). Blockade of α_1-adrenergic receptors may be therapeutic but also causes orthostatic hypotension and dizziness (Figure 5-13B). Tricyclic antidepressants also weakly block voltage-sensitive sodium channels in the heart and brain at therapeutic doses; in overdose, this action is thought to be the cause of coma and seizures due to central nervous system actions, and cardiac arrhythmias and cardiac arrest and death due to peripheral cardiac actions (Figure 7-68). The lethal dose of a TCA is only about a 30-day supply of drug. For this reason, it has been said that each time you are giving the patient a 1-month's prescription for a TCA, you are handing them a loaded gun. Obviously, this is often not a good idea in the treatment of a disorder associated with so much suicide; thus, TCAs have largely fallen out of favor except for patients who fail to respond to the various first-line drugs for depression discussed up to this point in this chapter.

Monoamine Oxidase Inhibitors (MAOIs)

The first clinically effective drugs for depression ever discovered were inhibitors of the enzyme monoamine oxidase (MAO). They were found by accident when an anti-tuberculosis drug was observed to help depression that coexisted in some of the patients who had tuberculosis. This anti-tuberculosis drug, iproniazid, was eventually found to work in depression by inhibiting the enzyme MAO. However, inhibition of MAO was unrelated to its anti-tubercular actions. Although best known as powerful drugs to treat depression, the monoamine oxidase inhibitors (MAOIs) are also highly effective therapeutic agents for certain anxiety disorders such as panic disorder and social anxiety disorder. MAOIs

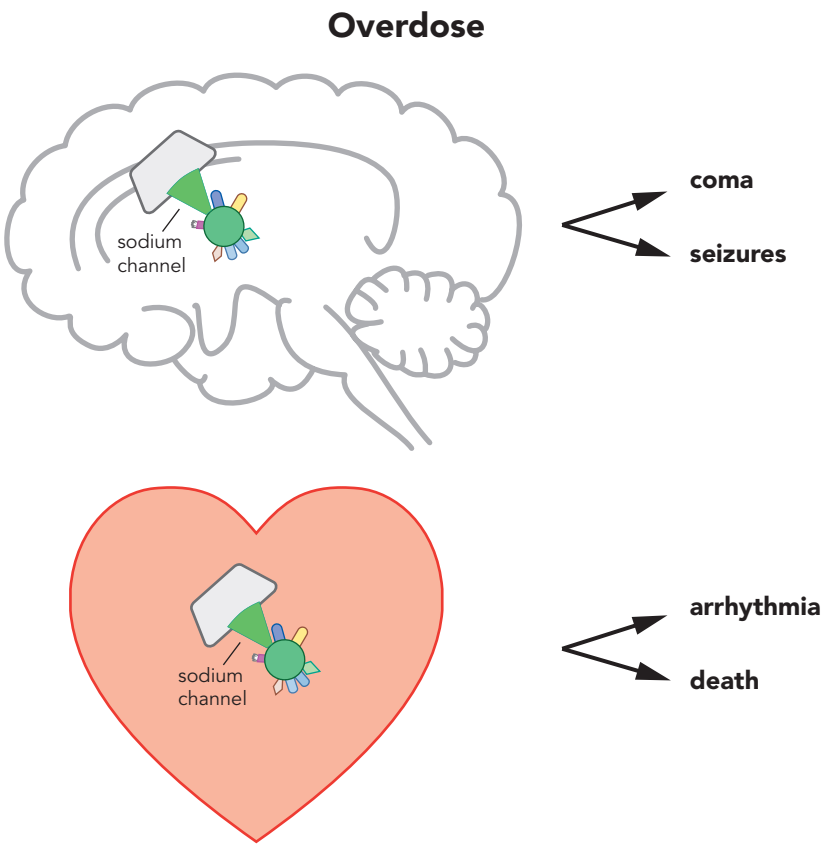


Figure 7-68 Tricyclic antidepressants and overdose. Tricyclic antidepressants block voltage-sensitive sodium channels in the brain (top) and heart (bottom). In overdose, this action can lead to coma, seizures, arrhythmia, and even death.

are barely prescribed any more today. Only about one in every 3,000 to 5,000 prescriptions for a drug to treat depression is a MAOI and only a few hundred experts prescribe MAOIs out of the hundreds of thousands who prescribe other drugs for depression in the US. Prescribing MAOIs is beginning to become a lost art in psychopharmacology as many familiar with them learned to use MAOIs before the 1990s when SSRIs were introduced and largely replaced MAOIs. Most of these prescribers of MAOIs are now retiring from practice. Nevertheless, MAOIs are a most powerful drug class for unipolar depression and those who prescribe them have seen many patients who respond to nothing else get better on MAOIs. The reader who is an advanced psychopharmacologist should gain familiarity and experience with these agents so that patients who still need them can get them. The reader is referred to specific reviews on MAOIs including some of the author, to help navigate dietary restrictions and drug interactions.

The MAOIs phenelzine, tranylcypromine, isocarboxazid, and selegiline are all irreversible enzyme inhibitors, and thus enzyme activity returns only after new enzyme is synthesized about 2–3 weeks later. Amphetamine is also a weak but reversible MAOI; some MAOIs have properties related to amphetamine. For example, tranylcypromine has a chemical structure modeled on amphetamine, and thus in addition to MAOI properties, it also has amphetamine-like dopamine-releasing properties. The MAOI selegiline itself does not have amphetamine-like properties, but is metabolized to both l-amphetamine and l-methamphetamine. Thus, there is a close mechanistic link between some MAOIs and additional amphetamine-like dopamine-releasing actions.

MAO Subtypes

MAO exists in two subtypes, A and B. The A form preferentially metabolizes the monoamines most closely linked to depression (i.e., serotonin and norepinephrine) whereas the B form preferentially metabolizes trace amines such as phenethylamine (see Chapter 5 and Figures 5-64 through 5-66 for further discussion on trace amines). Both MAO-A and MAO-B metabolize

dopamine and tyramine, another trace amine. Both MAO-A and MAO-B are in the brain. Noradrenergic neurons (Figure 6-13) and dopaminergic neurons (Figure 4-3) are thought to contain both MAO-A and MAO-B, with MAO-A activity perhaps predominant, whereas serotonergic neurons are thought to contain only MAO-B (Figure 4-37). MAO-A is the major form of this enzyme outside of the brain, with the exception of platelets and lymphocytes, which have MAO-B.

Brain MAO-A must be substantially inhibited for antidepressant efficacy to occur (Figure 7-69). This is not surprising, since this is the form of MAO that preferentially metabolizes serotonin and norepinephrine, two of the three monoamines linked to depression and to antidepressant actions, both of which demonstrate increased brain levels after MAO-A inhibition (Figure 7-69). MAO-A, along with MAO-B, also metabolizes dopamine, but inhibition of MAO-A alone does not appear to lead to robust increases in brain dopamine levels since MAO-B can still metabolize dopamine (Figure 7-69).

Inhibition of MAO-B is not effective as an antidepressant, as there is no direct effect on either serotonin or norepinephrine metabolism, and little or no dopamine accumulates due to the continued action of MAO-A (Figure 7-70). What therefore is the therapeutic value of MAO-B inhibition? When this enzyme is selectively inhibited, it can boost the action of concomitantly administered levodopa in Parkinson's disease and reduce on/off motor fluctuations. Three MAO-B inhibitors selegiline, rasagiline, and safinamide are approved for use in patients with Parkinson's disease, but are not effective at selective MAO-B doses for the treatment of depression.

When MAO-B is inhibited simultaneously with MAO-A, there is robust elevation of dopamine as well as serotonin and norepinephrine (Figure 7-71). This would theoretically provide the most powerful antidepressant efficacy across the range of depressive symptoms, from diminished positive affect to increased negative affect (see Figure 6-41). Thus, MAO-A plus MAO-B inhibition is one of the few therapeutic strategies available to increase dopamine in depression, and therefore to treat refractory symptoms of diminished positive affect.

The Dietary Tyramine Interaction

One of the biggest barriers to using MAOIs has traditionally been the concern that a patient taking a MAOI may develop a hypertensive crisis after ingesting tyramine in the diet, classically from cheese. Normally, the release of norepinephrine by tyramine is inconsequential because MAO-A safely destroys this released norepinephrine. However, tyramine in the presence of MAO-A inhibition can elevate blood pressure because norepinephrine is not safely destroyed. Every prescriber of MAOIs should counsel patients taking the classic MAOIs about diet and keep up to date with the tyramine content of foods their patients wish to eat.

Drug–Drug Interactions for MAOIs

While MAOIs are famous for their tyramine reactions, drug–drug interactions are potentially more important clinically. Drug–drug interactions may not only be more common than dietary interactions with tyramine, but some drug interactions can be dangerous or even lethal. Drug interactions with MAOIs are often poorly understood by many practitioners. Since most candidates for MAOI treatment will require treatment with many concomitant drugs over time, including treatment for coughs and colds and for pain, this can prevent psychopharmacologists from prescribing a MAOI if they do not know which drugs are safe to give and which ones must be avoided. There are two general types of potentially dangerous drug interactions with MAOIs for a practitioner to understand and avoid: those that can raise blood pressure by sympathomimetic actions and those that can cause a potentially fatal serotonin syndrome by serotonin reuptake inhibition. Every prescriber of MAOIs should counsel patients taking the classic MAOIs about drug interactions and keep up to date with the latest warnings about drug interactions of MAOIs with drugs their patients are concomitantly prescribed. Several reviews on these details are available, including some of the author's, and are referenced at the end of the book.

DRUGS FOR BIPOLAR DISORDER SPECTRUM

Serotonin/Dopamine Blockers: Not Just for Psychosis and Psychotic Mania

When D_2 blockers were approved for schizophrenia, it was not surprising that these agents would work for psychotic symptoms associated with mania, since the D_2 antagonist actions predict efficacy for psychosis in general (discussed in Chapter 5). However, it was somewhat surprising when these dopamine/serotonin blockers proved effective for the core nonpsychotic symptoms of mania (Figure 6-2) and for maintenance treatment to prevent the recurrence of mania. These latter actions are similar to the antimanic therapeutic actions of

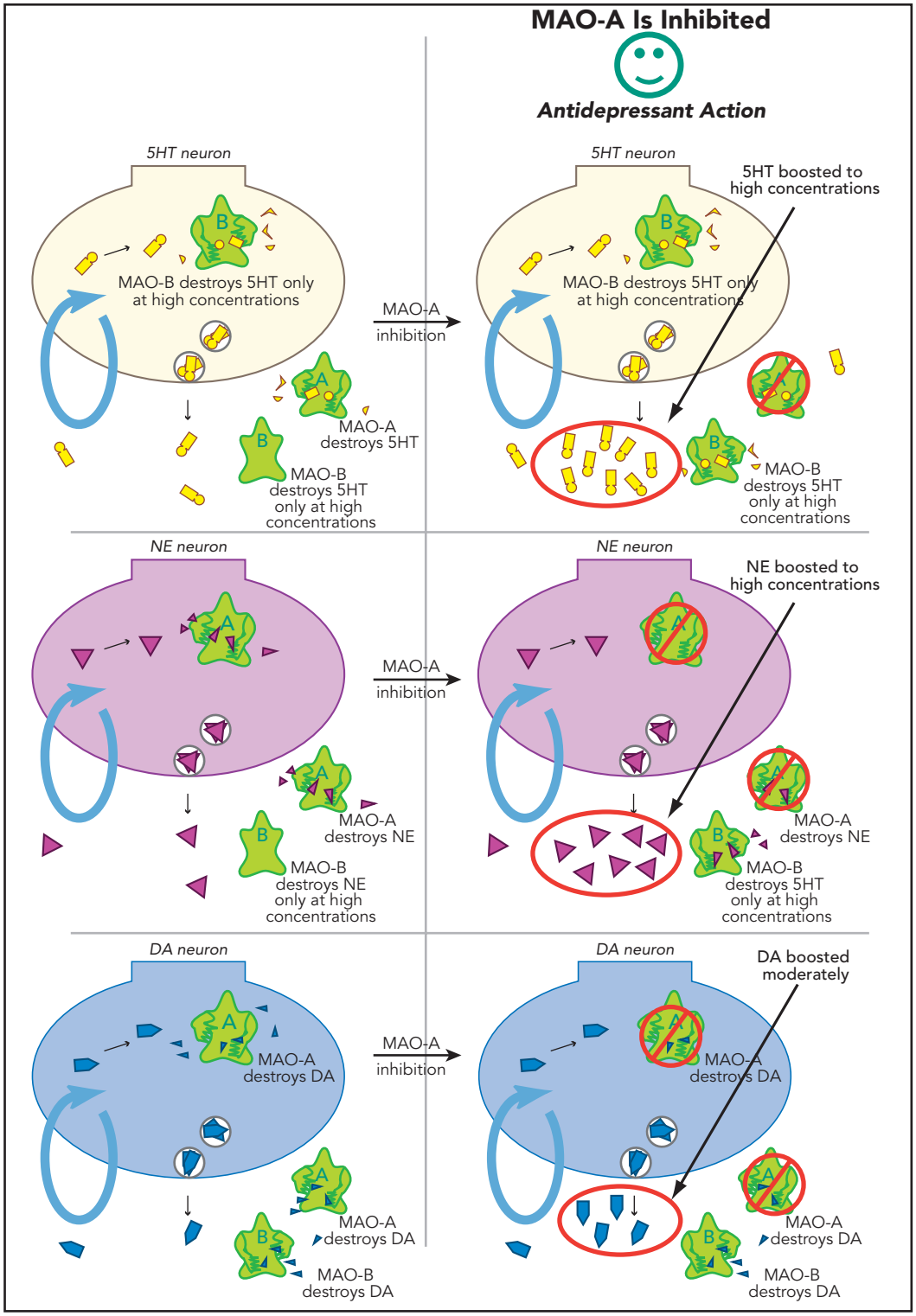


Figure 7-69 Monoamine oxidase A (MAO-A) inhibition. The enzyme MAO-A metabolizes serotonin (5HT) and norepinephrine (NE) as well as dopamine (DA) (left panels). Monoamine oxidase B (MAO-B) also metabolizes DA, but it metabolizes 5HT and NE only at high concentrations (left panels). This means that MAO-A inhibition increases 5HT, NE, and DA (right panels) but that the increase in DA is not as great as that of 5HT and NE because MAO-B can continue to destroy DA (bottom right panel). Inhibition of MAO-A is an efficacious antidepressant strategy.

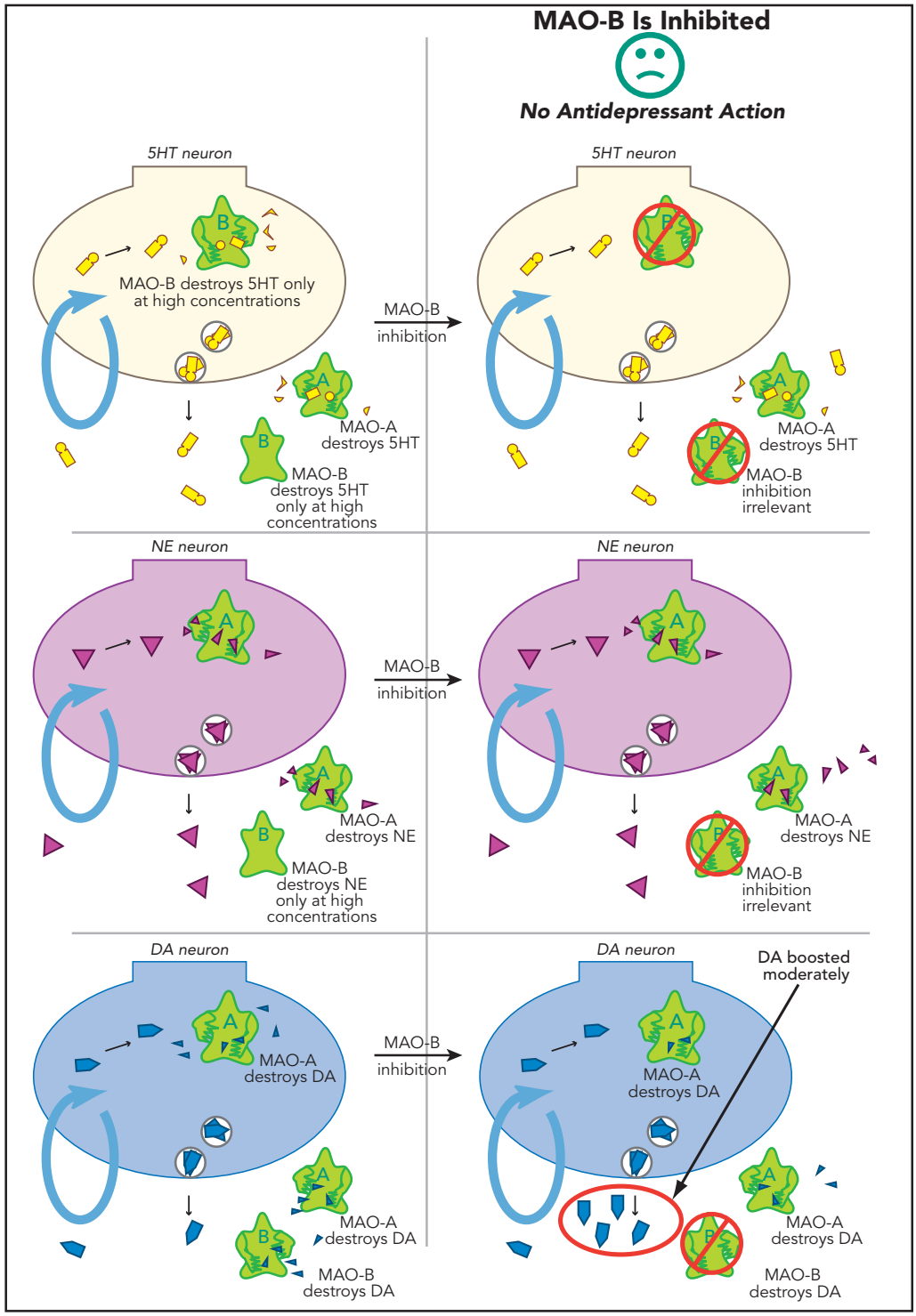


Figure 7-70 Monoamine oxidase B (MAO-B) inhibition. Selective inhibitors of MAO-B do not have antidepressant efficacy. This is because MAO-B metabolizes serotonin (5HT) and norepinephrine (NE) only at high concentrations (top two left panels). Since MAO-B's role in destroying 5HT and NE is small, its inhibition is not likely to be relevant to the concentrations of these neurotransmitters (top two right panels). Selective inhibition of MAO-B also has somewhat limited effects on dopamine (DA) concentrations, because MAO-A continues to destroy DA. However, inhibition of MAO-B does increase DA to some extent, which can be therapeutic in other disease states, such as Parkinson's disease.

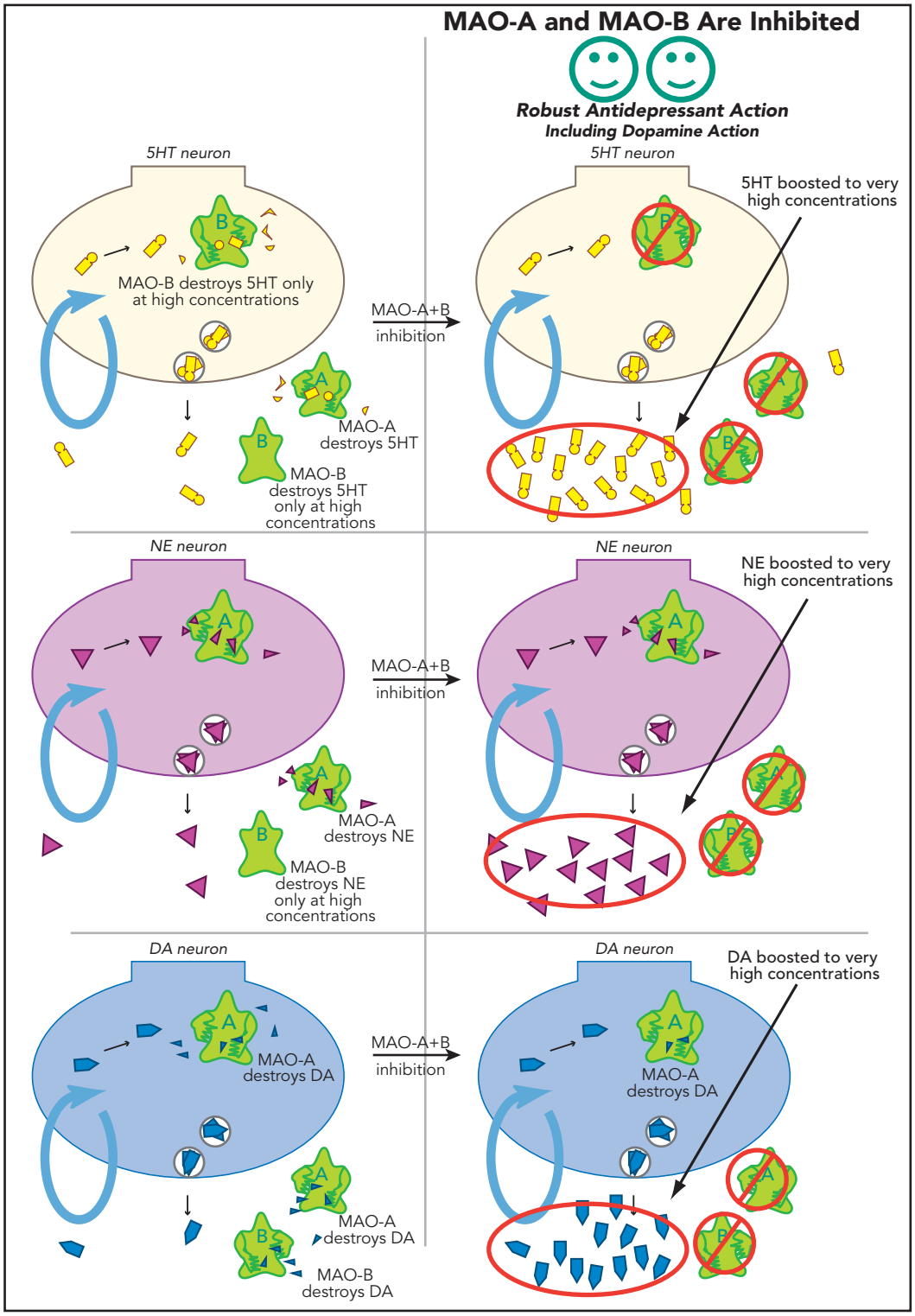


Figure 7-71 Combined inhibition of monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B). Combined inhibition of MAO-A and MAO-B may have robust antidepressant actions owing to increases not only in serotonin (5HT) and norepinephrine (NE) but also dopamine (DA). Inhibition of both MAO-A, which metabolizes 5HT, NE, and DA, and MAO-B, which metabolizes primarily DA (left panels), leads to greater increases in each of these neurotransmitters than inhibition of either enzyme alone (right panels).

lithium and various anticonvulsant ion channel blockers that act by very different mechanisms (described below). More surprising yet is that some of these same serotonin/dopamine antagonists/partial agonists are effective for bipolar depression, albeit by mechanisms likely distinct from D_2 antagonism/partial agonism. The questions that arise are how serotonin 2/dopamine 2 antagonists and dopamine 2/serotonin 1A partial agonists work in both the manic and depressed poles of bipolar disorder. More recently, some of these same serotonin/dopamine drugs have evidence of efficacy in unipolar depression as augmenting agents to SSRIs/SNRIs when there is inadequate response, as discussed above. Furthermore, some of these same serotonin/dopamine drugs now have additional evidence of efficacy in unipolar and bipolar depression with mixed features of mania. Do they work by the same mechanisms across the entire bipolar spectrum (Figure 6-7)? Is this a class effect of these drugs or do specific drugs work in some but not all parts of the bipolar spectrum?

Putative Pharmacological Mechanism of Serotonin/Dopamine Antagonists/Partial Agonists in Mania

The short answer to the question of how serotonin/dopamine blockers work in mania is that we do not really know. On the one hand, PET scans of patients with mania show the same excessive presynaptic dopamine levels and release in mesostriatal dopamine neurons in acute bipolar mania as for acute psychosis in schizophrenia, described extensively in Chapter 4 and illustrated in Figures 4-15, 4-16, and Figure 5-2. Thus, blocking the excessive dopamine at D_2 receptors should have as much of an antimanic effect in bipolar mania as it has an antipsychotic effect in schizophrenia. Indeed, acute bipolar mania is treated with serotonin/dopamine blockers in much the same manner as acute psychosis is treated in schizophrenia, including dosing and expected onset of action within minutes to hours. However, not all agents in the serotonin/dopamine blocker class approved to treat schizophrenia are also approved to treat acute bipolar mania, and not all of those approved for acute bipolar mania are approved for bipolar maintenance (see Table 7-1). Differences in receptor binding profiles could explain why some agents are approved in mania and others not; commercial considerations could also explain why some agents are not approved in mania. To enhance antimanic response and to prevent relapse into another episode of mania, lithium and valproate are commonly used in conjunction with those dopamine/serotonin blockers approved for the treatment of mania, but this is not done for the treatment of schizophrenia, as lithium and valproate do not clearly augment the efficacy of serotonin/dopamine blockers in schizophrenia.

Serotonin/Dopamine Antagonists/Partial Agonists across the Depression Spectrum: Bipolar Depression, Depression with Mixed Features, and as Adjuncts to SSRIs/SNRIs in Unipolar Major Depression

The serotonin/dopamine antagonists/partial agonists have proven to be quite versatile therapeutics: from schizophrenia, to mania, to adjuncts for SSRIs/SNRIs in unipolar depression, as we have discussed in this chapter so far. Here we consider the extension of therapeutic use of at least some of the agents in this class to the treatment of bipolar depression and the closely related state of major depressive episodes with mixed features of mania.

A major paradigm shift is afoot in the treatment of bipolar depression and depression with mixed features. We used to ask: "Don't we treat all forms of depression with so-called antidepressants, drugs that inhibit the reuptake of monoamines?" Although most patients with depression, including those with bipolar depression and depression with mixed features, do receive monoamine reuptake inhibiting drugs, the modern answer to this question is increasingly becoming a resounding "**No**!!" Practice guidelines and US FDA approvals are moving away from the treatment of bipolar depression or depression with mixed features with the standard monoamine reuptake inhibiting agents that are so commonly used for the treatment of unipolar depression. Reuptake inhibitors are increasingly reserved to treat patients with unipolar depression only if they do not have mixed features, and patients with bipolar depression only as second-line agents to augment other agents. Best practice is evolving for bipolar depression or depression with mixed features, so now first-line treatment is one of the specifically approved serotonin/dopamine blockers, not a monoamine reuptake inhibitor. However, there is plenty of controversy over this recommendation, as many prescribers and some experts still advocate for monoamine reuptake inhibitors in some patients with bipolar depression. But more and more studies are showing failure of the monoamine reuptake inhibiting drugs to work consistently in bipolar depression or in mixed features, and, furthermore, monoamine reuptake inhibitors can induce intolerable activating side effects and even manic episodes and suicidality in patients with bipolar/mixed depression. Other studies do show

some benefits of monoamine reuptake blockers in bipolar depression, and in fact fluoxetine combined with olanzapine is approved for bipolar depression (Table 7-1). However, no agent at all is approved for depression with mixed features. The studies that do exist suggest poor responses of mixed features to the well-known monoamine reuptake inhibitors and an expanding evidence base for the use of certain serotonin/dopamine blockers, particularly those already approved for bipolar depression, as the preferred treatment for mixed features as well (see Table 7-1).

We do not know whether any and all drugs with serotonin/dopamine blocking properties that are normally used to treat psychosis would be effective for bipolar depression, as some have not been studied and others have failed in clinical trials; nor are we certain of the antidepressant mechanism of action of those that are approved. However, each of the serotonin/dopamine agents now approved to treat bipolar depression was originally developed to treat psychosis, and their proposed mechanism of antidepressant therapeutic action in bipolar depression and depression with mixed features is presented in the following sections.

Olanzapine–Fluoxetine

As previously mentioned, olanzapine–fluoxetine combination (Figures 5-44 and 7-16) is approved for schizophrenia, bipolar mania, treatment-resistant unipolar depression, and bipolar depression. Post hoc analyses of mania with mixed features of depression also suggest efficacy of olanzapine for mania with mixed features of depression, although the counterpart to this condition at the other end of the spectrum, depression with mixed features of mania (Figures 6-3 through 6-7), has not been studied (Table 7-1).

$5HT_{2A}$ antagonist actions combined with $5HT_{2C}$ antagonism are likely candidates to be linked to antidepressant action in bipolar depression ("treatment from below"; see Figure 7-8). D_2 antagonism could theoretically help keep the lid on treatment from below so it doesn't spill over into activation and mania.

Quetiapine

As previously mentioned, quetiapine (Figure 5-45) is approved for schizophrenia, bipolar mania, and for augmentation of SSRIs/SNRIs in treatment-resistant unipolar depression. It is also approved in bipolar depression. Like olanzapine, post hoc analyses of quetiapine treatment of mania with mixed features of depression also suggest efficacy, although depression with mixed features of mania has not been studied (Table 7-1).

$5HT_{2A}$ antagonist actions combined with $5HT_{2C}$ and α_2 antagonism, as well as agonist actions at $5HT_{1A}$ receptors, are likely candidates to be linked to antidepressant action in bipolar depression (treatment from below). Like olanzapine, D_2 antagonism by quetiapine could theoretically help keep the lid on treatment from below so it doesn't spill over into activation and mania.

Lurasidone

Although approved for the treatment of schizophrenia, lurasidone (Figure 5-53) was never tested nor approved for the treatment of mania (Table 7-1). Lurasidone has several hypothetical antidepressant receptor binding properties: blockade of $5HT_{2A}$ (Figure 5-17C), $5HT_7$ (7-53C), and α_2 receptors (Figure 7-41), with agonist actions at $5HT_{1A}$ receptors (Figure 5-22). It is one of the only agents to show on post hoc analysis of bipolar depression that those with bipolar depression and mixed features respond as well to lurasidone as patients with bipolar depression without mixed features. Perhaps more importantly, lurasidone is the only agent to be studied in a large, randomized multicenter trial of unipolar depression with mixed features and to demonstrate robust antidepressant efficacy in this group without induction of mania. Lurasidone is prescribed for bipolar depression and for mixed features at doses lower than those generally used for the treatment of psychosis in schizophrenia, and is generally well tolerated with little propensity for weight gain or metabolic disturbances and is one of the most widely prescribed agents for bipolar depression.

Cariprazine

Cariprazine (Figure 5-58) is a $D_3/D_2/5HT_{1A}$ partial agonist approved for the treatment of acute bipolar mania and for bipolar depression, with ongoing trials as an adjunct to SSRI/SNRIs in unipolar depression (Table 7-1). Cariprazine has $5HT_{1A}$ partial agonist actions as well as α_1 (Figure 7-58) and α_2 (Figure 7-41) antagonist actions, each with potential antidepressant mechanisms. What sets cariprazine apart from other agents in this group of serotonin/dopamine antagonists/partial agonists is its unique highly potent action at D_3 dopamine receptors as a partial agonist. Cariprazine is the most potent of any available agent and much more potent than dopamine itself for the D_3 receptor. How is D_3 antagonism/partial

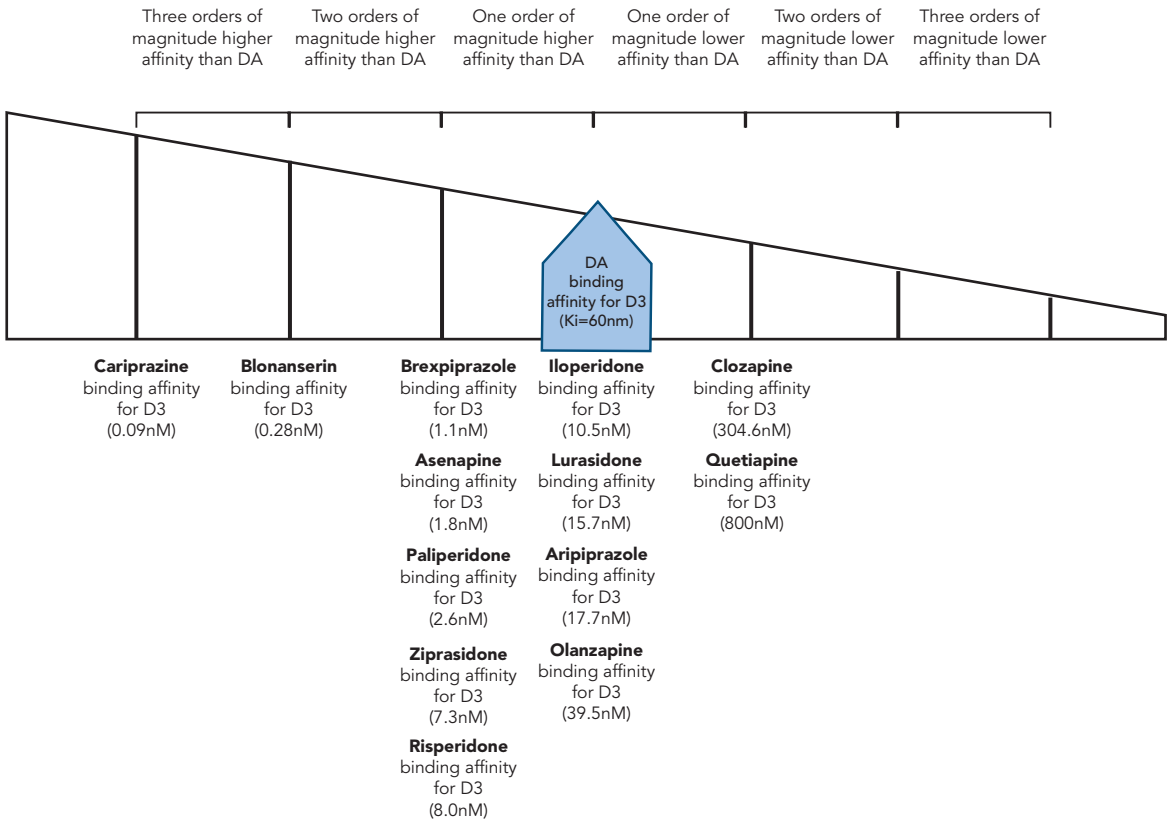


Figure 7-72 Dopamine 3 binding affinity: dopamine versus serotonin/dopamine antagonists/partial agonists. Dopamine 3 antagonism/partial agonism may confer therapeutic benefit in bipolar depression with or without mixed features. Although many agents may bind to the D_3 receptor, only two – cariprazine and blonanserin – have multiple orders of magnitude higher affinity for the D_3 receptor than does dopamine (DA) itself, thus allowing them to compete successfully with dopamine for receptor occupancy.

agonism linked to therapeutic efficacy in bipolar depression with or without mixed features?

We extensively discussed drugs that are antagonists or partial agonists at D_2 receptors in Chapter 5 and how they are used for psychotic illnesses. The same agents also act at D_3 receptors, but at clinical doses only two of them – cariprazine and blonanserin (Chapter 5, Figure 5-62) – can highly successfully compete with dopamine itself for the D_3 receptor (Figure 7-72). That is, in the brain, drugs compete with dopamine itself for the D_3 receptor and only those drugs with an affinity for the D_3 receptor significantly higher than dopamine's affinity for the D_3 receptor will actually block the D_3 receptor. Several agents have somewhat higher affinity for the D_3 receptor than dopamine, and may have some net effect blocking the D_3 receptor, but cariprazine clearly has the most potent action at the D_3 receptor and would be expected to block D_3 receptors substantially at clinical dosing (Figure 7-72).

What happens when you block a D_3 receptor? Recall that dopamine has five receptor subtypes (see discussion in Chapter 4 and Figure 4-5) in two different groups (Figure 4-4). D_3 receptors can be presynaptic and postsynaptic (Figures 4-4 through 4-9). Postsynaptic blockade of D_3 receptors in limbic regions may contribute to antipsychotic actions but it is the presynaptic actions of D_3 antagonism/partial agonism in the ventral tegmental area (VTA) that are of most interest for explaining cariprazine's antidepressant actions (Figure 7-73).

So, what is the consequence of blocking D_3 receptors in the VTA and why might this contribute to antidepressant actions of cariprazine? Recall also that dopamine input to the cortex is thought to be deficient in mood, motivation, and cognitive symptoms of depression and also in the negative symptoms of schizophrenia, due in part to hypothetically deficient dopamine release from mesocortical dopamine neurons. These neurons are depicted in Figure 7-73A and show D_3 presynaptic

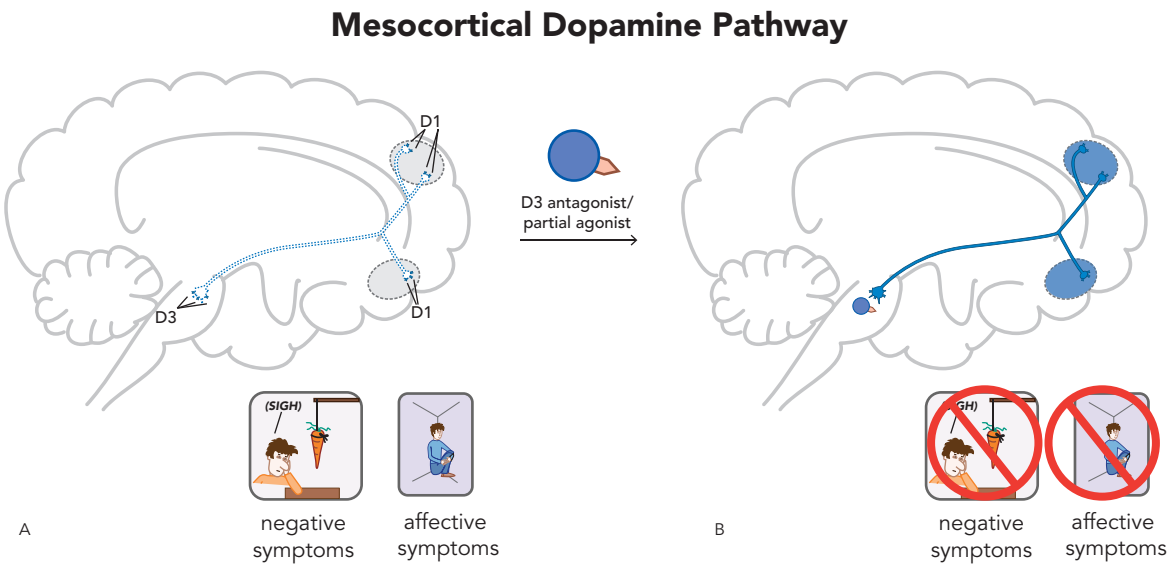


Figure 7-73 Dopamine 3 antagonism/partial agonism in the ventral tegmental area (VTA). (A) Presynaptic D_3 receptors detect dopamine and inhibit further dopamine release. These receptors are present in the VTA but not in the prefrontal cortex. There are, however, postsynaptic D_2 receptors in the prefrontal cortex, which are stimulated by dopamine. Shown here is the mesocortical dopamine pathway, with stimulation of D_3 receptors resulting in reduced dopamine release in the prefrontal cortex. Low levels of dopamine in the prefrontal cortex is hypothesized to contribute to depressed mood, reduced motivation, and cognitive symptoms, all of which occur in mood disorders, as well as to negative symptoms in schizophrenia. (B) Antagonism/partial agonism of D_3 receptors in the VTA can increase dopamine release in the prefrontal cortex. Because there are no D_3 receptors in the prefrontal cortex, D_3 antagonists/partial agonists have no effect there. Dopamine is free to stimulate D_1 receptors, hypothetically improving symptoms of depression.

autoreceptors in the VTA on dopamine cell bodies for a population of mesocortical neurons. The function of these D_3 receptors is to detect dopamine and inhibit further dopamine release (Figure 7-73A). However, these same neurons projecting to the prefrontal cortex do not have presynaptic autoreceptors on their axon terminals (see Chapter 4 discussion and Figure 4-9; see also Figure 7-73). D_3 antagonists will have no effect in the prefrontal cortex since there are few D_3 receptors there. In Chapter 4 we discussed how most of the dopamine receptors in prefrontal cortex are postsynaptic and D_1 (Figure 4-9). What this means is that when D_3 antagonists/partial agonists act in the VTA to block them, this disinhibits the dopamine neurons projecting to prefrontal cortex and they release dopamine onto D_1 receptors (Figure 7-73B). This action hypothetically improves symptoms of depression and is one explanation for why cariprazine has antidepressant actions, and also why it has more robust improvement of negative symptoms of schizophrenia than other drugs for psychosis. Improvement in energy, motivation, and "brightening" are observed after D_3 antagonism in patients with both mood disorders and schizophrenia, and animal models demonstrate precognitive actions and also improvements in substance abuse.

Cariprazine is approved for acute bipolar mania and for acute bipolar depression (Table 7-1). Post hoc analyses show significant clinical improvement both in mania with mixed features of depression and bipolar depression with mixed features of mania. Studies as adjunctive treatment for patients with unipolar depression on SSRIs/SNRIs have early indications of efficacy reported. Thus, cariprazine has some of the most robust and wide-ranging efficacy known across the entire bipolar spectrum (Figure 6-7).

Lithium, the Classic "Antimanic" and "Mood Stabilizer"

Bipolar mania has classically been treated with lithium for more than 50 years. Lithium is an ion whose mechanism of action is not certain. Candidates for its mechanism of action are various signal transduction sites beyond neurotransmitter receptors (Figure 7-74). This includes second messengers such as the phosphatidyl inositol system, where lithium inhibits the enzyme inositol monophosphatase; modulation of G proteins; and, most recently, regulation of gene expression for growth factors and neuronal plasticity by interaction with downstream signal transduction cascades, including

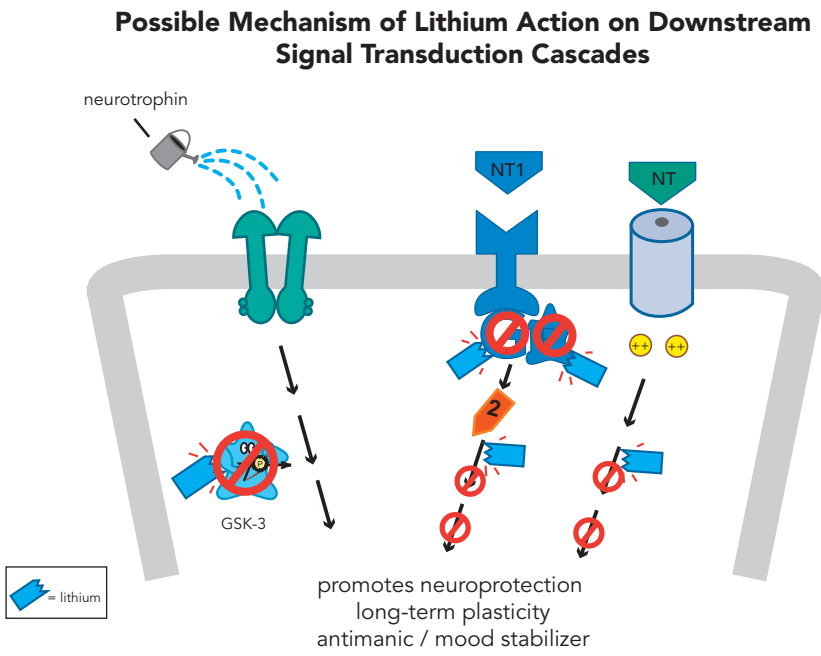


Figure 7-74 Lithium's mechanism of action. Although lithium is the oldest treatment for bipolar disorder, its mechanism of action is still not well understood. Several possible mechanisms exist and are shown here. Lithium may work by affecting signal transduction, perhaps through its inhibition of second-messenger enzymes such as inositol monophosphatase (right), by modulation of G proteins (middle), or by interaction at various sites within downstream signal transduction cascades, including glycogen synthase kinase 3 (GSK-3) (left).

inhibition of GSK-3 (glycogen synthase kinase 3) and protein kinase C (Figure 7-74).

However lithium works, it is proven effective in manic episodes, and in maintenance of recurrence, especially for manic episodes and, perhaps to a lesser extent, for depressive episodes. Lithium is well established to help prevent suicide in patients with mood disorders. It is also used to treat depressive episodes in bipolar disorder and as an augmenting agent to drugs for depression in treatment-resistant unipolar depression, but is not formally approved for these uses.

A number of factors have led to an unfortunate decline in the use of lithium in recent years, including the entry of multiple new treatment options into the therapeutic armamentarium for bipolar disorder, the side effects of lithium, and the monitoring burden that is part of prescribing lithium. The modern use of lithium by experts departs from its classic use as a high-dose monotherapy for euphoric mania, with lithium often utilized now as one member of a portfolio of treatments, often allowing once-daily administration and at lower doses when combined with other mood stabilizers.

Well-known side effects of lithium include gastrointestinal symptoms such as dyspepsia, nausea, vomiting, and diarrhea, as well as weight gain, hair loss, acne, tremor, sedation, decreased cognition, and incoordination. There are also potential long-term adverse effects upon the thyroid and kidney. Lithium has a narrow therapeutic window, requiring monitoring of plasma drug levels.

Anticonvulsants as "Mood Stabilizers"

Based upon theories that mania may "kindle" further episodes of mania, a logical parallel with seizure disorders was drawn, since seizures can "kindle" more seizures. Several anticonvulsants (Table 7-3) are categorized on the basis of whether they are "mania-minded," i.e., treat from above and stabilize from above (Figure 7-7); "depression-minded," i.e., treat from below and stabilize from below (Figure 7-8); or both. Because the known anticonvulsants carbamazepine and valproate proved effective in treating the manic phase of bipolar disorder, this has led to the idea that any anticonvulsant would be a mood stabilizer, especially for mania. However, this has not proven to be the case (Table 7-3) since anticonvulsants do not all act by the same pharmacological mechanisms, as discussed below. These agents for mania or bipolar depression are better classified for their pharmacological mechanism of action at ion channels rather than as "mood stabilizers" or "anticonvulsants." Numerous mood stabilizers that are also anticonvulsants are discussed below, including not only those with proven efficacy in different phases of bipolar disorder, but also those with dubious efficacy in bipolar disorder (Table 7-3).

Table 7-3 Anticonvulsant mood stabilizers

Agent	Putative clinical actions				
	Epilepsy	Mania-minded		Depression-minded	
		Treat from above	Stabilize from above	Treat from below	Stabilize from below
Valproate	++++	++++	++	+	+/–
Carbamazepine	++++	++++	++	+	+/–
Lamotrigine	++++	+/–	++++	+++	++++
Oxcarbazepine/licarbazepine	++++	++	+	+/–	+/–
Riluzole	+			+	+/–
Topiramate	++++	+/–	+/–		
Gabapentin	++++	+/–	+/–		
Pregabalin	++++	+/–	+/–		

Anticonvulsants with Proven Efficacy in Bipolar Disorder

Valproic Acid (Valproate, Sodium Valproate)

As for all anticonvulsants, the exact mechanism of action of valproic acid (also, sodium valproate, valproate) is uncertain; however, even less may be known about the mechanism of valproate than for other anticonvulsants. Various hypotheses are discussed here, and summarized in Figures 7-75 through 7-78. At least three possibilities exist for how valproic acid works: inhibiting voltage-sensitive sodium channels (Figure 7-76), boosting the actions of the neurotransmitter GABA (γ-aminobutyric acid) (Figure 7-77), and regulating downstream signal transduction cascades (Figure 7-78). It is not known whether these actions explain the mood-stabilizing actions, the anticonvulsant actions, the anti-migraine actions, or the side effects of valproic acid. Obviously, this simple molecule has multiple and complex clinical effects, and research is trying to determine which of the various possibilities explain the "mood-stabilizing" antimanic effects of valproic acid so that new agents with more efficacy and fewer side effects can be developed by targeting the relevant pharmacological mechanism for bipolar disorder.

One hypothesis to explain mood-stabilizing antimanic actions is the possibility that valproate acts to diminish excessive neurotransmission by diminishing the flow of ions through voltage-sensitive sodium channels (VSSCs) (Figure 7-76). VSSCs are discussed in Chapter 3 and illustrated in Figures 3-19 through 3-21. No specific molecular site of action for valproate has been identified, but it is possible that valproate may change the sensitivity of sodium channels by altering phosphorylation of

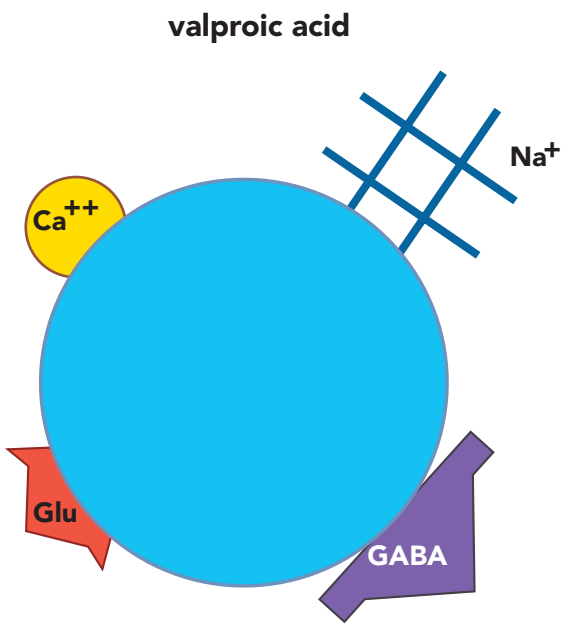


Figure 7-75 Valproic acid. Shown here is an icon of the pharmacological actions of valproic acid, an anticonvulsant used in the treatment of bipolar disorder. Valproic acid (also valproate) may work by interfering with voltage-sensitive sodium channels, enhancing the inhibitory actions of γ-aminobutyric acid (GABA), and regulating downstream signal transduction cascades, although which of these actions may be related to mood stabilization is not clear. Valproate may also interact with other ion channels, such as voltage-sensitive calcium channels, and also indirectly block glutamate (Glu) actions.

Possible Sites of Action of Valproate on VSSCs

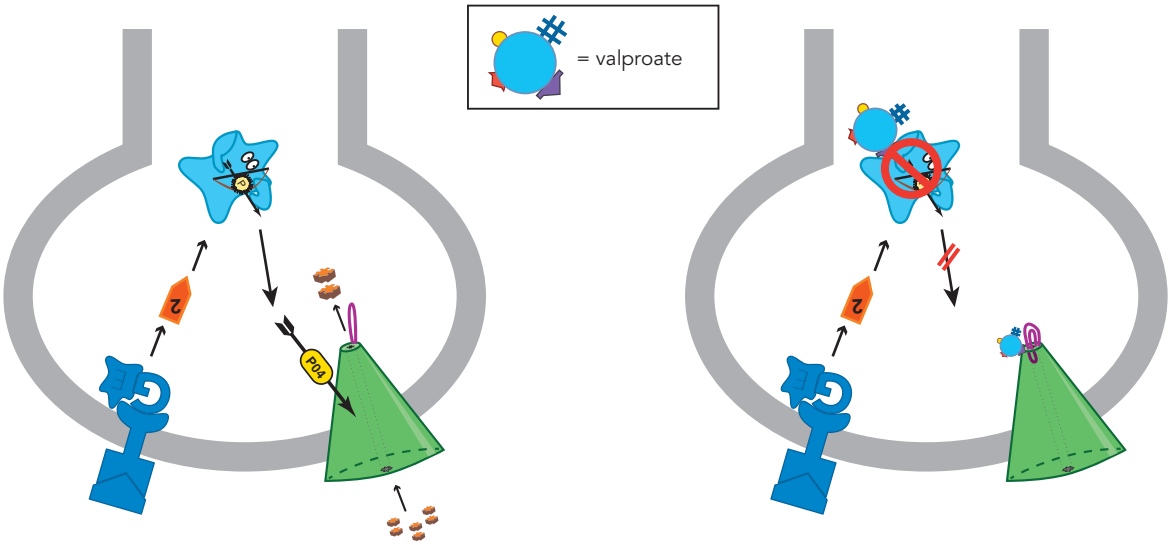


Figure 7-76 Possible sites of action of valproate on voltage-sensitive sodium channels (VSSCs). Valproate may exert antimanic effects by changing the sensitivity of VSSCs, perhaps by directly binding to channel subunits or inhibiting phosphorylating enzymes that regulate the sensitivity of these ion channels. Inhibition of VSSCs would lead to reduced sodium influx and, in turn, potentially to reduced glutamate excitatory neurotransmission, which is a possible mechanism for mania efficacy.

Possible Sites of Action of Valproate on GABA

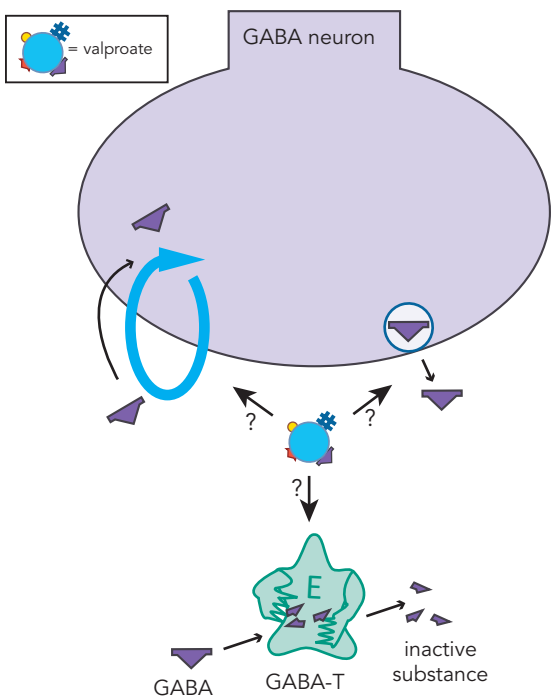


Figure 7-77 Possible sites of action of valproate on γ-aminobutyric acid (GABA). Valproate's antimanic effects may be due to enhancement of GABA neurotransmission, perhaps by inhibiting GABA reuptake, enhancing GABA release, or interfering with the metabolism of GABA by GABA-T (GABA transaminase).

sodium channels, either by binding directly to the VSSC or its regulatory units, or by inhibiting phosphorylating enzymes (Figure 7-76). If less sodium is able to pass into neurons, this may lead to diminished release of glutamate and therefore less excitatory neurotransmission, but this is only a theory. There may be additional effects of valproate on other voltage-sensitive ion channels, but these are poorly characterized and may relate to side effects as well as to therapeutic effects.

Another idea is that valproate enhances the actions of GABA, either by increasing its release, decreasing its reuptake, or slowing its metabolic inactivation (Figure 7-77). The direct site of action of valproate that causes the enhancement of GABA remains unknown, but there is good evidence that the downstream effect of valproate ultimately does result in more GABA activity, and thus more inhibitory neurotransmission, possibly explaining antimanic actions.

Finally, a number of downstream actions on complex signal transduction cascades have been described (Figure 7-78). Like lithium, valproate may inhibit GSK-3, but it may also target many other downstream sites, from blockade of phosphokinase C (PKC) and MARCKS (myristoylated alanine-rich C kinase substrate), to activating various signals that promote neuroprotection and long-term plasticity such as ERK (extracellular signal-regulated kinase) kinase, BCL2 (cytoprotective protein B-cell lymphoma/leukemia-2 gene), GAP43 (growth associated protein 43), and others (Figure 7-78). The effects of these signal transduction cascades are only now being clarified, and which of these possible effects of valproate might be relevant to mood-stabilizing actions are not yet understood.

Valproate is proven effective for the acute manic phase of bipolar disorder, and is commonly used long-term to prevent recurrence of mania, although its prophylactic effects have not been as well established as its acute effects in mania (Table 7-3). Antidepressant actions of valproate have also not been well established, nor has it been shown to convincingly stabilize against recurrent depressive episodes, but there may be some efficacy for the depressed phase of bipolar disorder in some patients. Some experts believe valproic acid is more effective than lithium for rapid cycling and mixed episodes of mania. In reality, such episodes are very difficult to treat, and combinations of two or more mood stabilizers, including lithium plus valproate plus serotonin/dopamine blockers, are usually in order. For optimum efficacy, it may be ideal to push the dose of valproate, but no drug works if your patient refuses to take it, and valproic acid often

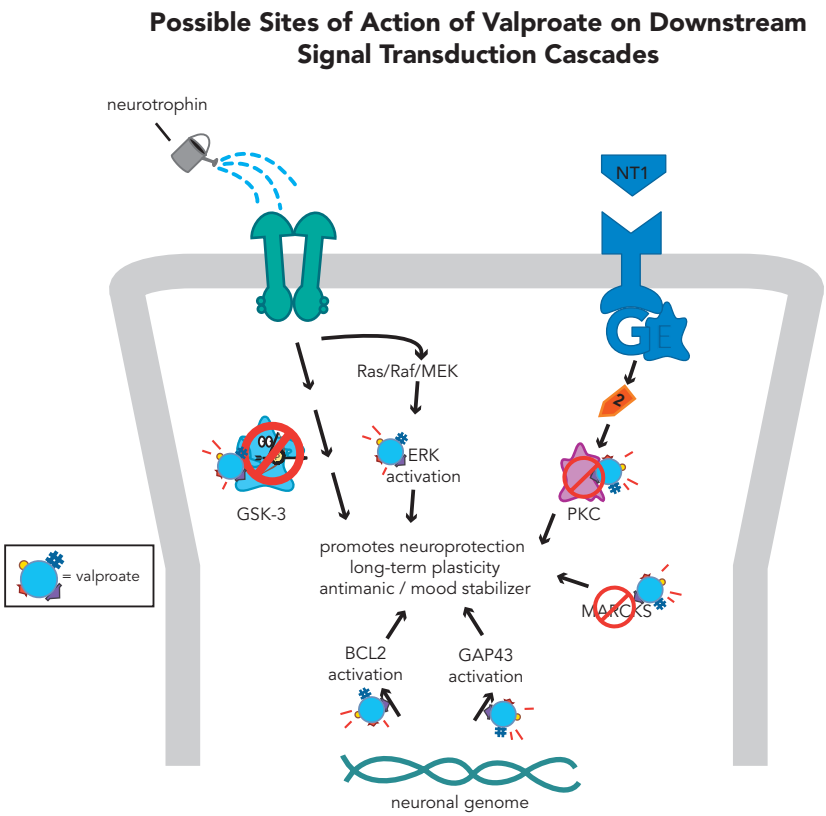


Figure 7-78 Possible sites of action of valproate on downstream signal transduction cascades. Valproate has been shown to have multiple downstream effects on signal transduction cascades, which may be involved in its antimanic effects. Valproate inhibits glycogen synthase kinase 3 (GSK-3), phosphokinase C (PKC), and myristoylated alanine-rich C kinase substrate (MARCKS). In addition, valproate activates signals that promote neuroprotection and long-term plasticity, such as extracellular signal-regulated kinase (ERK), cytoprotective protein B-cell lymphoma/leukemia-2 gene (BCL2), and growth associated protein 43 (GAP43).

has unacceptable side effects such as hair loss, weight gain, and sedation. Certain problems can be avoided by lowering the dose, but this will generally lower efficacy, and thus there may be the requirement to combine valproate with other mood stabilizers, especially when valproate is given in lower doses. Some side effects may be related more to chronicity of exposure rather than to dose and thus may not be avoidable by reducing the dose. This includes warnings for bone marrow, liver, pancreatic, and fetal toxicities such as neural-tube defects, as well as concerns about weight gain, metabolic complications, and possible risk of amenorrhea and polycystic ovaries in women of child-bearing potential. A syndrome of menstrual disturbances, polycystic ovaries, hyperandrogenism, obesity, and insulin resistance may be associated with valproic acid therapy in such women.

Carbamazepine

Carbamazepine (Figure 7-79) was actually the first to be shown to be effective in the manic phase of bipolar disorder, but did not receive US FDA approval until recently as a once-daily controlled-release formulation. Although carbamazepine and valproate both act effectively on the manic phase of bipolar disorder (Table 7-3), they appear to have different pharmacological mechanisms of action, including different side-effect profiles. Thus, carbamazepine is hypothesized to act by blocking voltage-sensitive sodium channels (VSSCs) (Figure 7-80), perhaps at a site within the channel itself, also known as the α subunit of VSSCs. As mentioned earlier, VSSCs are discussed in Chapter 3 and illustrated in Figures 3-19 through 3-21. The hypothesized action of carbamazepine upon the α subunit of VSSCs (Figure 7-80) is different from the hypothesized actions of valproate on these sodium channels (Figure 7-76), but may be similar to how the anticonvulsants oxcarbazepine and its active metabolite eslicarbazepine also act.

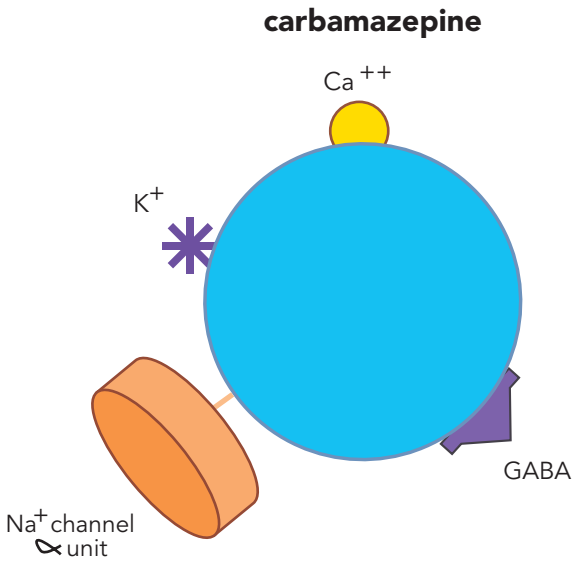


Figure 7-79 Carbamazepine. Shown here is an icon of the pharmacological actions of carbamazepine, an anticonvulsant used in the treatment of bipolar disorder. Carbamazepine may work by binding to the α subunit of voltage-sensitive sodium channels (VSSCs) and could perhaps have actions at other ion channels for calcium and potassium. By interfering with voltage-sensitive channels, carbamazepine may enhance the inhibitory actions of γ-aminobutyric acid (GABA).

Although both carbamazepine and valproate are anticonvulsants and both treat mania from above, there are differences between these two "anticonvulsants" beyond their presumed pharmacological mechanisms of therapeutic action in mania. For example, valproate is proven effective in migraine, but carbamazepine is proven effective in neuropathic pain. Furthermore, carbamazepine has a different side-effect profile than valproate, including more profound immediate suppressant effects upon the bone marrow, requiring initial monitoring of blood counts (blood counts including platelets should also be periodically monitored on valproate), and notable induction of the cytochrome P450 enzyme 3A4. Both carbamazepine and valproate are sedating and can cause fetal toxicity such as neural-tube defects.

Lamotrigine

Lamotrigine (Figure 7-81) is approved as a "mood stabilizer" for entirely different clinical indications than the anticonvulsant mood stabilizers valproate and carbamazepine, making the point that anticonvulsants do *not* all have the same therapeutic actions in bipolar disorder. Lamotrigine is not approved to treat mania or depression in bipolar disorder, but is approved to prevent recurrence of both mania and depression in bipolar disorder. There are many curious things about lamotrigine as a "mood stabilizer." First, the US FDA has not approved its use for acute bipolar depression, yet most experts believe that lamotrigine is effective for bipolar depression. A second interesting thing about lamotrigine is that even though it has some overlapping mechanistic actions with carbamazepine, namely binding to the open-channel conformation of VSSCs (Figure 7-82), lamotrigine is not approved for bipolar mania. Perhaps lamotrigine's pharmacological actions are not potent enough at sodium channels, or perhaps the long

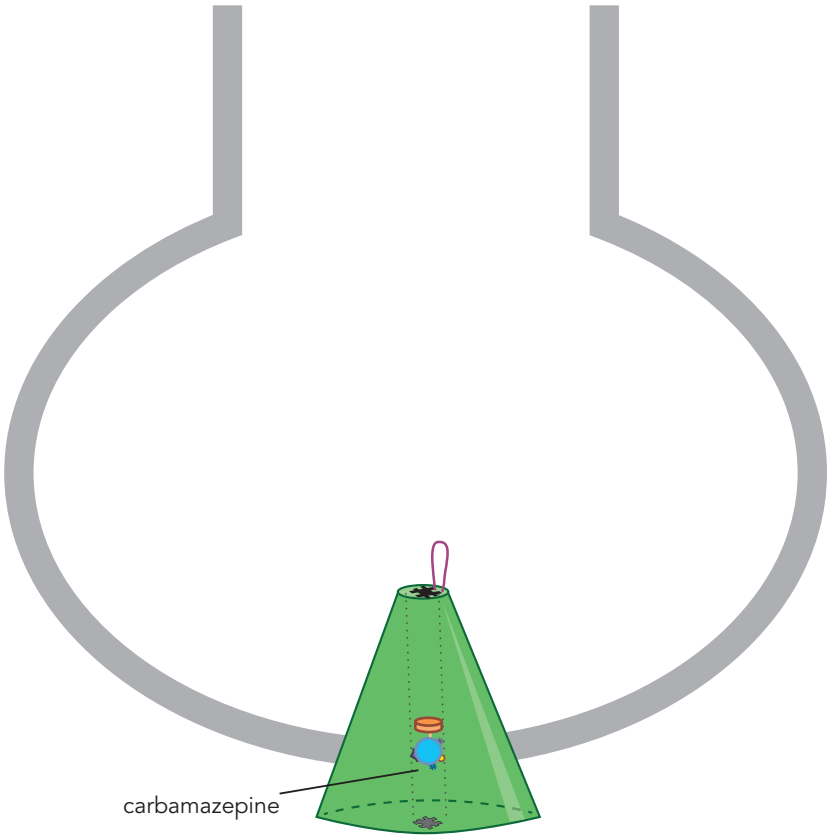


Figure 7-80 Binding site of carbamazepine. Carbamazepine is believed to bind to a site located within the open-channel conformation of the voltage-sensitive sodium channel (VSSC) α subunit.

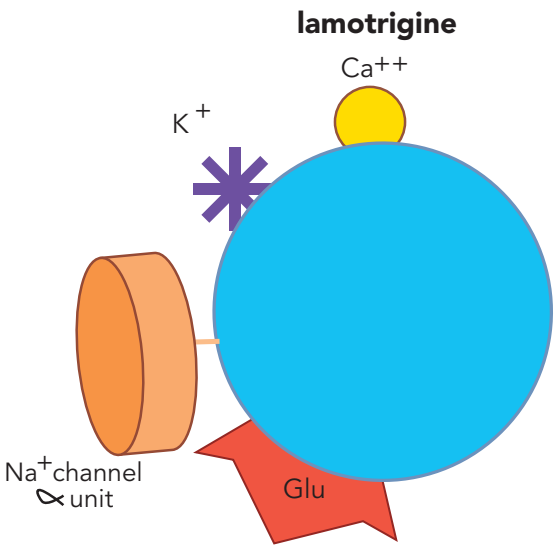


Figure 7-81 Lamotrigine. Shown here is an icon of the pharmacological actions of lamotrigine, an anticonvulsant used in the treatment of bipolar disorder. Lamotrigine may work by blocking the alpha subunit of voltage-sensitive sodium channels (VSSCs) and could perhaps also have actions at other ion channels for calcium and potassium. Lamotrigine is also thought to reduce the release of the excitatory neurotransmitter glutamate.

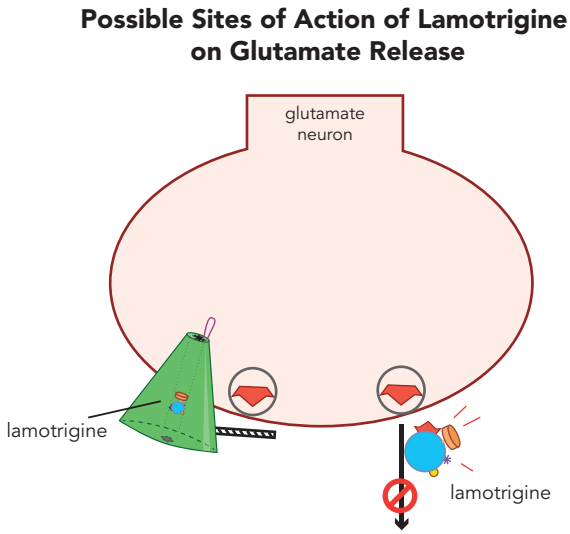


Figure 7-82 Possible site of action of lamotrigine on glutamate release. It is possible that lamotrigine reduces glutamate release through its blockade of voltage-sensitive sodium channels (VSSCs). Alternatively, lamotrigine may have this effect via an additional synaptic action that has not yet been identified.

titration period required when starting lamotrigine makes it difficult to show any useful effectiveness for mania, which generally requires treatment with drugs that can work quickly. A third aspect of lamotrigine is that it is generally well tolerated, with one glaring exception: a propensity to cause rashes, including (rarely) the life-threatening Stevens Johnson syndrome (toxic epidermal necrolysis). Rashes caused by lamotrigine can be minimized by very slow up-titration of the drug during initiation of therapy, avoiding or managing drug interactions, such as those with valproate that raise lamotrigine levels, and by understanding how to identify and manage serious rashes, including being able to distinguish them from benign rashes (see discussion of lamotrigine in *Stahl's Essential Psychopharmacology: the Prescriber's Guide*). Finally, lamotrigine seems to have some unique aspects to its mechanism of action (Figure 7-82), namely to reduce the release of the excitatory neurotransmitter glutamate. It is not clear whether this action is secondary to blocking the activation of VSSCs (Figure 7-82) or to some additional synaptic action. Reducing excitatory glutamatergic neurotransmission, especially if excessive during bipolar depression, may be a unique mechanism of action of lamotrigine and explain why it has such a different clinical profile as a treatment from below and a stabilizer from below for bipolar depression.

Anticonvulsants with Uncertain or Doubtful Efficacy in Bipolar Disorder

Oxcarbazepine/Eslicarbazepine

Oxcarbazepine is structurally related to carbamazepine, but is not a metabolite of carbamazepine. Oxcarbazepine is actually not the active form of the drug, but a prodrug that is immediately converted into a 10-hydroxy derivative, also called the monohydroxy derivative, and most recently has been named licarbazepine. The active form of licarbazepine is the S enantiomer, known as eslicarbazepine. Thus, oxcarbazepine really works via conversion to eslicarbazepine, which is itself now available as an anticonvulsant.

Oxcarbazepine has a presumed mechanism of anticonvulsant action the same as that for carbamazepine, namely, binding to the open-channel conformation of the VSSC at a site within the channel itself on the α subunit (as in Figure 7-80). However, oxcarbazepine seems to have some important differences from carbamazepine, including being less sedating, having less bone marrow toxicity, and also having less CYP450 3A4 interactions, making it a more tolerable agent that is easier to dose. On the other hand, oxcarbazepine has never been proven to work in acute bipolar mania or depression. Nevertheless, because of a similar postulated mechanism of action but a better tolerability profile, oxcarbazepine and more recently eslicarbazepine have been utilized "off-label" by many clinicians especially for the manic phase of bipolar disorder.

Topiramate

Topiramate is another compound approved as an anticonvulsant and for migraine, and recently, in combination with bupropion, for weight loss in obesity. Topiramate has been tested in bipolar disorder, but with ambiguous results (Table 7-3). It does seem to be associated with weight loss and is sometimes given as an adjunct to drugs for psychosis or to mood stabilizers that cause weight gain, but can cause unacceptable sedation in some patients. Topiramate is also being tested in various substance abuse disorders, including stimulant abuse and alcoholism. However, topiramate is not clearly effective as a mood stabilizer, either from evidence-based randomized controlled trials (which are not consistently positive) or from clinical practice.

Gabapentin and Pregabalin

These anticonvulsants seem to have little or no action as mood stabilizers, yet are robust treatments for various pain conditions, from neuropathic pain to fibromyalgia, and for various anxiety disorders, and are discussed in more detail in Chapter 8 on anxiety and Chapter 9 on pain.

Calcium Channel Blockers (L-Type)

There are several types of calcium channels, not only the N or P/Q channels linked to secretion of neurotransmitters, targeted by $\alpha_2\delta$ ligands and discussed in Chapter 3 (see Figures 3-23 and 3-24), but also L channels localized on vascular smooth muscle and which are targeted by various antihypertensive and antiarrhythmic drugs, commonly called "calcium channel blockers." L-type channels are located on neurons where their function is still being debated, and some anecdotal evidence suggests that calcium channel blockers, especially dihydropyridine-type calcium channel blockers, may be useful for some patients with bipolar disorder.

Riluzole

This agent has anticonvulsant actions in preclinical models, but was developed to slow the progression

of amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease). Theoretically, riluzole binds to VSSCs and prevents glutamate release, in an action similar to that postulated for lamotrigine (see Figure 7-82). The idea is that diminishing glutamate release in ALS would prevent the postulated excitotoxicity that may be causing death of motor neurons in ALS. Excessive glutamate activity may be occurring not only in ALS, but also in bipolar depression, although this is not necessarily so severe as to cause widespread neuronal loss.

Combinations are the Standard for Treating Bipolar Disorder

Given the disappointing number of patients who attain satisfactory response in bipolar disorder from monotherapy, it is more the rule than the exception that bipolar patients receive combination treatments. Although first-line treatment may be one of the serotonin/dopamine agents, if this fails to adequately control mania, another treatment for mania such as valproate or lithium may be added (Figure 7-83). On the other hand, if serotonin/dopamine agents fail to adequately control depression, lamotrigine may be added or, controversially, a monoamine reuptake inhibitor (Figure 7-83). The goal is four treatments for fullest remission of symptoms: treat from above and stabilize from above (Figure 7-7) and treat from below and stabilize from below (Figure 7-8).

FUTURE TREATMENTS FOR MOOD DISORDERS

Dextromethorphan-Bupropion and Dextromethorphan-Quinidine

As discussed above, one of the most interesting developments in the treatment of resistant unipolar depression in recent years has been the observation that infusions of subanesthetic doses of ketamine or intranasal administration of esketamine can exert an immediate antidepressant effect and can often immediately reduce suicidal thoughts. Since the effects are often not sustained for more than a few days, investigators have searched for oral ketamine-like agents that could have rapid onset, sustained efficacy, greater ease of administration, and better tolerability in patients with treatment-resistant illness. Several such possibilities are in development, namely various NMDA antagonists with additional pharmacological properties. One agent combines the NMDA antagonist dextromethorphan with the CYP450 2D6 inhibitor and NDRI bupropion (also known as AXS-05), and the other

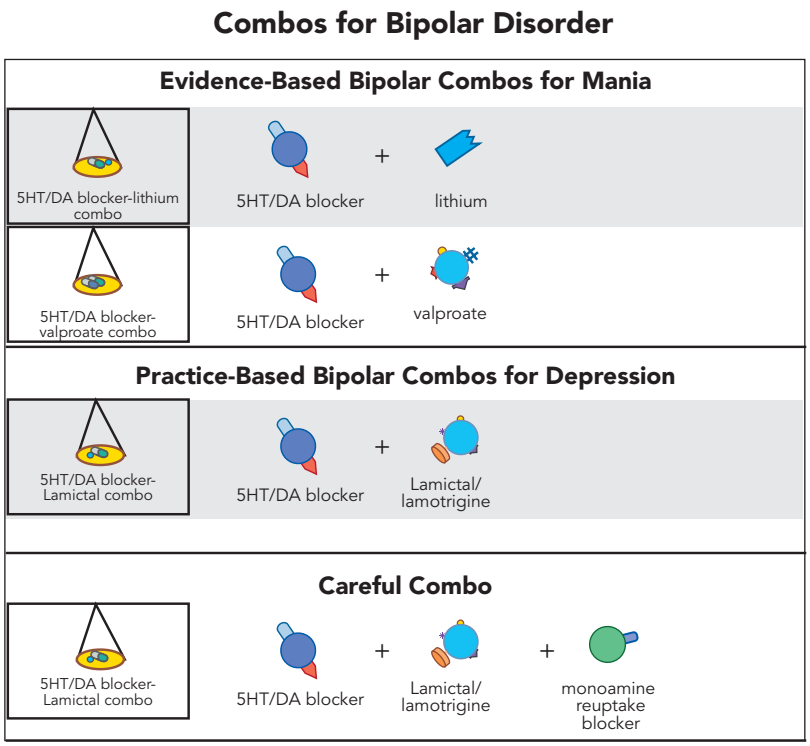


Figure 7-83 Bipolar disorder combinations. Most patients with bipolar disorder will require treatment with two or more agents. The combinations with the most evidence for mania include addition of a serotonin/dopamine antagonist to either lithium or valproate. Combinations that are not well studied in controlled trials but that have some practice-based evidence for depression include a serotonin/dopamine antagonist plus lamotrigine. Although controversial, some clinicians add a monoamine reuptake inhibitor to a serotonin/dopamine antagonist for bipolar depression.

combines dextromethorphan with the CYP450 2D6 inhibitor quinidine (Figure 7-84). The latter combination has already been approved to treat pathological laughing and crying in pseudobulbar affect. A newer version of the latter combination has deuterated the dextromethorphan molecule and altered the dose of quinidine (Figure 7-85). Deuteration extends the half-life of a compound and allows re-patenting for commercial development (deuteration of tetrabenazine was previously discussed in Chapter 5 in the section on treatment of tardive dyskinesia and illustrated in Figure 5-11B). Although it is clear that dextromethorphan has clinically relevant affinity for the NMDA receptor, other binding properties are less well characterized, including σ_1 receptor binding, SERT inhibition, and weak μ-opioid binding (Figure 7-84). As for all NMDA receptor antagonists studied for treatment-resistant depression, it is unclear which subtypes of NMDA receptor are engaged by dextromethorphan, which are most important, and what the role of σ_1 or μ-opioid binding is in rapid antidepressant action.

Dextromethorphan is rapidly metabolized by CYP450 2D6 making it difficult to achieve therapeutic blood levels following oral administration without concomitant administration of a CYP450 2D6 inhibitor. Each combination product adds a 2D6 inhibitor (Figure 7-84). Quinidine is a 2D6 inhibitor at doses below its cardiovascular actions, and bupropion is not only an NDRI (Figures 7-34 and 7-35) but also a 2D6 inhibitor. For bupropion, as discussed above and illustrated in Figures 7-34 and 7-35, in addition to 2D6 inhibition there is the monoamine-associated antidepressant mechanism of NRDIs (Figure 7-84) with the potential for synergy with the NMDA antagonist mechanism of dextromethorphan. Both combination products are in trials for treatment-resistant depression with some promising initial results, especially for dextromethorphan–bupropion, which has been awarded breakthrough therapy status by the US FDA for major depressive disorder and fast-track designation for treatment-resistant depression. Both combination products are also in trials for agitation in Alzheimer disease and show some promising initial results, especially for dextromethorphan–bupropion, wh ich was given fast-track designation by the FDA. Dextromethorphan–bupropion treatment of agitation in dementia is discussed further in Chapter 12 on dementia.

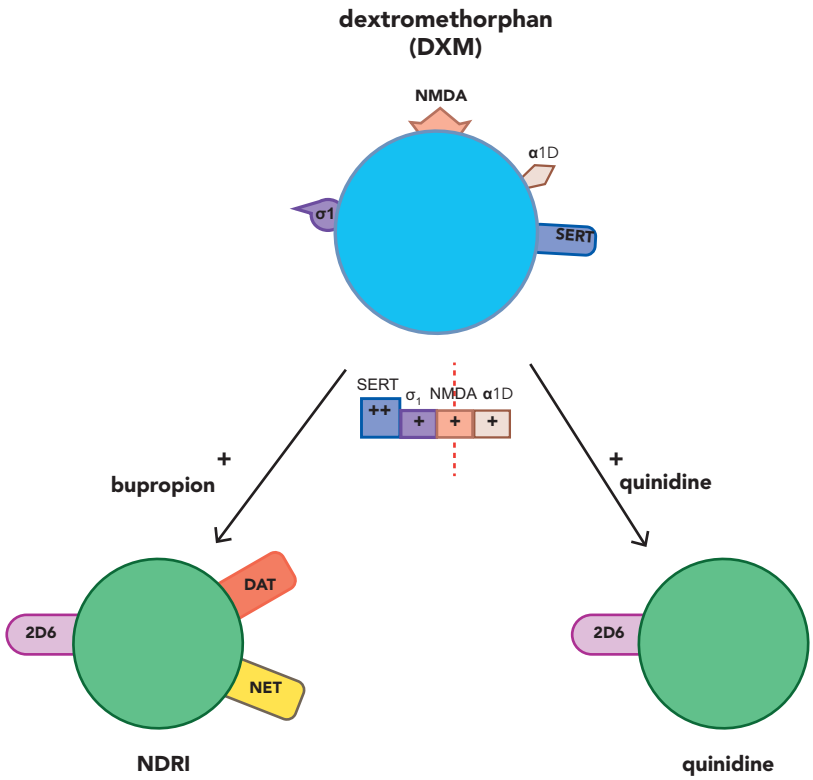


Figure 7-84 Dextromethorphan–bupropion and dextromethorphan–quinidine. Dextromethorphan is a weak *N*-methyl-D-aspartate (NMDA) receptor antagonist, with stronger binding affinity for the serotonin transporter (SERT) and σ_1 receptors. It is rapidly metabolized by CYP450 2D6, making it difficult to achieve therapeutic blood levels without concomitant administration of a CYP450 2D6 inhibitor. Dextromethorphan is being studied in combination with the norepinephrine–dopamine reuptake inhibitor (NDRI) bupropion, which also inhibits CYP450 2D6, and in combination with the CYP450 2D6 inhibitor quinidine.

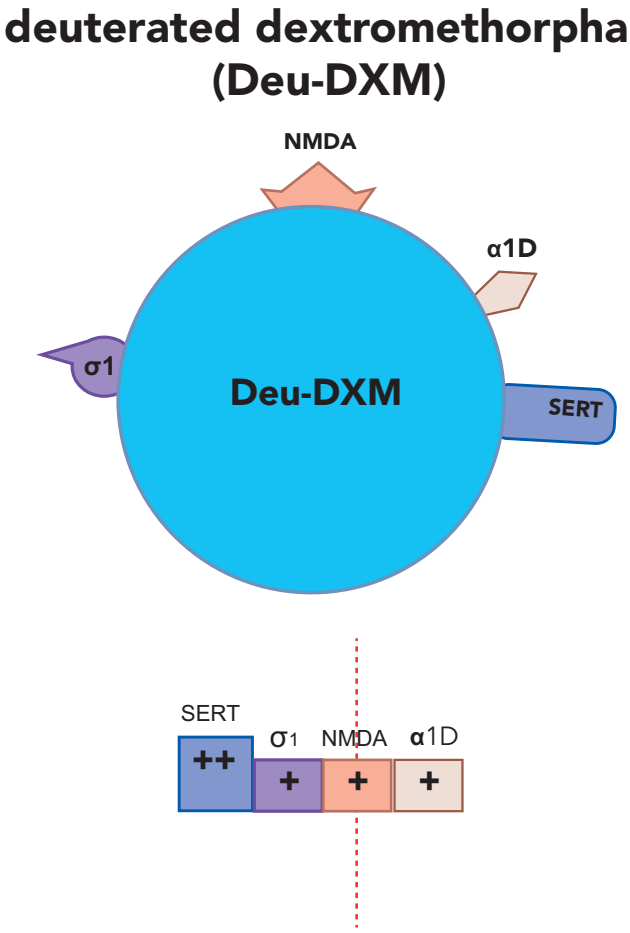


Figure 7-85 **Deuterated dextromethorphan.** A deuterated formulation of dextromethorphan in combination with quinidine is in development. Deuteration extends the half-life of dextromethorphan, which in turn affects the required dose of quinidine.

Dextromethadone

Methadone is a racemic mixture of dextro- and levomethadone and is given orally as a μ-opioid agonist for medication-assisted treatment of opioid use disorder. The μ-opioid activity resides mostly in the levo enantiomer, and the dextro enantiomer has relatively more potent NMDA antagonist activity, without as potent μ-opioid agonist activity. The dextro enantiomer (Figure 7-86) is in clinical development as a rapid-onset treatment of major depression with some promising early clinical results. Just as for all NMDA antagonists for treatment-resistant depression (i.e., ketamine, esketamine, and dextromethorphan), the relative importance of NMDA antagonism, the specific NMDA receptors targeted, and the downstream consequences of NMDA antagonism are just now being clarified, including the potential differences amongst these various NMDA antagonists. Furthermore, the additional binding properties of each of these agents, including dextromethadone, are less well characterized, such as σ_1 receptor binding, SERT inhibition, and weak μ-opioid binding (Figure 7-86). It is possible that these agents do not act simply as NMDA antagonists, but that some degree of μ-opioid agonist activity may shepherd dimers of NMDA and μ receptors by exploiting their natural oppositional actions, to create a greater NMDA effect in the presence of μ stimulation than in the absence of it. This is the subject of much further research as the field attempts to clarify the mechanism of rapid antidepressant response associated with NMDA antagonism, and which portfolio of receptor actions is optimal.

Hallucinogen-Assisted Psychotherapy

Psychotherapy has traditionally competed with psychopharmacology. More recently, psychotherapy and psychopharmacology have come to be seen as complementary and most good mental health prescribers also practice psychotherapy. It has long been recognized

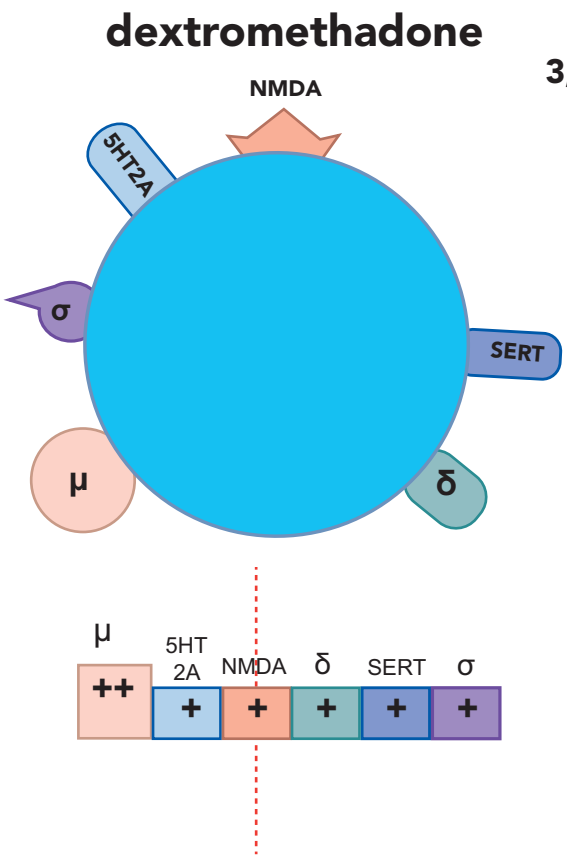


Figure 7-86 Dextromethadone. Methadone consists of two enantiomers, dextro and levo. The levo enantiomer is a potent μ-opioid receptor agonist, while the dextro enantiomer has less potent μ-opioid agonism and is also an antagonist at *N*-methyl-D-aspartate (NMDA) receptors. The dextro enantiomer of methadone, dextromethadone, is in clinical development as a rapid-onset treatment for major depressive disorder.

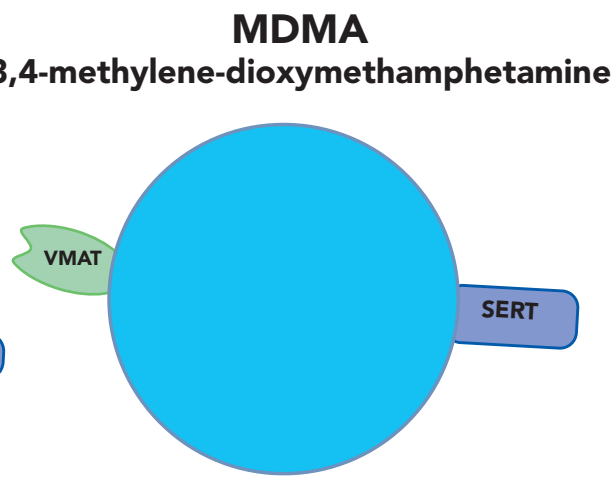


Figure 7-87 3,4-Methylene-dioxymethamphetamine (MDMA). MDMA is an amphetamine derivative. Amphetamine is a norepinephrine–dopamine reuptake inhibitor (NDRI) with additional inhibition of VMAT2 causing enhanced dopamine release. MDMA is a serotonin inhibitor, with additional inhibition of VMAT2 causing enhanced serotonin release. MDMA is intesting for PTSD, anxiety, and treatment-resistant depression.

that using both psychotherapy and medication can be synergistic for many patients in terms of therapeutic efficacy and favorable long-term outcomes, perhaps by sharing some common neurobiological links since both can change brain circuits. Preclinical research increasingly documents psychotherapy as a form of learning which can induce epigenetic changes in brain circuits, which can enhance the efficiency of information processing in malfunctioning neurons to improve symptoms in psychiatric disorders, just like drugs. A recent clinical exploitation of the combination of psychotherapy with psychopharmacology is a resurrection in the use of hallucinogens to induce a state of dissociation in which the patient may be more amenable to psychotherapeutic input. One idea is to provide more insight and clarity to underlying suppressed memories. Another idea is to use psychotherapy-guided re-experiencing of memories, coupled with techniques to interfere with reconsolidation of traumatic memories so they are "forgotten." Animal studies show that memories are initially consolidated into relatively permanent memory files, but become labile when reactivated, and if not reconsolidated after having or modifying that memory, it can theoretically be erased. That is the goal of some types of hallucinogen-assisted psychotherapies: to prevent the reconsolidation of painful traumatic memories. Numerous agents have been tested in this paradigm of dissociation-assisted psychotherapy, from ketamine to the hallucinogens MDMA and psilocybin, described below.

3,4-Methylene-dioxymethamphetamine (MDMA)

3,4-Methylene-dioxymethamphetamine (MDMA) (Figure 7-87) is an amphetamine derivative that transforms amphetamine itself from being predominantly a norepinephrine–dopamine reuptake inhibitor with

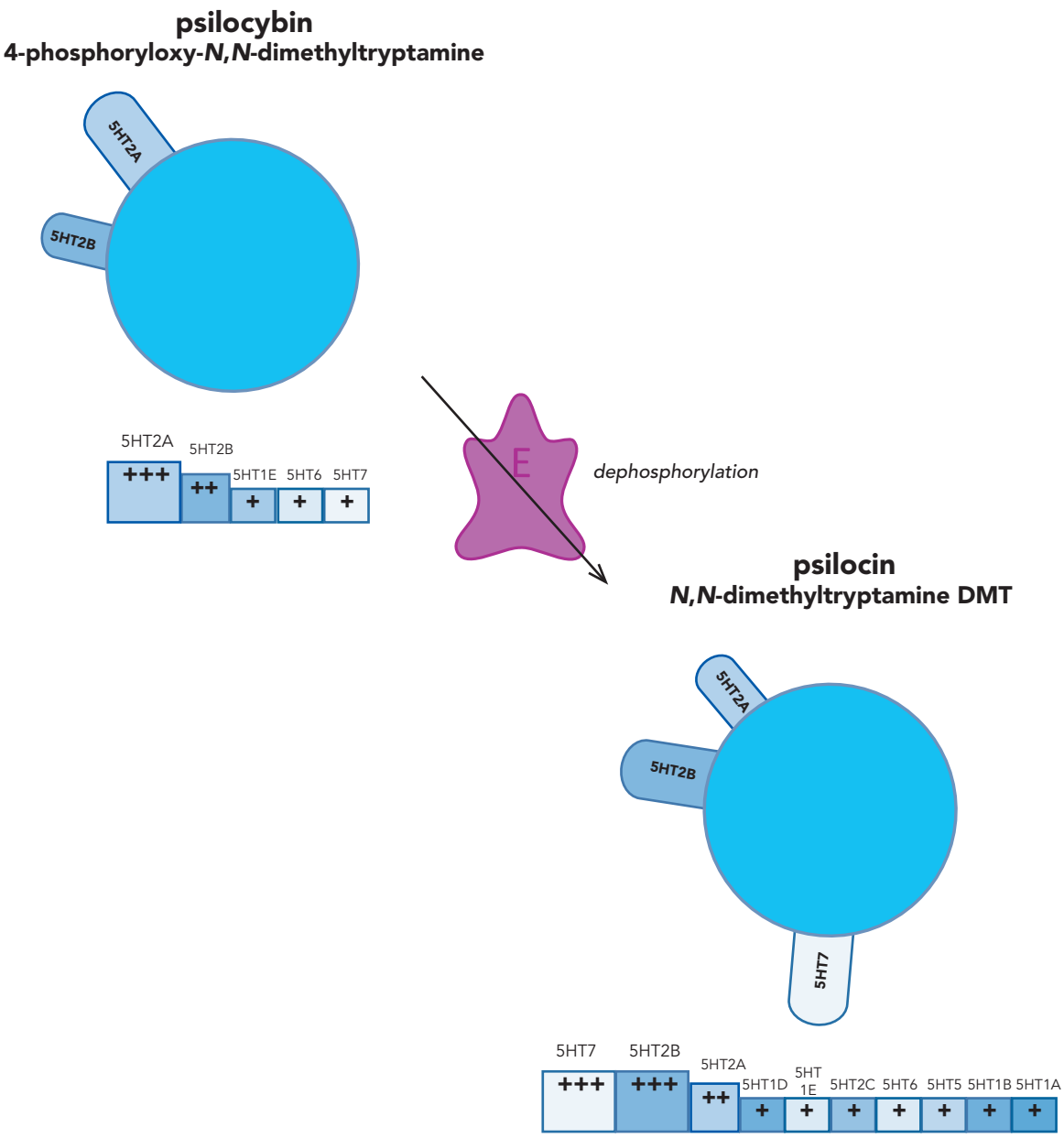


Figure 7-88 **Psilocybin.** The hallucinogen psilocybin is predominantly a $5HT_{2A}$ agonist, with actions at some additional serotonin receptors. It is rapidly converted by dephosphorylation to its active metabolite, psilocin. Psilocybin is being studied in depression, anxiety, and PTSD.

vesicular monoamine transporter 2 (VMAT2) inhibition causing enhanced dopamine release (see Chapter 11 and Figures 11-30 through 11-32) into a more powerful serotonin reuptake inhibitor with VMAT2 inhibition causing enhanced serotonin release as well. The released serotonin is free to act at all serotonin receptors but seems to have profound actions in stimulating the $5HT_{2A}$ receptor, not unlike other hallucinogens.

The reason MDMA may be helpful in psychotherapy is that it can produce feelings of increased energy, pleasure,

and emotional warmth, and it can promote trust and closeness but cause distortions and hallucinations of sensory and time perception. MDMA, also known as "Ecstasy" or "Molly" (slang for Molecular), was once popular in the nightclub scene and at "raves" (all-night dance parties). Its agonist actions at $5HT_{2A}$ receptors may be responsible for the spike in body temperature that can occur after taking MDMA, with organ damage and even death, especially when dancing all night and when dehydrated. MDMA obtained on the street is often contaminated with "bath salts" (synthetic cathinones), methamphetamine, dextromethorphan, ketamine, and/or cocaine, and is often taken along with marijuana and alcohol. Pure MDMA is obviously what is studied in hallucinogen-assisted psychotherapy. MDMA is in testing for PTSD, anxiety and existential distress in terminally ill patients, social anxiety in autism, treatment refractory depression, substance abuse, and more.

Psilocybin

Psilocybin (4-phosphoryloxy-*N*,*N*-dimethyltryptamine) (Figure 7-88), also known as an hallucinogen in "magic mushrooms," has a structure similar to LSD (lysergic acid diethylamide) and has been used and abused for its ability to cause hallucinogenic, psychedelic, and euphoric "trips." Psilocybin is rapidly converted to its active metabolite psilocin (*N*,*N*-dimethyltryptamine or DMT) by dephosphorylation. Both agents bind to a number of serotonin receptor subtypes ($5HT_{1A}$, $5HT_{2A}$, $5HT_{2C}$, and others), but the hallucinogenic actions of both agents are linked most closely with agonist actions on $5HT_{2A}$ receptors (Figure 7-88), since $5HT_{2A}$ antagonists (but not selective dopamine D_2 antagonists) reverse the effects of psilocybin in humans. Hallucinogen-mediated $5HT_{2A}$-stimulated psychosis was discussed in Chapter 4 as one of the three major theories of psychosis and illustrated in Figure 4-52B. Psilocybin has been designated a breakthrough therapy by the US FDA for treatment of depression. Psilocybin is also being widely investigated for anxiety and existential distress in terminally ill patients, substance abuse, PTSD, and several other conditions.

SUMMARY

In this extensive chapter, we have summarized the pharmacological mechanisms of actions of the many agents used to treat unipolar major depression, especially those acting on monoamine systems. More recently introduced have been agents working outside the monoamine system, namely on glutamate and GABA neurotransmission. Combining drugs for treatment resistance in unipolar depression is also discussed. Not only is the treatment of unipolar depression presented, but this is compared and contrasted with the treatment of bipolar disorder, from mania, to bipolar depression, to depression with mixed features. The specific agents for these conditions, which are mostly different from those for the treatment of unipolar depression, are discussed. Many of these same agents are used in the treatment of psychosis and that use is discussed in Chapter 5. A brief synopsis of future treatments for mood disorders is also presented.

8 Anxiety, Trauma, and Treatment

Symptom Dimensions in Anxiety Disorders 359
When Is Anxiety an Anxiety Disorder? 359
Overlapping Symptoms of Major Depression and Anxiety Disorders 360
Overlapping Symptoms of Different Anxiety Disorders 362
The Amygdala and the Neurobiology of Fear 364
Cortico-Striato-Thalamo-Cortical (CSTC) Loops and the Neurobiology of Worry 365
Benzodiazepines as Drugs for Anxiety 366
Alpha-2-Delta Ligands as Anxiolytics 366
Serotonin and Anxiety 368
Noradrenergic Hyperactivity in Anxiety 370
Fear Conditioning versus Fear Extinction 370
Novel Approaches to the Treatment of Anxiety Disorders 374
Treatments for Anxiety Disorder Subtypes 377
Generalized Anxiety Disorder 377
Panic Disorder 377
Social Anxiety Disorder 377
PTSD 377
Summary 378

This chapter will provide a brief overview of anxiety disorders, traumatic disorders, and their symptoms and their treatments. Included here are descriptions of how the symptoms of anxiety disorders overlap with each other, and also with the symptoms of major depressive disorder and with the symptoms of trauma and stress-related disorders. Clinical descriptions and formal diagnostic criteria are mentioned here only in passing. The reader should consult standard reference sources for this material. The discussion here will emphasize how the functioning of various brain circuits and neurotransmitters – especially those centered on the amygdala – impact our understanding of the symptoms of fear, worry, and traumatic memories.

The goal of this chapter is to acquaint the reader with ideas about the clinical and biological aspects of anxiety/traumatic symptoms in order to understand the mechanisms of action of the various treatments. Many of the psychopharmacological treatments are extensively discussed in other chapters. For details of mechanisms of the many agents used to treat anxiety that are also used to treat unipolar depression (monoamine reuptake inhibitors), the reader is referred to Chapter 7 on mood disorders and their treatments; for those agents used to treat anxiety and traumatic disorders that are also used to treat chronic pain (i.e., certain ion-channel-inhibiting anticonvulsants), the reader is referred to Chapter 9 on chronic pain and its treatment. Although all psychiatric disorders can benefit from psychotherapy, anxiety/traumatic disorders may be especially effectively treated with psychotherapy. In many cases, psychotherapy for anxiety disorders can be even more effective than drug treatment or can enhance the efficacy of anxiolytic agents. Novel psychotherapies aiming to prevent or reverse fear conditioning and fear reconsolidation are mentioned briefly here but for more details of psychotherapy for anxiety, the reader is referred to general psychiatry and clinical psychology texts as well as to books by the author that cover both psychopharmacology and psychotherapy (see reference list). The discussion of anxiety and its disorders in this chapter emphasizes the neurobiology of anxiety and the mechanism of action of drugs for anxiety. The reader should consult standard drug handbooks (such as *Stahl's Essential Psychopharmacology: the Prescriber's Guide*) for details of doses, side effects, drug interactions, and other issues relevant to the prescribing of these drugs in clinical practice.

SYMPTOM DIMENSIONS IN ANXIETY DISORDERS

When Is Anxiety an Anxiety Disorder?

Anxiety is a normal emotion under circumstances of threat and is thought to be part of the evolutionary "fight

or flight" reaction of survival. Whereas it may be normal or even adaptive to be anxious when a saber-tooth tiger (or its modern-day equivalent) is attacking, there are many circumstances in which the presence of anxiety is maladaptive or excessive and constitutes a psychiatric disorder. The idea of anxiety as a psychiatric disorder is evolving rapidly, and is characterized by the concept of core symptoms of excessive fear and worry (symptoms at the center of anxiety disorders in Figure 8-1), compared to major depression, which is characterized by core symptoms of depressed mood or loss of interest (symptoms at the center of major depressive disorder in Figure 8-1). Some disorders associated with the symptoms of anxiety such as obsessive–compulsive disorder (OCD) are no longer classified as anxiety disorders in some diagnostic manuals, and here OCD is discussed in Chapter 13 on impulsive and compulsive disorders. Other disorders associated with the symptoms of anxiety such as posttraumatic stress disorder (PTSD) are also no longer classified as anxiety disorders in certain diagnostic manuals, but are discussed here in this chapter.

Anxiety disorders have considerable symptom overlap with major depression (see those symptoms surrounding core features shown in Figure 8-1), particularly sleep disturbance, problems concentrating, and fatigue and psychomotor/arousal symptoms. Each anxiety disorder also has a great deal of symptom overlap with other anxiety disorders (Figures 8-2 through 8-5; see also Figure 13-30). Anxiety disorders are also extensively comorbid, not only with major depression, but also with each other, since many patients qualify over time for a second or even third concomitant anxiety disorder (Figures 8-2 through 8-5). Finally, anxiety disorders are frequently comorbid with many other conditions such as substance abuse, attention deficit hyperactivity disorder (ADHD), bipolar disorder, pain disorders, sleep disorders, and more.

So, what is an anxiety disorder? These disorders all seem to maintain the core features of some form of anxiety or fear coupled with some form of worry, but their natural history over time shows them to morph from one into another, to evolve into full syndrome expression of anxiety-disorder symptoms (Figure 8-1) and then to recede into subsyndromal levels of symptoms, only to reappear again as the original anxiety disorder, a different anxiety disorder (Figures 8-2 through 8-5), or major depression (Figure 8-1). If anxiety disorders all share core symptoms of fear and worry (Figures 8-1 and 8-6) – and as we shall see later in this chapter, are all basically treated with the same drugs, including many of the same drugs that treat major depression – the question now arises as to what the difference is between one anxiety disorder and another. Also, one could ask what the difference is between major depression and anxiety disorders. Are all these entities really different disorders or are they instead different aspects of the same illness?

Overlapping Symptoms of Major Depression and Anxiety Disorders

Although the core symptoms of major depression (depressed mood or loss of interest) differ from the core symptoms of anxiety disorders (fear and worry), there is a great deal of overlap with the other symptoms considered diagnostic for both a major depression episode and for several different anxiety disorders (Figure 8-1). These overlapping symptoms include problems with sleep, concentration, and fatigue as well as psychomotor/arousal symptoms (Figure 8-1). It is thus easy to see how the gain or loss of just a few additional symptoms can morph a major depressive episode into an anxiety

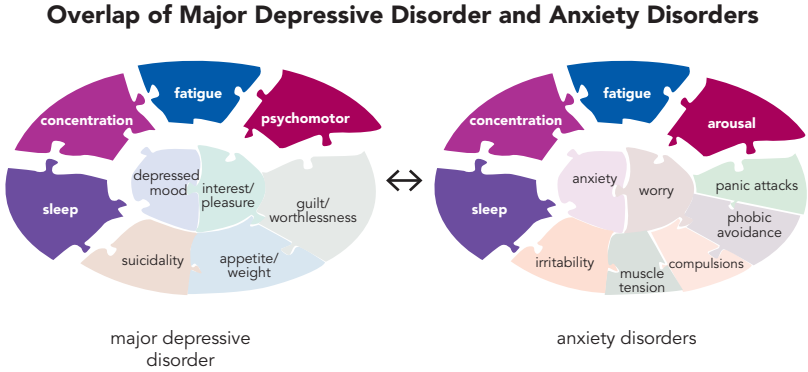


Figure 8-1 Overlap of major depressive disorder and anxiety disorders. Although the core symptoms of anxiety disorders (anxiety and worry) differ from the core symptoms of major depression (loss of interest and depressed mood), there is considerable overlap among the rest of the symptoms associated with these disorders (compare the "anxiety disorders" puzzle on the right to the "major depressive disorder" puzzle on the left). For example, fatigue, sleep difficulties, problems concentrating, and psychomotor/arousal symptoms are common to both types of disorders.

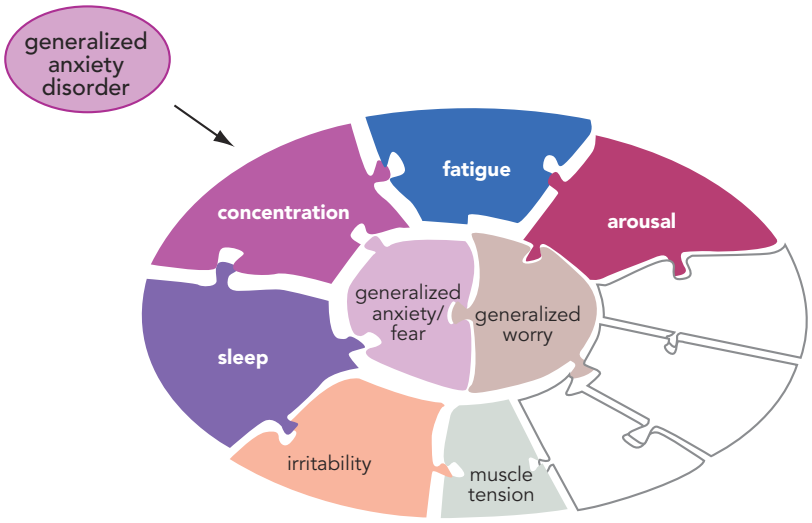


Figure 8-2 Generalized anxiety disorder. The symptoms typically associated with generalized anxiety disorder are shown here. These include the core symptoms of generalized anxiety and worry as well as increased arousal, fatigue, difficulty concentrating, sleep problems, irritability, and muscle tension. Many of these symptoms, including the core symptoms, are present in other anxiety disorders as well.

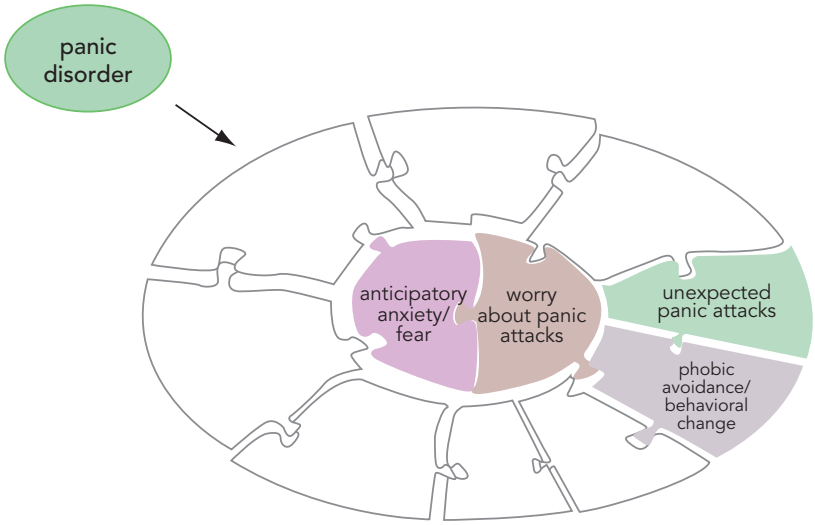


Figure 8-3 Panic disorder. The characteristic symptoms of panic disorder are shown here and include the core symptoms of anticipatory anxiety as well as worry about panic attacks; associated symptoms are the unexpected panic attacks themselves and phobic avoidance or other behavioral changes associated with concern over panic attacks.

disorder (Figure 8-1) or one anxiety disorder into another (Figures 8-2 through 8-5).

From a therapeutic point of view, it may matter little what the specific diagnosis is across this spectrum of disorders (Figures 8-1 through 8-5). That is, psychopharmacological treatments may not be much different for a patient who currently qualifies for a major depressive episode plus the symptom of anxiety (but not an anxiety disorder) versus a patient who currently qualifies for a major depressive episode plus a comorbid anxiety disorder. Although it can be useful to make specific diagnoses for following patients over time and for documenting the evolution of symptoms, the emphasis from a psychopharmacological point of view is increasingly to take a symptom-based therapeutic strategy for patients with any of these disorders because the brain is not organized according to the DSM, but according to brain circuits with topographical localization of function. That is, specific treatments can be tailored to the individual patient by deconstructing whatever disorder the patient has into a list of the specific symptoms a given patient is experiencing (see Figures 8-2 through 8-5). These symptoms are then matched to hypothetically malfunctioning brain circuits, regulated by specific neurotransmitters, in order to rationally select and

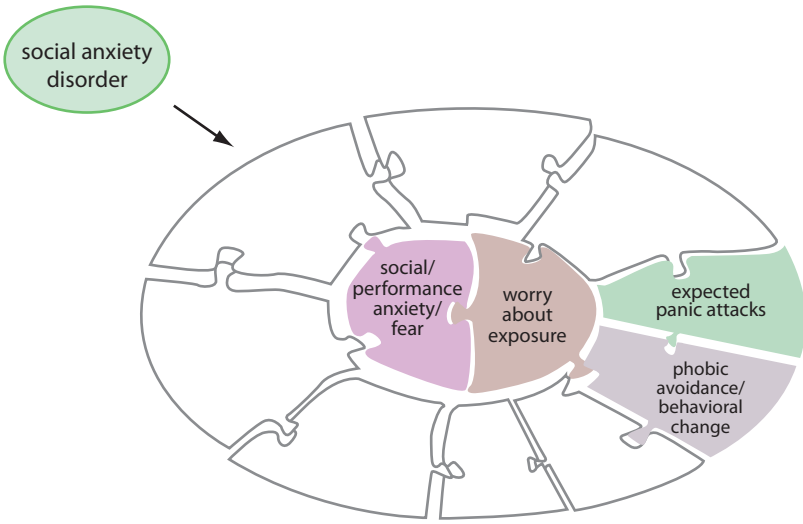


Figure 8-4 Social anxiety disorder. Symptoms of social anxiety disorder, shown here, include the core symptoms of anxiety or fear over social performance plus worry about social exposure. Associated symptoms are panic attacks that are predictable and expected in certain social situations as well as phobic avoidance of those situations.

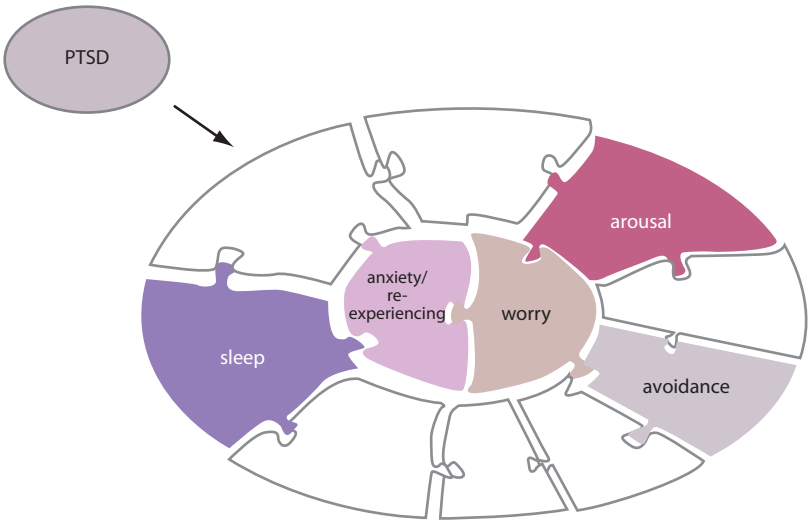


Figure 8-5 Posttraumatic stress disorder (PTSD). The characteristic symptoms of PTSD are shown here. These include the core symptoms of anxiety while the traumatic event is being re-experienced as well as worry about having the other symptoms of PTSD, such as increased arousal and startle responses, sleep difficulties including nightmares, and avoidance behaviors. PTSD is now categorized as a stress-related disorder rather than as an anxiety disorder, and is considered a disorder of hyperarousal.

combine psychopharmacological treatments to eliminate symptoms by increasing the efficiency of information processing in the malfunctioning brain circuits, and thereby get the patient into remission. This was discussed extensively in Chapter 6 on mood disorders and illustrated in Figures 6-42 through 6-44.

Overlapping Symptoms of Different Anxiety Disorders

Although there are different diagnostic criteria for different anxiety disorders (Figures 8-2 through 8-5), these are constantly changing and many do not even consider OCD or PTSD to be anxiety disorders any longer (OCD is discussed in Chapter 13 on impulsivity). All anxiety disorders have overlapping symptoms of anxiety/fear coupled with worry (Figure 8-6). Remarkable progress has been made in understanding the circuitry underlying the core symptom of anxiety/fear based upon an explosion of neurobiological research on the amygdala (Figures 8-7 through 8-14). The links between the amygdala, fear circuits, and treatments for the symptom of anxiety/fear across the spectrum of anxiety, trauma, and stress disorders are discussed throughout the rest of this chapter.

Worry is the second core symptom shared across the spectrum of anxiety disorders (Figure 8-7). This symptom is hypothetically linked to the functioning of cortico-striato-thalamo-cortical(CSTC) loops. The links between the CSTC "worry loops" and treatments

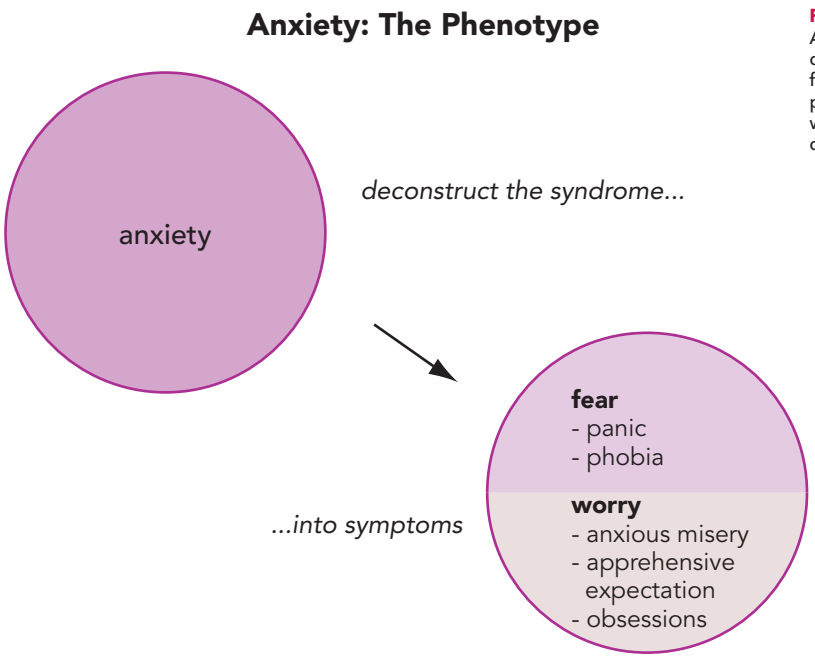


Figure 8-6 Anxiety: the phenotype. Anxiety can be deconstructed, or broken down, into the two core symptoms of fear and worry. These symptoms are present in all anxiety disorders, although what triggers them may differ from one disorder to the next.

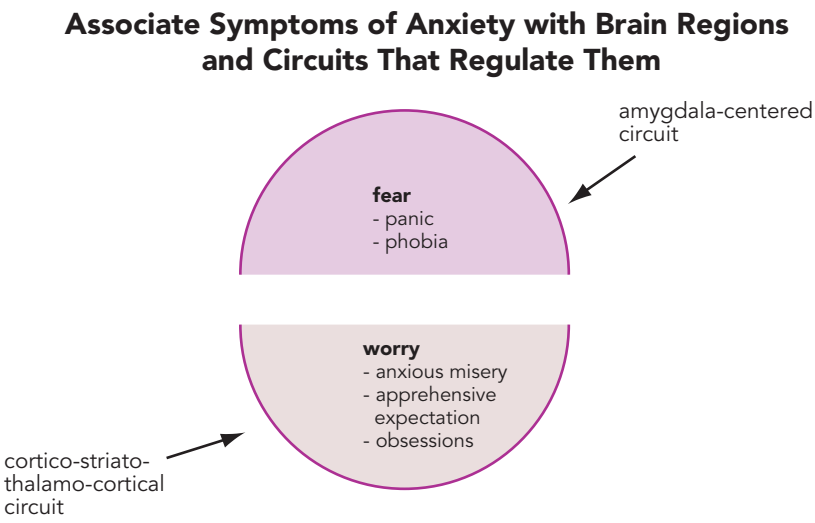


Figure 8-7 Linking anxiety symptoms to circuits. Anxiety and fear symptoms (e.g., panic, phobias) are regulated by an amygdala-centered circuit. Worry, on the other hand, is regulated by a cortico-striato-thalamo-cortical (CSTC) circuit. These circuits may be involved in all anxiety disorders, with the different phenotypes reflecting not unique circuitry but rather divergent malfunctioning within those circuits.

for the symptom of worry across the spectrum of anxiety disorders are discussed later in this chapter (see also Figures 8-15 through 8-20). We shall see that what differentiates one anxiety disorder from another may not be the anatomical localization or the neurotransmitters regulating fear and worry in each of these disorders (Figures 8-6 and 8-7), but the specific nature of malfunctioning within these same circuits in various anxiety disorders. That is, in generalized anxiety disorder, malfunctioning in the amygdala and CSTC worry loops may be hypothetically persistent, and unremitting, yet not severe (Figure 8-2), whereas malfunctioning may be theoretically intermittent but catastrophic in an unexpected manner for panic disorder (Figure 8-3) or in an expected manner for social anxiety (Figure 8-4). Circuit malfunctioning may be traumatic in origin and conditioned in PTSD (Figure 8-5).

THE AMYGDALA AND THE NEUROBIOLOGY OF FEAR

The amygdala, an almond-shaped brain center located near the hippocampus, has important anatomical connections that allow it to integrate sensory and cognitive information, and then determine whether there will be a fear response. Specifically, the affect or feeling of fear may be regulated via the reciprocal connections the amygdala shares with key areas of prefrontal cortex that regulate emotions, namely the orbitofrontal cortex and the anterior cingulate cortex (Figure 8-8). However, fear is not just a feeling. The fear response can also include motor responses. Depending upon the circumstances and one's temperament, those motor responses could be fight, flight, or freezing in place. Motor responses of fear are regulated in part by connections between the amygdala and the periaqueductal gray area of the brainstem (Figure 8-9).

There are also endocrine reactions that accompany fear, in part due to connections between the amygdala and the hypothalamus, causing changes in the HPA (hypothalamic-pituitary-adrenal) axis, and thus of cortisol levels. A quick boost of cortisol may enhance survival when encountering a real, but short-term, threat. However, chronic and persistent activation of this aspect of the fear response can lead to increased medical comorbidity, including increased rates of coronary artery disease, type 2 diabetes, and stroke (Figure 8-10), and also potentially to hippocampal atrophy, as discussed in Chapter 6 and shown in Figure 6-30. Breathing can also change during a fear response, regulated in part by the connections between the amygdala and the parabrachial nucleus in the brainstem (Figure 8-11). An adaptive response to fear is to accelerate respiratory rate when having a fight/flight reaction to enhance survival, but, in excess, this can lead to unwanted symptoms of shortness of breath, exacerbation of asthma, or a false sense of being smothered (Figure 8-11), all symptoms common during anxiety, and especially during attacks of anxiety such as panic attacks.

The autonomic nervous system is attuned to fear, and is able to trigger responses from the cardiovascular system, such as increased pulse and blood pressure for fight/flight reactions and survival during real threats. These autonomic and cardiovascular responses are mediated by connections between the amygdala and the locus coeruleus, home of the noradrenergic cell bodies (Figure 8-12; noradrenergic neurons are discussed in

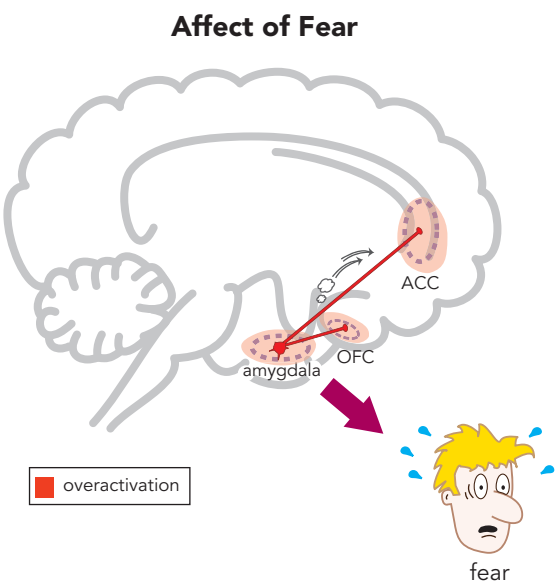


Figure 8-8 Affect of fear. Feelings of fear are regulated by reciprocal connections between the amygdala and the anterior cingulate cortex (ACC) and the amygdala and the orbitofrontal cortex (OFC). Specifically, it may be that overactivation of these circuits produces feelings of fear.

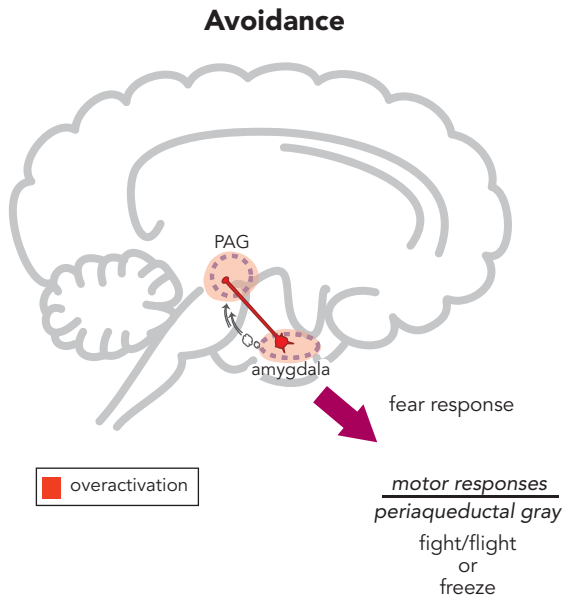


Figure 8-9 Motor responses of fear. Feelings of fear may be expressed through behaviors such as avoidance, which is partly regulated by reciprocal connections between the amygdala and the periaqueductal gray (PAG). Avoidance in this sense is a motor response and may be analogous to freezing under threat. Other motor responses are to fight or to run away (flight) in order to survive threats from the environment.

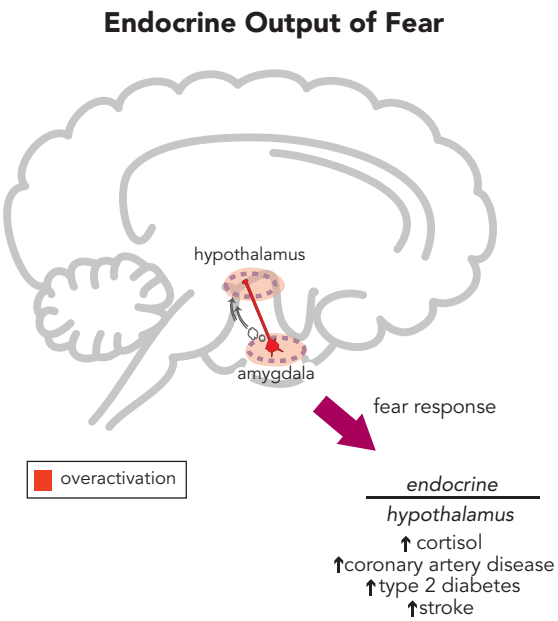


Figure 8-10 Endocrine output of fear. The fear response may be characterized in part by endocrine effects such as increases in cortisol, which occur because of amygdala activation of the hypothalamic-pituitary-adrenal (HPA) axis. Prolonged HPA activation and cortisol release can have significant health implications, such as increased risk of coronary artery disease, type 2 diabetes, and stroke.

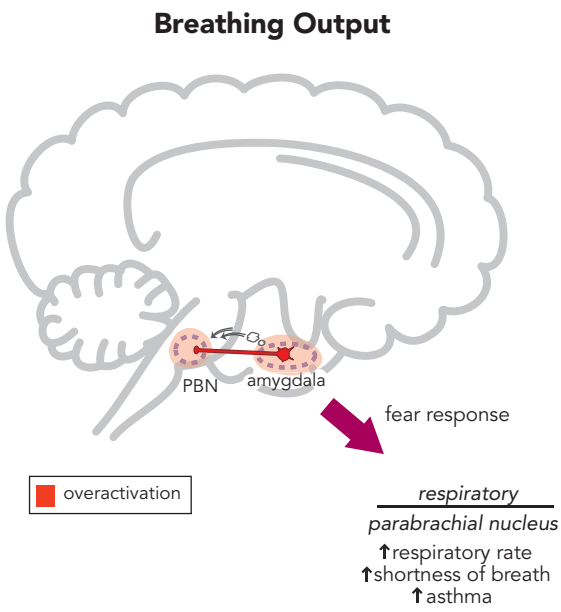


Figure 8-11 Breathing output. Changes in respiration may occur during a fear response; these changes are regulated by activation of the parabrachial nucleus (PBN) via the amygdala. Inappropriate or excessive activation of the PBN can lead not only to increases in the rate of respiration but also to symptoms such as shortness of breath, exacerbation of asthma, or a sense of being smothered.

Chapter 6 and noradrenergic pathways and neurons are illustrated in Figures 6-12 through 6-16). When autonomic responses are repetitive, inappropriately or chronically triggered as part of an anxiety disorder, this can lead to increases in atherosclerosis, cardiac ischemia, hypertension, myocardial infarction, and even sudden death (Figure 8-12). "Scared to death" may not always be an exaggeration or a figure of speech! Finally, anxiety can be triggered internally from traumatic memories stored in the hippocampus and activated by connections with the amygdala (Figure 8-13), especially in conditions such as PTSD.

The processing of the fear response is regulated by the numerous neuronal connections flowing into and out of the amygdala. Each connection utilizes specific neurotransmitters acting at specific receptors (Figure 8-14). What is known about these connections is not only that several neurotransmitters are involved in the production of symptoms of anxiety at the level of the amygdala, but that numerous anxiolytic drugs have actions upon these specific neurotransmitter systems to relieve the symptoms of anxiety and fear (Figure 8-14). The known neurobiological regulators of the amygdala include the neurotransmitters GABA, serotonin, and norepinephrine, and the voltage-gated calcium channels. Not surprisingly, known anxiolytics act upon these same neurotransmitters hypothetically in order to mediate their therapeutic actions.

CORTICO-STRIATO-THALAMO-CORTICAL (CSTC) LOOPS AND THE NEUROBIOLOGY OF WORRY

The second core symptom of anxiety disorders, namely, worry, hypothetically involves another unique circuit (Figure 8-15). Worry, which can include anxious misery, apprehensive expectations, catastrophic thinking, and obsessions, is hypothetically linked to CSTC feedback loops from the prefrontal cortex (Figure 8-15 and Figure 8-16). Some experts theorize that similar CSTC feedback loops regulate the related symptoms of ruminations, obsessions, and delusions, all of these symptoms being types of recurrent thoughts. Several neurotransmitters and regulators are known to modulate these circuits, including serotonin, GABA, dopamine, norepinephrine,

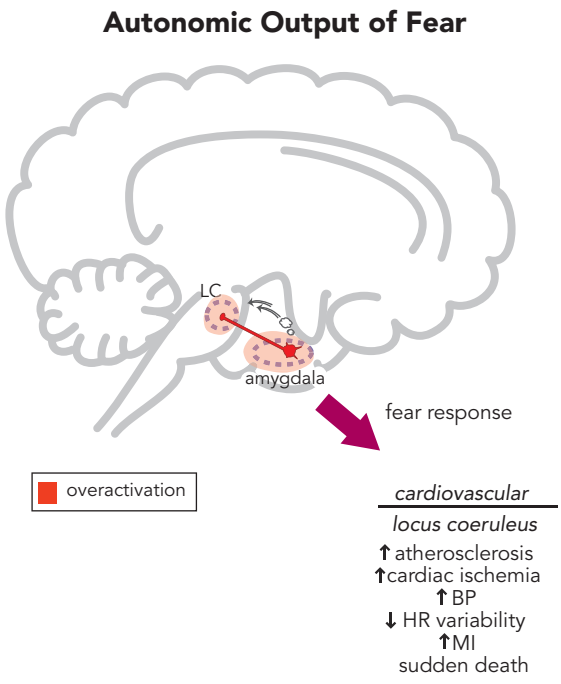


Figure 8-12 Autonomic output of fear. Autonomic responses are typically associated with feelings of fear. These include increases in heart rate (HR) and blood pressure (BP), which are regulated by reciprocal connections between the amygdala and the locus coeruleus (LC). Long-term activation of this circuit may lead to increased risk of atherosclerosis, cardiac ischemia, change in BP, decreased HR variability, myocardial infarction (MI), or even sudden death.

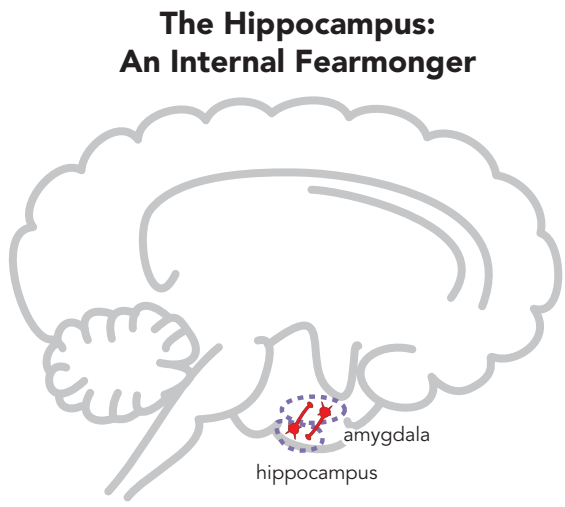


Figure 8-13 The hippocampus and re-experiencing. Anxiety can be triggered not only by an external stimulus but also by an individual's memories. Traumatic memories stored in the hippocampus can activate the amygdala, causing the amygdala, in turn, to activate other brain regions and generate a fear response. This is termed re-experiencing and is a particular feature of posttraumatic stress disorder.

glutamate, and voltage-gated ion channels (Figure 8-15), greatly overlapping with many of the same neurotransmitters and regulators known to modulate the amygdala (Figure 8-14).

BENZODIAZEPINES AS DRUGS FOR ANXIETY

A simplified notion of how benzodiazepines might modulate excessive output from the amygdala during fear responses in anxiety disorders is shown in Figure 8-18. Excessive amygdala activity (shown in Figures 8-8 through Figure 8-12 and in Figure 8-17A) is theoretically reduced by benzodiazepines. These agents enhance phasic inhibition of GABA (γ-aminobutyric acid) by positive allosteric modulation of postsynaptic $GABA_A$ receptors (see Chapter 6 for explanation of positive allosteric modulation by benzodiazepines at $GABA_A$ receptors and Figures 6-20 through 6-23). The anxiolytic actions of benzodiazepines are hypothetically at $GABA_A$ receptors localized within the amygdala, where benzodiazepines hypothetically blunt fear-associated outputs, thereby reducing the symptom of fear (Figure 8-17B). Benzodiazepines interacting at subtypes of $GABA_A$ receptors are discussed in Chapter 6 and illustrated in Figures 6-19 through 6-23. Benzodiazepines also theoretically modulate excessive output from worry loops (Figure 8-18A) by enhancing the actions of inhibitory interneurons in CSTC circuits (Figure 8-18B), thereby reducing the symptom of worry.

ALPHA-2-DELTA LIGANDS AS ANXIOLYTICS

We have discussed voltage-sensitive calcium channels (VSCCs) in Chapter 3 and have illustrated presynaptic N and P/Q subtypes of VSCCs and their role in excitatory neurotransmitter release (see Figures 3-18 and 3-22 through 3-24). Gabapentin and pregabalin, also known as $\alpha_2\delta$ ligands since they bind to the $\alpha_2\delta$ subunit of presynaptic N and P/Q VSCCs, block the release of excitatory neurotransmitters such as glutamate that occurs when neurotransmission is excessive, as postulated in the amygdala to cause fear (Figure 8-17A) and in CSTC circuits to cause worry (Figure 8-18A). Hypothetically, $\alpha_2\delta$ ligands bind to open, overly active VSCCs in the amygdala (Figure 8-17C) to reduce fear, and in CSTC circuits (Figure 8-18C) to reduce worry. The $\alpha_2\delta$ ligands pregabalin and

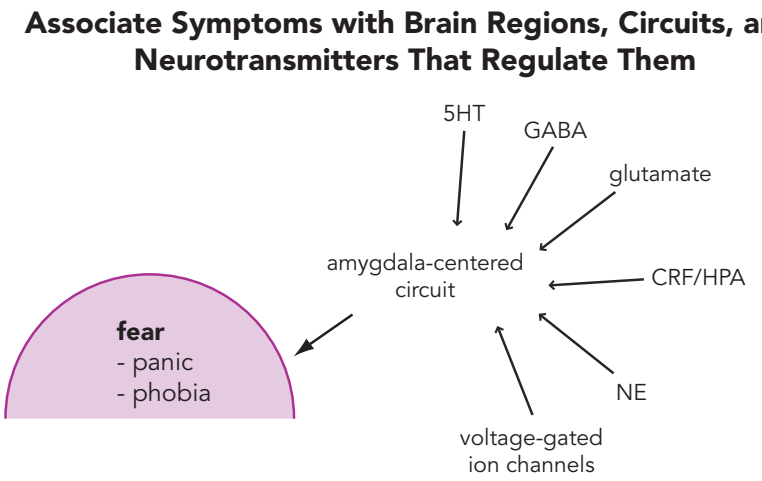


Figure 8-14 Linking anxiety symptoms to circuits to neurotransmitters. Symptoms of anxiety/fear are associated with malfunctioning of amygdala-centered circuits; the neurotransmitters that regulate these circuits include serotonin (5HT), γ-aminobutyric acid (GABA), glutamate, corticotropin releasing factor (CRF), and norepinephrine (NE), among others. In addition, voltage-gated ion channels are involved in neurotransmission within these circuits.

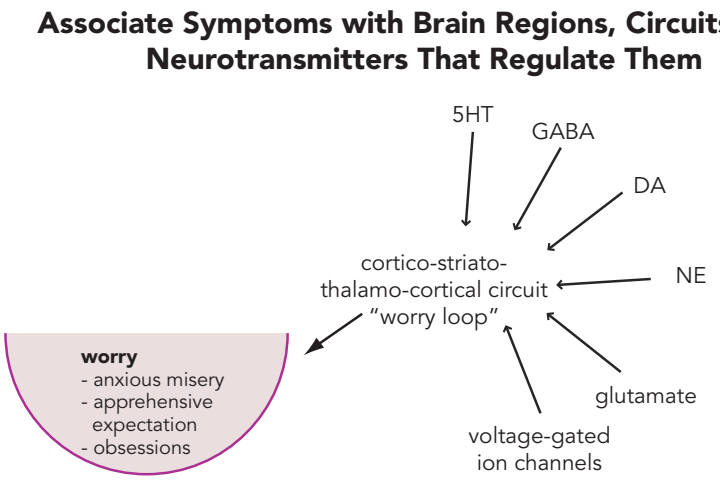


Figure 8-15 Linking worry symptoms to circuits to neurotransmitters. Symptoms of worry, such as anxious misery, apprehensive expectations, catastrophic thinking, and obsessions, are associated with malfunctioning of cortico-striato-thalamo-cortical loops, which are regulated by serotonin (5HT), γ-aminobutyric acid (GABA), dopamine (DA), norepinephrine (NE), glutamate, and voltage-gated ion channels.

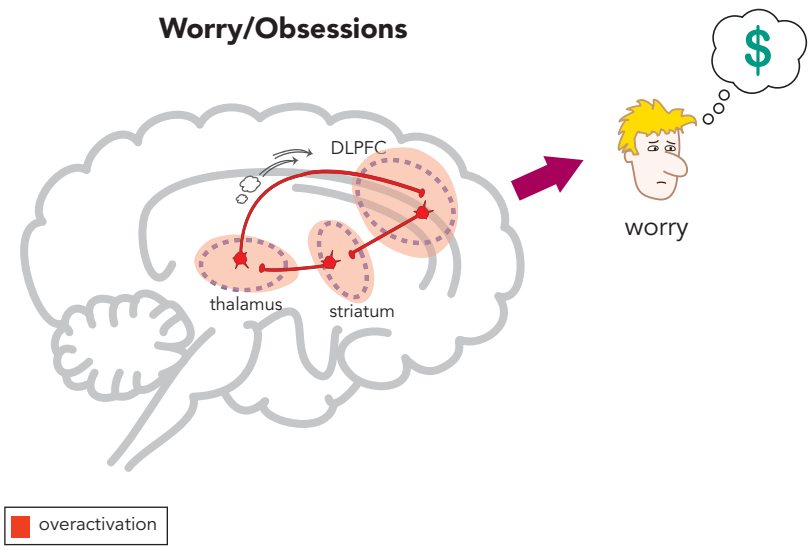


Figure 8-16 Worry/obsessions circuit. Shown here is a cortico-striato-thalamo-cortical loop originating and ending in the dorsolateral prefrontal cortex (DLPFC). Overactivation of this circuit may lead to worry or obsessions.

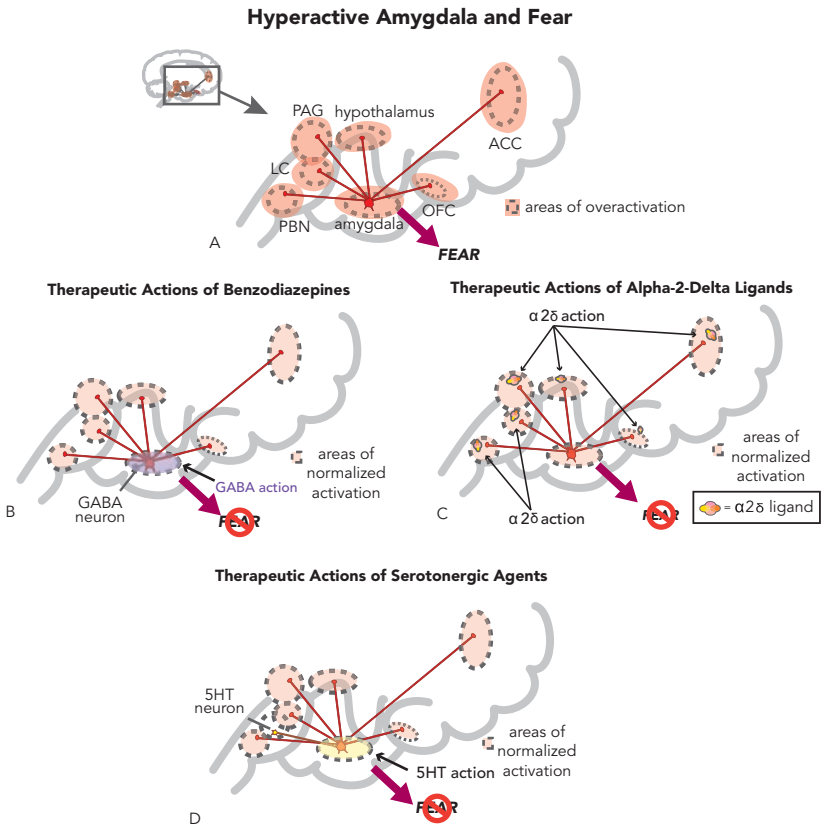


Figure 8-17 Potential therapeutic actions of medications on anxiety/fear. (A) Pathological anxiety/fear may be caused by overactivation of amygdala circuits. (B) GABAergic agents such as benzodiazepines may alleviate anxiety/fear by enhancing phasic inhibitory actions at postsynaptic $GABA_A$ receptors within the amygdala. (C) Agents that bind to the $\alpha_2\delta$ subunit of presynaptic N and P/Q voltage-sensitive calcium channels can block the excessive release of glutamate in the amygdala and thereby reduce the symptoms of anxiety. (D) The amygdala receives input from serotonergic neurons, which can have an inhibitory effect on some of its outputs. Thus, serotonergic agents may alleviate anxiety/fear by enhancing serotonin input to the amygdala.

gabapentin have demonstrated anxiolytic actions in social anxiety disorder and panic disorder, are approved for the treatment of anxiety in some countries, and are also proven to be effective for the treatment of epilepsy and certain pain conditions, including neuropathic pain and fibromyalgia. The actions of $\alpha_2\delta$ ligands on VSCCs are discussed and illustrated in Chapter 9 on pain. Alpha-2-delta ligands clearly have different mechanisms of action compared to selective serotonin reuptake inhibitors (SSRIs) or benzodiazepines, and thus can be useful for patients who do not do well on SSRIs/SNRIs (serotonin–norepinephrine reuptake inhibitors) or benzodiazepines. Also, $\alpha_2\delta$ ligands can be useful to combine with SSRIs/SNRIs or benzodiazepines in patients who are partial responders and are not in remission.

SEROTONIN AND ANXIETY

Since the symptoms, circuits, and neurotransmitters linked to anxiety disorders overlap extensively with those for major depressive disorder (Figure 8-1), it is not surprising that many drugs developed as drugs for depression have proven to be effective treatments for anxiety disorders. Indeed, the leading treatments for anxiety disorders today are increasingly drugs originally developed as drugs for depression. Serotonin is a key neurotransmitter that innervates the amygdala as well as all the elements of CSTC circuits, namely, the prefrontal cortex, striatum, and thalamus, and thus is poised to regulate both the symptoms of fear and worry (serotonin pathways are discussed in Chapters 5 and 6 and illustrated in Figure 6-40). Most of the drugs for depression that can increase serotonin output by blocking the serotonin transporter (SERT) are also effective in reducing symptoms of anxiety and fear in one or another of the anxiety/trauma disorders illustrated in Figures 8-2 through 8-5, namely, generalized anxiety disorder, panic disorder, social anxiety disorder, and PTSD (and also OCD in Figure 13-30). Such agents include the well-known SSRIs (in Chapter 7, with their mechanism of action illustrated in Figures 7-11 through 7-15), as well as the SNRIs (serotonin–norepinephrine reuptake inhibitors; also discussed in Chapter 7, with their mechanism of action illustrated in Figure 7-32 and Figures 7-11 through 7-15).

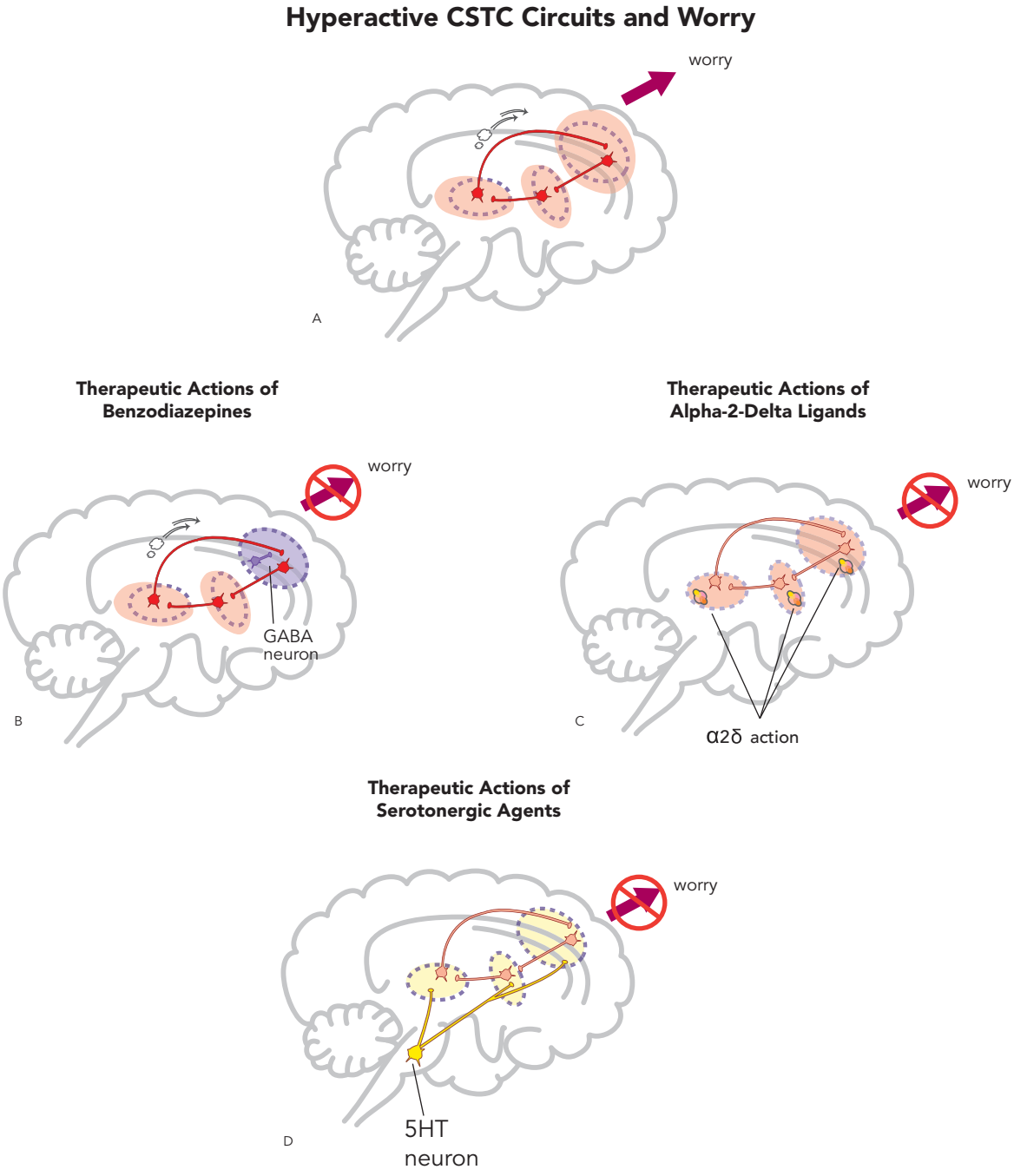


Figure 8-18 **Potential therapeutic actions of medications on worry.** (A) Pathological worry may be caused by overactivation of cortico-striato-thalamo-cortical (CSTC) circuits. (B) GABAergic agents such as benzodiazepines may alleviate worry by enhancing the actions of inhibitory GABA interneurons within the prefrontal cortex. (C) Agents that bind to the $\alpha_2\delta$ subunit of presynaptic N and P/Q voltage-sensitive calcium channels can block the excessive release of glutamate in CSTC circuits and thereby reduce the symptoms of worry. (D) The prefrontal cortex, striatum, and thalamus receive input from serotonergic neurons, which can have an inhibitory effect on output. Thus, serotonergic agents may alleviate worry by enhancing serotonin (5HT) input within CSTC circuits.

A serotonin 1A ($5HT_{1A}$) partial agonist, buspirone, is recognized as a drug for generalized anxiety disorder, but not for treatment of the other anxiety/trauma disorder subtypes. $5HT_{1A}$ partial agonists as augmenting agents to drugs for depressions are mentioned also in Chapter 7, as are drugs for depression that combine $5HT_{1A}$ partial agonism with serotonin reuptake inhibition (i.e., serotonin partial agonist reuptake inhibitors [SPARIs] and vilazodone, see Figures 7-23 through 7-27), which should theoretically have anxiolytic actions as well as antidepressant action. The $5HT_{1A}$ partial agonist properties of numerous drugs for psychosis are also discussed in Chapter 5 and illustrated in Figures 5-22 and 5-23, and the downstream actions of $5HT_{1A}$ receptor stimulation are discussed in Chapter 4 and illustrated in Figure 4-44.

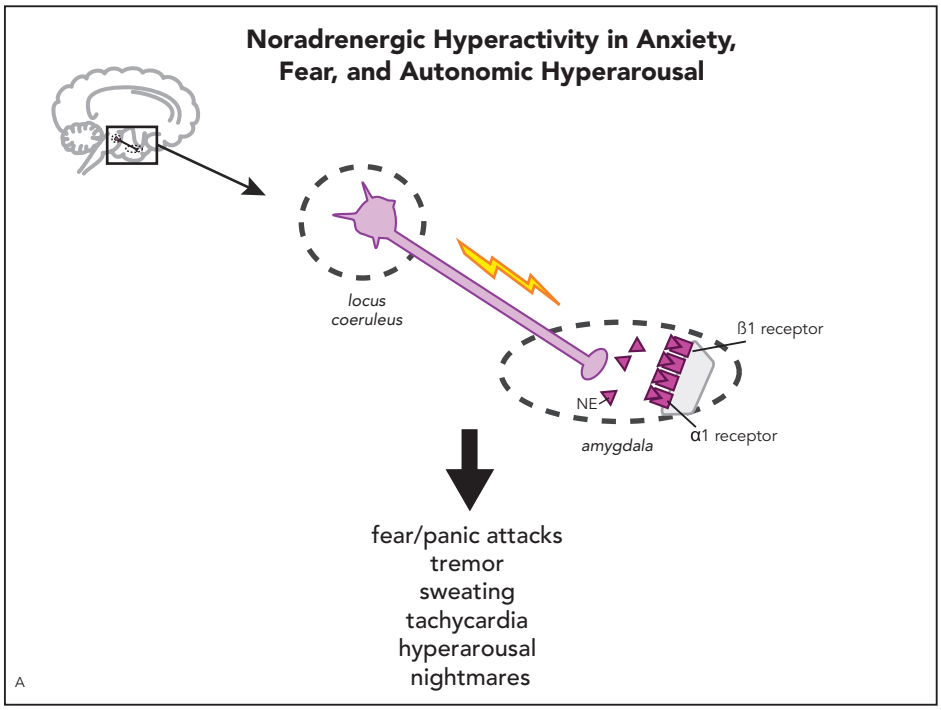
The potential anxiolytic actions of buspirone could theoretically be due to $5HT_{1A}$ partial agonist actions at both presynaptic and postsynaptic $5HT_{1A}$ receptors (Figures 7-23 through 7-27), actions at both sites resulting in enhanced serotonergic activity in projections to the amygdala (Figure 8-17D), prefrontal cortex, striatum, and thalamus (Figure 8-18D), and thus reduce fear and worry, as well as other symptoms of both generalized anxiety disorder and major depression (Figure 8-1). SSRIs and SNRIs theoretically do the same thing (Figures 8-17D and 8-18D). Since the onset of anxiolytic action for buspirone is delayed, just as it is for drugs for depressions, this has led to the belief that $5HT_{1A}$ agonists exert their therapeutic effects by virtue of adaptive neuronal events and receptor events (Figures 7-10 through 7-15 and Figures 7-23 through 7-27), rather than simply by the acute occupancy of $5HT_{1A}$ receptors. In this way, the presumed mechanism of action of $5HT_{1A}$ partial agonists is analogous to the use of various drugs for depression, including SSRIs and SNRIs. These actions are quite different in timing from the use of benzodiazepines for anxiety – since benzodiazepines act acutely by occupancy of benzodiazepine receptors and not with a delay due to adaptation of the receptors.

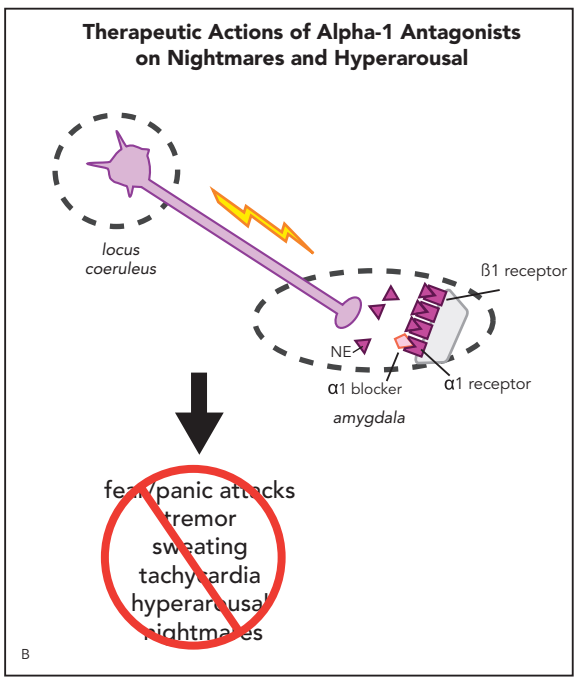
NORADRENERGIC HYPERACTIVITY IN ANXIETY

Norepinephrine is another neurotransmitter with important regulatory input to the amygdala (Figure 8-19A) and to the prefrontal cortex and thalamus in CSTC circuits (Figure 8-20A). Excessive noradrenergic output from the locus coeruleus can result not only in numerous peripheral manifestations of autonomic overdrive, as discussed above and as illustrated in Figures 8-8 through 8-12, but also can trigger numerous central symptoms of anxiety and fear, such as nightmares, hyperarousal states, flashbacks, and panic attacks (Figure 8-19A). Excessive noradrenergic activity can also reduce the efficiency of information processing in the prefrontal cortex and thus in CSTC circuits, and theoretically cause worry (Figure 8-20A). Hypothetically, these symptoms may be mediated in part by excessive noradrenergic input onto α_1- and β_1-adrenergic postsynaptic receptors in the amygdala (Figure 8-19A) or prefrontal cortex (Figure 8-20A). Symptoms of hyperarousal like nightmares can be reduced in some patients with α_1-adrenergic blockers such as prazocin (Figure 8-19B), and symptoms of fear (Figure 8-19C) and worry (Figure 8-20B) can be reduced by norepinephrine reuptake inhibitors (also called norepinephrine transporter [NET] inhibitors). The clinical effects of NET inhibitors can be confusing because symptoms of anxiety can actually be made transiently worse immediately following initiation of an SNRI or selective NET inhibitor, when noradrenergic activity is initially increased but the postsynaptic receptors have not yet adapted. However, these same NET inhibitory actions, if sustained over time, will downregulate and desensitize postsynaptic norepinephrine receptors such as β_1 receptors, and hypothetically lead to the delayed reduction in symptoms of fear and worry long term (Figure 8-20B).

FEAR CONDITIONING VERSUS FEAR EXTINCTION

Fear conditioning is a concept as old as Pavlov's dogs. If an aversive stimulus such as footshock is coupled with a neutral stimulus such as a bell, the animal learns to associate the two, and will develop fear when it hears a bell. In humans, fear can be "learned" during stressful experiences associated with emotional trauma, and is influenced by an individual's genetic predisposition as well as by an individual's prior exposure to environmental stressors that can cause stress sensitization of brain circuits (e.g., child abuse; see Chapter 6 and Figures 6-28 and 6-33). Often, fearful situations are managed successfully and then forgotten. Some fears are crucial for survival, such as appropriately fearing dangerous situations, and thus the mechanism of learned fear, called fear conditioning, has been extremely well conserved across species, including humans. However, other fears that are "learned" and, if not "forgotten," may hypothetically progress to anxiety disorders or a major depressive episode. This is a big problem since almost





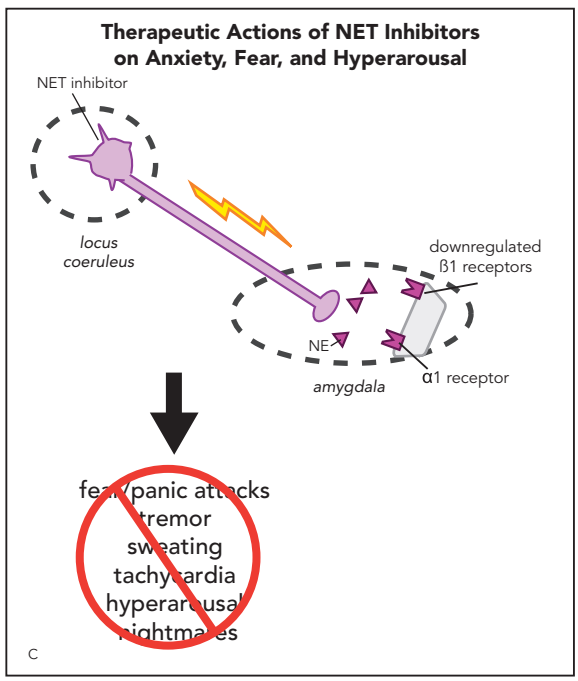


Figure 8-19 **Noradrenergic hyperactivity in anxiety/fear.** (A) Norepinephrine provides input not only to the amygdala but also to many regions to which the amygdala projects; thus it plays an important role in the fear response. Noradrenergic hyperactivation can lead to anxiety, panic attacks, tremors, sweating, tachycardia, hyperarousal, and nightmares. Alpha-1 and β_1-adrenergic receptors may be specifically involved in these reactions. (B) Noradrenergic hyperactivity may be blocked by the administration of α_1-adrenergic antagonists, which can lead to the alleviation of anxiety and other stress-related symptoms. (C) Noradrenergic hyperactivity may also be blocked by the administration of a norepinephrine transporter (NET) inhibitor, which can have the downstream effect of downregulating β_1-adrenergic receptors. Reduced stimulation via β_1-adrenergic receptors could therefore lead to the alleviation of anxiety and stress-related symptoms.

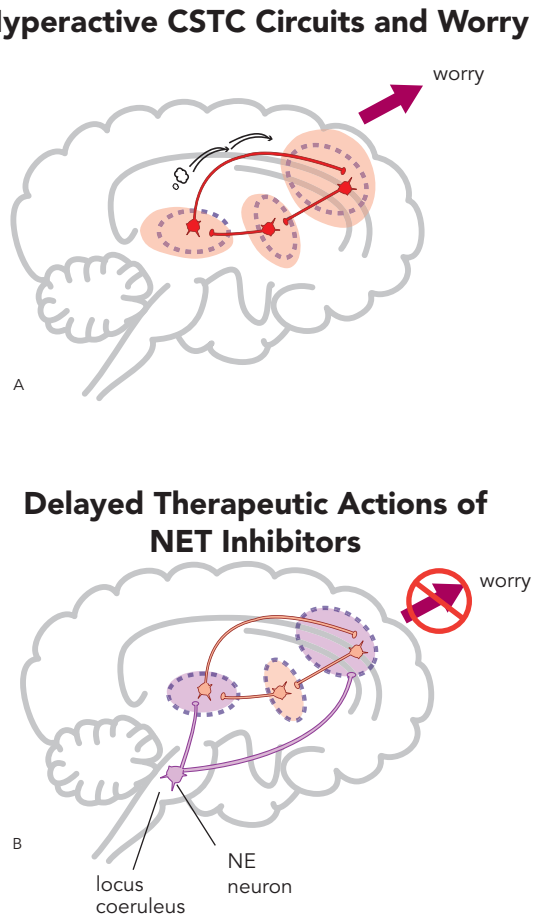


Figure 8-20 **Noradrenergic hyperactivity in worry.** (A) Pathological worry may be caused by overactivation of cortico-striato-thalamo-cortical (CSTC) circuits. Specifically, excessive noradrenergic activity within these circuits can reduce the efficiency of information processing and theoretically cause worry. (B) Noradrenergic hyperactivity in CSTC circuits may be blocked by the administration of a norepinephrine transporter (NET) inhibitor, which can have the downstream effect of downregulating β_1-adrenergic receptors. Reduced stimulation via β_1-adrenergic receptors could therefore lead to the alleviation of worry.

30% of the population will develop an anxiety disorder, due in large part to stressful environments, including exposure to fearful events during normal activities in twenty-first-century society, but in particular during early life, if experiencing abuse or adversity as a child, and during war and natural disasters, and abusive relationships, as an adult.

Repetition of a sensory experience associated with an earlier exposure to a fearful event, such as hearing or seeing an explosion, smelling burning rubber, seeing a picture of a wounded civilian, seeing or hearing flood waters, can trigger traumatic re-experiencing and generalized hyperarousal and fear in emotionally traumatized patients with PTSD. Panic associated with social situations will "teach" the patient to panic in social situations in social anxiety disorder. Panic randomly associated with an attack that happens to occur in a crowd, on a bridge, or in shopping centers will also trigger another panic attack when the same environment is encountered in panic disorder. These and other symptoms of anxiety disorders are all forms of learning known as fear conditioning (Figure 8-21).

The amygdala is theoretically involved in "remembering" the various stimuli associated with a given fearful situation. Hypothetically, the amygdala does this by increasing the efficiency of neurotransmission at glutamatergic synapses in the lateral amygdala as sensory input about those stimuli comes in from the thalamus or sensory cortex (Figure 8-21). This input is then relayed to the central amygdala, where fear conditioning also improves the efficiency of neurotransmission at another glutamate synapse there (Figure 8-21). Both synapses are hypothetically restructured and potentially permanent learning is embedded into this circuit by NMDA receptors, triggering long-term potentiation and synaptic plasticity so that subsequent input from the sensory cortex and thalamus is very efficiently processed to trigger the same fear response caused by the original experience, since output occurs from the central amygdala every time there is the re-experiencing of the same sensory input associated with the original fearful event (Figure 8-21; see also Figures 8-8 through 8-13).

Input to the lateral amygdala is modulated by the prefrontal cortex, especially the ventromedial prefrontal cortex (VMPFC), and by the hippocampus. If the VMPFC is unable to suppress the fear response before it arrives at the level of the amygdala, fear conditioning is thought to proceed. The hippocampus hypothetically "remembers" the context of the fear conditioning, and makes sure fear is triggered when the fearful stimulus and all its associated stimuli are encountered again. Most contemporary psychopharmacological treatments for anxiety and fear act by suppressing the fear output from the amygdala (see Figure 8-17) and therefore are not cures since the fundamental neuronal learning underlying fear conditioning in these patients remains in place. On the other hand, psychotherapeutic approaches perhaps enhanced by drugs targeting the "unlearning"

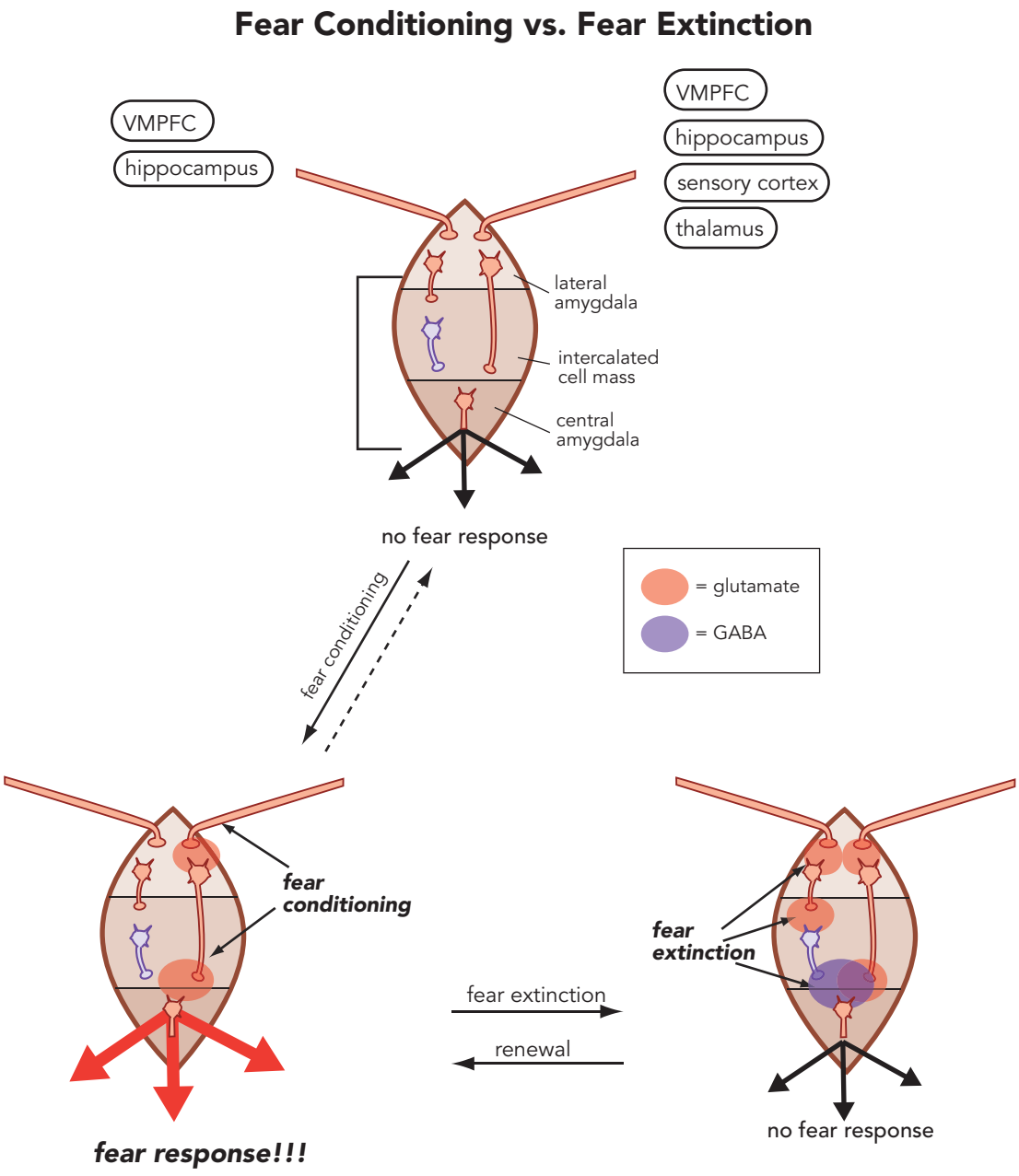


Figure 8-21 **Fear conditioning versus fear extinction.** When an individual encounters a stressful or fearful experience, the sensory input is relayed to the amygdala, where it is integrated with input from the ventromedial prefrontal cortex (VMPFC) and hippocampus, so that a fear response can be either generated or suppressed. The amygdala may "remember" stimuli associated with that experience by increasing the efficiency of glutamate neurotransmission, so that on future exposure to stimuli, a fear response is more efficiently triggered. If this is not countered by input from the VMPFC to suppress the fear response, fear conditioning proceeds. Fear conditioning is not readily reversed, but it can be inhibited through new learning. This new learning is termed fear extinction and is the progressive reduction of the response to a feared stimulus that is repeatedly presented without adverse consequences. Thus the VMPFC and hippocampus learn a new context for the feared stimulus and send input to the amygdala to suppress the fear response. The "memory" of the conditioned fear is still present, however.

of fear conditioning provide hope for a more long-lasting solution to symptoms of anxiety.

Novel Approaches to the Treatment of Anxiety Disorders

Once fear conditioning is in place, it can be very difficult to reverse. Nevertheless, there may be two ways to neutralize fear conditioning: either by facilitating a process called extinction or by blocking a process called reconsolidation. Research on extinction and reconsolidation are leading the way in order to find novel, more robust, and more long-lasting treatments for anxiety symptoms, especially in patients who do not respond to standard treatment with serotonergic, benzodiazepine, and $\alpha_2\delta$ drug therapies or to standard psychotherapies such as exposure treatment or cognitive behavioral therapy. Preventing or minimizing "stress" – especially early life adversity in young children, and chronic stress and catastrophic stress in adults – is also under investigation but difficult to implement.

Fear Extinction

Fear extinction is the progressive reduction of the response to a feared stimulus, and occurs when the stimulus is repeatedly presented without any adverse consequence. When fear extinction occurs, it appears that the original fear conditioning is not really "forgotten" even though the fear response can be profoundly reduced over time by the active process of fear extinction. Rather than reversing the synaptic changes described above for fear conditioning, leading theories propose that a new form of learning with additional synaptic changes in the amygdala occurs during fear extinction. These changes hypothetically suppress symptoms of anxiety and fear by inhibiting the original learning but not by removing it (Figure 8-21). Specifically, if activation of the amygdala by the VMPFC occurs again and again without any fear being triggered, such as during exposure therapy, the hippocampus hypothetically begins to "remember" this new context in which the feared stimulus did not have any adverse consequences and fear is no longer activated (Figure 8-21). Over time, the original stimulus no longer activates fear due to this process of progressive desensitization called fear extinction. Such fear extinction hypothetically occurs when inputs from the VMPFC and hippocampus now "learn" to activate glutamatergic neurons in the lateral amygdala that synapse upon inhibitory GABAergic interneurons, located within the intercalated cell mass of the amygdala (Figure 8-21). According to this theory, such an action sets up a gate within the central amygdala, with fear output occurring if the fear-conditioning circuit predominates, and no fear output occurring if the fear-extinction circuit predominates.

Modern research thus suggests that fear extinction theoretically predominates over fear conditioning when synaptic strengthening and long-term potentiation in the new circuit are able to produce an inhibitory GABAergic drive that can overcome the excitatory glutamatergic drive produced by the pre-existing fear-conditioning circuitry (Figure 8-21). When fear extinction exists simultaneously with fear conditioning, memory for both are present, but the output hypothetically depends upon which system is "stronger" and "better-remembered," and which has the most robust synaptic efficiency. These factors will hypothetically determine which gate will open, the one with the fear response or the one that keeps the fear response in check. Unfortunately, over time, fear conditioning in experimental models and in clinical practice may have the upper hand over fear extinction. Fear extinction appears to be more labile than fear conditioning, and tends to reverse over time. Also, fear conditioning can return if the old fear is presented in a context different from the one "learned" to suppress the fear during fear extinction, a process termed "renewal."

Therapeutic Facilitation of Fear Extinction

A novel treatment approach to reducing anxiety symptoms is to facilitate fear extinction with a combination of psychotherapy and drugs directed at facilitating synapse formation. This approach contrasts with how current effective anxiolytic drugs act, namely by pharmacologically suppressing the fear response (Figures 8-17 through 8-20). Among currently effective psychotherapies for anxiety used in clinical practice today, cognitive behavioral therapies that employ exposure techniques and that require the patient to confront the fear-inducing stimuli in a safe environment may come closest to facilitating fear extinction, hypothetically because when these therapies are effective, they are able to trigger the learning of fear extinction in the amygdala (Figure 8-21). Unfortunately, because the hippocampus "remembers" the context of this extinction, such therapies are often context-specific and do not always generalize once the patient is outside the safe therapeutic environment of a therapist's office, and thus fear and worry may be "renewed" in the real world. Current psychotherapy research is investigating how contextual cues can be used to strengthen extinction

learning so that the therapeutic learning generalizes to other environments. Current psychopharmacology research is investigating how specific drugs might also strengthen extinction learning by pharmacologically strengthening the synapses on the fear-extinction side of the amygdala gate disproportionately to the synapses on the fear-conditioned side of the amygdala gate. How could this be done?

Based on successful animal experiments of extinction learning, one idea shown in Figure 8-22 is to pharmacologically boost *N*-methyl-D-aspartate (NMDA) receptor activation at the very time when a patient receives systematic exposure to feared stimuli during cognitive behavioral therapy sessions. The idea is that as psychotherapy progresses, learning occurs, because glutamate release is provoked in the lateral amygdala and in the intercalated cell mass at inhibitory GABA neurons by the psychotherapy. If NMDA receptors at these two glutamate synapses could be pharmacologically boosted to trigger disproportionately robust long-term potentiation and synaptic plasticity, timed to occur at the exact time this learning and therapy is taking place and thus exactly when these synapses are selectively activated, it could theoretically result in the predominance of the extinction pathway over the conditioned pathway. Animal studies support this possibility and early clinical studies are encouraging but not always robust or consistent, to date. In the meantime, prudent psychopharmacologists are increasingly leveraging their current anxiolytic drug portfolio with concomitant psychotherapy, since many patients already receive enhanced therapeutic benefit from this combination.

Blocking Fear Conditioning and Fear Memories

Blocking either *consolidation* or *reconsolidation* of fear memories is another approach to developing novel treatments for anxiety symptoms. When fear is first conditioned, that memory is said to be "consolidated" via a molecular process that some have thought was essentially permanent. Hints at the mechanism of the initial consolidation of fear conditioning come from observations that both β blockers and opioids can potentially mitigate the conditioning of the original traumatic memory, even in humans, and some studies show that these agents can potentially reduce the chances of getting PTSD after a traumatic injury (Figure 8-23). This therapeutic approach is to treat the acutely exposed patient immediately after a traumatic experience in order to block the initial fear from ever becoming conditioned or consolidated.

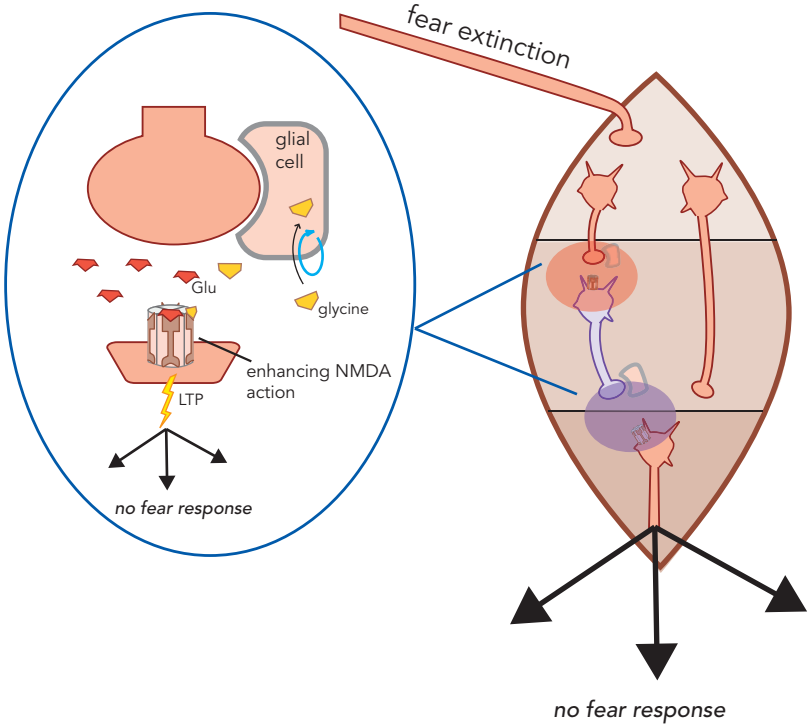


Figure 8-22 Facilitating fear extinction with NMDA receptor activation. Strengthening of synapses involved in fear extinction could help enhance the development of fear-extinction learning in the amygdala and reduce symptoms of anxiety disorders. Administration of an agent that enhances *N*-methyl-D-aspartate (NMDA) action while an individual is receiving exposure therapy could increase the efficiency of glutamate (Glu) neurotransmission at synapses involved in fear extinction. If this leads to long-term potentiation (LTP) and synaptic plasticity while the synapses are activated by exposure therapy, it could result in structural changes in the amygdala associated with the fear-extinction pathway and thus the predominance of the extinction pathway over the conditioned pathway.

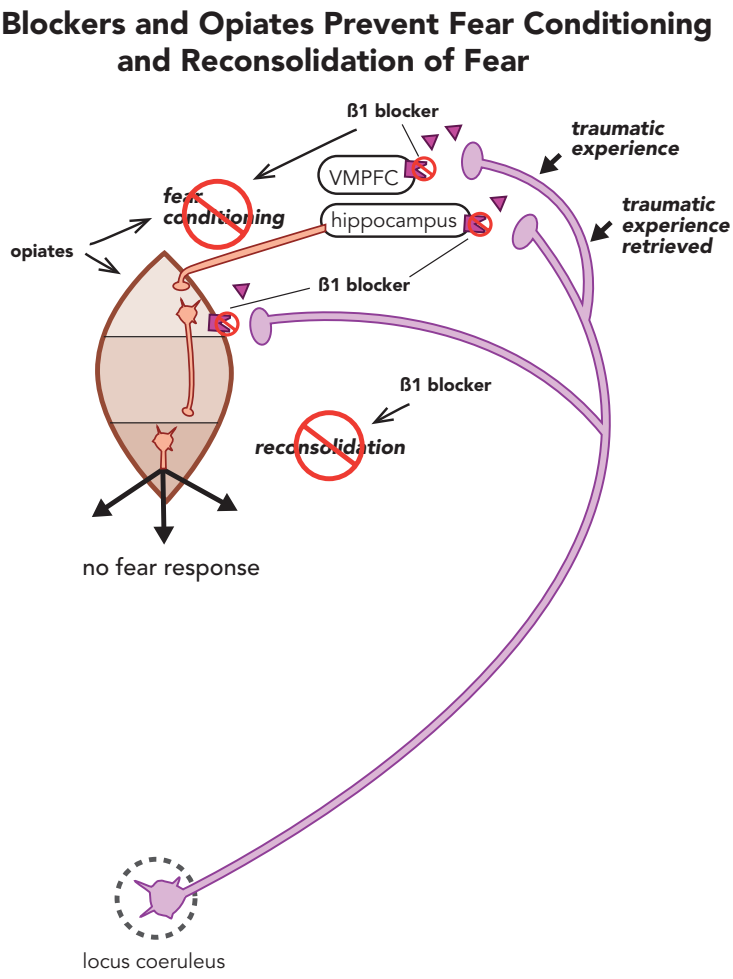


Figure 8-23 Blocking fear conditioning and reconsolidation. When fear is first conditioned, the memory is said to be "consolidated" via a molecular process that once was thought to be permanent. However, there is some research to suggest that administration of either β-adrenergic blockers or opiates can potentially mitigate the conditioning of the original traumatic memory. Furthermore, research also now shows that even when emotional memories have been consolidated as fear conditioning, they can change when they are retrieved. Reconsolidation is the state in which reactivation of a consolidated fear memory makes it labile. This requires protein synthesis to keep the memory intact and, like fear conditioning, may also be disrupted by β blockers.

Although, classically, emotional memories that have already been "fear conditioned" were thought to last forever, recent animal experiments show that emotional memories can in fact be weakened or even erased at the time they are re-experienced. Current theories now suggest that at the time emotional memories are re-experienced, they are in a labile state capable of being modified, and then, once the re-experiencing of the emotion and any modification of it is complete, the memory is restored or "reconsolidated" with those modifications. Reconsolidation is the state in which reactivation of a consolidated fear memory makes it labile, and requires protein synthesis to keep the memory intact.

If emotional memories consolidated as fear conditioning are not permanent, as animal experiments suggest, and can change when they are retrieved, the idea is to use both psychotherapeutic and psychopharmacological approaches to block reconsolidation of the fear memory. Blocking reconsolidation would hypothetically allow the patient to "forget" their emotional memory.

Early studies of β blockers suggest that they may also disrupt reconsolidation of fear memories as well as formation of fear conditioning (Figure 8-23). More recently, hallucinogens, dissociatives, and entactogens such as psilocybin, MDMA (3,4-methylenedioxymethamphetamine), and ketamine have been employed in an attempt to block reconsolidation of activated memories during psychotherapy sessions. These are discussed in more detail in Chapter 13 on substance abuse; psilocybin and MDMA are discussed

briefly in Chapter 7 and illustrated in Figures 7-87 and 7-88. Ketamine is more extensively discussed in Chapter 7 as well. Future research is trying to determine how to use psychotherapy to provoke emotional memories and reactivate them by producing a state where a pharmacological agent such as a hallucinogen producing a dissociative state, including ketamine as well as psilocybin or MDMA, could be administered to disrupt reconsolidation of these emotional memories and thereby relieve symptoms of anxiety, trauma, re-experiencing and other emotional memories of PTSD and anxiety disorders, and existential distress in terminally ill patients. These are early days in terms of applying this concept in clinical settings, but this notion supports the growing idea that psychotherapy and psychopharmacology can be synergistic. Much more needs to be learned as to how to exploit this theoretical synergy.

TREATMENTS FOR ANXIETY DISORDER SUBTYPES

Generalized Anxiety Disorder

Psychopharmacological treatments for generalized anxiety disorder overlap greatly with those for other anxiety disorders and depression and include SSRIs, SNRIs, benzodiazepines, buspirone, and $\alpha_2\delta$ ligands such as pregabalin and gabapentin. While benzodiazepines should not be prescribed to a patient with generalized anxiety disorder who is abusing other substances, particularly alcohol, benzodiazepines can be useful in patients who are not substance abusers for short terms when initiating an SSRI or SNRI, since these serotonergic agents are often activating, difficult to tolerate early in dosing, and have a delayed onset of action. In other patients, benzodiazepines can be useful to "top up" an SSRI or SNRI for patients who have experienced only partial relief of symptoms and have stabilized on SSRI/SNRI therapy. Benzodiazepines can also be useful for occasional intermittent use when symptoms surge and sudden relief is needed. Alpha-2-delta ligands are a good alternative to benzodiazepines in some patients. These ligands are approved for the treatment of anxiety in Europe and other countries but not in the US, yet can be useful "off-label" as augmenting agents.

Other "off-label" treatments for anxiety can include mirtazapine, trazodone, vilazodone, tricyclic antidepressants, or even sedating antihistamines such as hydroxyzine.

Panic Disorder

Panic attacks occur in many conditions, not just panic disorder, and panic disorder is frequently comorbid with the other anxiety disorders and with major depression. It is thus not surprising that contemporary treatments for panic disorder overlap significantly with those for the other anxiety disorders and with those for major depression. Treatments include SSRIs and SNRIs, as well as benzodiazepines, and $\alpha_2\delta$ ligands. "Off-label" treatments of panic attacks in anxiety disorders can also include mirtazapine and trazodone. The monoamine oxidase inhibitors (MAOIs), discussed in Chapter 7, are much neglected in psychopharmacology in general and for the treatment of treatment-resistant panic disorder in particular. However, MAOIs can have powerful efficacy in panic and should be considered when other agents fail. Cognitive behavioral psychotherapy is both an alternative or an augmentation to psychopharmacological approaches, and can help modify cognitive distortions, and, through exposure, diminish phobic avoidance behaviors.

Social Anxiety Disorder

The treatment options for this anxiety disorder are very similar to those for panic disorder with a few noteworthy differences. The SSRIs and SNRIs and $\alpha_2\delta$ ligands are certainly useful treatments, but the utility of benzodiazepine is not as widely accepted as it might be for generalized anxiety disorder and panic disorder. There is also less evidence for the utility of older drugs for depression for use in social anxiety disorder. Beta blockers, sometimes with benzodiazepines, can be useful for some patients with very discrete types of social anxiety, such as performance anxiety. One drug that is (unfortunately) quite effective but obviously should not be used is alcohol for the treatment of social anxiety symptoms. Many patients of course are aware of this and abuse alcohol before they seek safer and more effective treatment. Cognitive behavioral psychotherapy can be a powerful intervention, sometimes better than drugs for certain patients, and often helpful in combination with drugs.

PTSD

Although some treatments such as certain SSRIs are approved for PTSD, psychopharmacological treatments for PTSD are not as effective as these same treatments are in anxiety disorders. Also, PTSD is so highly comorbid that many of the psychopharmacological treatments are more effectively aimed at comorbidities such as

depression, insomnia, substance abuse, and pain, than at core symptoms of PTSD. SSRIs often leave the patient with residual symptoms, including sleep problems. Thus, most patients with PTSD do not take monotherapy. Benzodiazepines are to be used with caution, not only because of limited evidence from clinical trials for efficacy in PTSD, but also because many PTSD patients abuse alcohol and other substances. A unique treatment for PTSD is the administration of α_1 antagonists at night to prevent nightmares. Much more effective medication treatments for PTSD are greatly needed. Much of the advance in treatment of PTSD has been in using drugs to treat comorbidities and psychotherapies to treat core symptoms. Exposure therapy is perhaps most effective among psychotherapies, but many forms of cognitive behavioral therapy are being investigated and used in clinical practice, depending upon the training of the therapist and the specific needs of the individual. Use of techniques to block reconsolidation of emotional memories with the combination of psychotherapy and drugs (especially MDMA) are in testing now for PTSD. Brexpiprazole, discussed in Chapter 5 as a drug for psychosis, is in testing along with the SSRI sertraline for PTSD, with promising initial findings.

SUMMARY

Anxiety/trauma disorders have core features of fear and worry that cut across the entire spectrum of anxiety disorder subtypes, from generalized anxiety disorder to panic disorder, social anxiety disorder, and posttraumatic stress disorder. The amygdala hypothetically plays a central role in the fear response in these conditions, and cortico-striato-thalamo-cortical (CSTC) circuits are thought to play a key role in mediating the symptom of worry. Numerous neurotransmitters are involved in regulating the circuits that underlie the anxiety disorders. Serotonin, norepinephrine, $\alpha_2\delta$ ligands and GABA are all key modulators of the hypothetical fear and worry circuits. Known effective drug treatments all target these neurotransmitters. The concept of opposing actions of fear conditioning versus fear extinction within amygdala circuits hypothetically is linked to the production and maintenance of symptoms in anxiety disorder and provides a substrate for potential novel therapeutics combining psychotherapy and drugs. The concept of disruption of the reconsolidation of fear memories is undergoing testing at this time as a novel therapeutic approach to anxiety symptoms.

9 Chronic Pain and Its Treatment

What is Pain? 379
"Normal" Pain and the Activation of Nociceptive Nerve Fibers 381
Nociceptive Pathway to the Spinal Cord 381
Nociceptive Pathway from the Spinal Cord to the Brain 382
Neuropathic Pain 382
Peripheral Mechanisms in Neuropathic Pain 382
Central Mechanisms in Neuropathic Pain 382
The Spectrum of Mood and Anxiety Disorders with Pain Disorders 387
Fibromyalgia 387
Decreased Gray Matter in Chronic Pain Syndromes? 387
Descending Spinal Synapses in the Dorsal Horn and the Treatment of Chronic Pain 390
Targeting Sensitized Circuits in Chronic Pain Conditions 395
Targeting Ancillary Symptoms in Fibromyalgia 399
Summary 400

This chapter will provide a brief overview of chronic pain conditions associated with different psychiatric disorders and treated with psychotropic drugs. Included here are discussions of the symptomatic and pathophysiological overlap between disorders with pain and many other disorders treated in psychopharmacology, especially depression and anxiety. Clinical descriptions and formal criteria for how to diagnose painful conditions are only mentioned here in passing. The reader should consult standard reference sources for this material. The discussion here will emphasize how discoveries about the functioning of various brain circuits and neurotransmitters – especially those acting upon the central processing of pain – have impacted our understanding of the pathophysiology and treatment of many painful conditions that may occur with or without various psychiatric disorders. The goal of this chapter is to acquaint the reader with ideas about the clinical and biological aspects of the symptom of pain, how it can hypothetically be caused by alterations of pain processing within the central nervous system, how it can be associated with many of the symptoms of depression and anxiety, and finally, how it can be treated with several of the same agents that can treat depression and anxiety. The discussion in this chapter is at the conceptual level, and not at the pragmatic level. The reader should consult standard drug handbooks (such as *Stahl's Essential Psychopharmacology: the Prescriber's Guide*) for details of doses, side effects, drug interactions, and other issues relevant to the prescribing of these drugs in clinical practice.

WHAT IS PAIN?

No experience rivals pain for its ability to capture our attention, focus our actions, and cause suffering (see Table 9-1 for some useful definitions regarding pain). The powerful experience of pain, especially acute pain, can serve a vital function – to make us aware of damage to our bodies, and to rest the injured part until it has healed. When acute pain is *peripheral* in origin (i.e., originating outside of the central nervous system) but continues as chronic pain, it can cause changes in central nervous system pain mechanisms that enhance or perpetuate the original peripheral pain. For example, osteoarthritis, low back pain, and diabetic peripheral neuropathic pain all begin as peripheral pain, but over time these conditions can trigger central pain mechanisms that amplify peripheral pain and generate additional pain centrally. This may explain why research has recently shown that chronic pain conditions of peripheral origin can be successfully targeted for relief by psychotropic drugs that work on central pain mechanisms.

Many other chronic pain conditions may start *centrally* and never have a peripheral causation to the pain, especially conditions associated with multiple unexplained painful physical symptoms such as depression, anxiety, and fibromyalgia. Because these centrally mediated pain conditions are associated with emotional symptoms, that type of pain has until recently often not been considered "real" but rather a nonspecific outcome of unresolved psychological

Table 9-1 Pain: some useful definitions

Pain	An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage
Acute pain	Pain that is of short duration and resolves; usually directly related to the resolution or healing of tissue damage
Chronic pain	Pain that persists for longer than would be expected; an artificial threshold for chronicity (e.g., 1 month) is not appropriate
Neuropathic pain	Pain that arises from damage to, or dysfunction of, any part of the peripheral or central nervous system
Nociception	The process by which noxious stimuli produce activity in the sensory pathways that convey "painful" information
Allodynia	Pain caused by a stimulus that does not normally provoke pain
Hyperalgesia	An increased response to a stimulus that is not normally painful
Analgesia	Any process that reduces the sensation of pain, while not affecting normal touch
Local anesthesia	Blockade of all sensation (innocuous and painful) from a local area
Noxious stimulus	Stimulus that inflicts damage, or would potentially inflict damage, on tissues of the body
Primary afferent neuron (PAN)	The first neuron in the somatosensory pathway; detects mechanical, thermal, or chemical stimuli at its peripheral terminals and transmits action potentials to its central terminals in the spinal cord; all PANs have a cell body in the dorsal root ganglion
Nociceptor	A primary afferent (sensory) neuron that is only activated by a noxious stimulus
Nociception	The process by which a nociceptor detects a noxious stimulus and generates a signal (action potentials) that is propagated towards higher centers in the nociceptive pathway
Dorsal root ganglion (DRG)	Contains the cell bodies of PANs; proteins, including transmitters, receptors, and structural proteins, are synthesized here and transported to peripheral and central terminals
Interneuron	Neuron with its cell body, axon, and dendrites within the spinal cord; can be excitatory (e.g., containing glutamate) or inhibitory (e.g., containing GABA)
Projection neurons	Neuron in the dorsal horn that receives input from PANs and/or interneurons, and projects up the spinal cord to higher processing centers
Spinothalamic tract	Tract of neurons that project from the spinal cord to the thalmus
Spinobulbar tracts	Several different tracts of neurons that project from the spinal cord to brainstem nuclei
Somatosensory cortex	Region of the cerebral cortex that receives input mainly from cutaneous sensory nerves; the cortex is topographically arranged, with adjacent areas receiving input from adjacent body areas; stimulation of the somatosensory cortex creates sensations from the body part that projects to it

conflicts that would improve when the associated psychiatric condition improved, and therefore that this type of pain did not need to be targeted specifically for treatment. Today, however, many painful conditions without identifiable peripheral lesions that were once linked only to psychiatric disorders are now hypothesized to be forms of chronic neuropathic pain syndromes and can be treated with the same agents that successfully treat neuropathic pain syndromes that are not associated with psychiatric disorders. These treatments include the SNRIs (serotonin–norepinephrine reuptake inhibitors, discussed in Chapter 7 on treatment for mood disorders [Figures 7-28 through 7-33]) and the $\alpha_2\delta$ ligands (anticonvulsants that block voltage-gated calcium channels or VSCCs, discussed in Chapter 8 on anxiety disorders [Figures 8-17 and 8-18]). Additional psychotropic agents acting centrally at various other sites are also used to treat a variety of chronic pain conditions and will be mentioned below. Many additional drugs are being tested as potential novel pain treatments as well.

Since pain is clearly associated with some psychiatric disorders, and psychotropic drugs that treat various psychiatric conditions are also effective for a wide variety of pain conditions, the detection, quantification, and treatment of pain are rapidly becoming standardized parts of a psychiatric evaluation. Modern psychopharmacologists increasingly consider pain to be a psychiatric "vital sign," thus requiring routine evaluation and symptomatic treatment. In fact, elimination of pain is increasingly recognized as necessary in order to have full symptomatic remission not only of chronic pain conditions, but also of many psychiatric disorders.

"Normal" Pain and the Activation of Nociceptive Nerve Fibers

The nociceptive pain pathway is the series of neurons that begins with detection of a noxious stimulus and ends with the subjective perception of pain. This so-called "nociceptive pathway" starts from the periphery, enters the spinal cord, and projects to the brain (Figure 9-1). It is important to understand the processes by which incoming information can be modulated to increase or decrease the perception of pain associated with a given stimulus because these processes can explain not only why maladaptive pain states arise but also why drugs that work in psychiatric conditions such as depression and anxiety can also be effective in reducing pain.

Nociceptive Pathway to the Spinal Cord

Primary afferent neurons detect sensory inputs including pain (Figure 9-1). They have their cell bodies in the dorsal root ganglion located along the spinal column outside the central nervous system and thus are considered peripheral and not central neurons (Figure 9-1). Nociception begins with transduction – the process by which specialized membrane proteins located on the peripheral projections of these neurons detect a stimulus and generate a voltage change at their peripheral neuronal membranes. A sufficiently strong stimulus will lower the voltage at the membrane (i.e., depolarize the membrane) enough to activate voltage-sensitive sodium channels (VSSCs) and trigger an action potential that will be propagated along the length of the axon to the central terminals of the neuron in the spinal cord (Figure 9-1). VSSCs are introduced in Chapter 3 and illustrated in Figures 3-19 and 3-20. Nociceptive impulse flow from primary afferent neurons into the central nervous system can be reduced or stopped when VSSCs are blocked by peripherally administered local anesthetics such as lidocaine.

The specific response characteristics of primary afferent neurons are determined by the specific receptors and channels expressed by that neuron in the periphery (Figure 9-1). For example, primary afferent neurons that express a stretch-activated ion channel are mechanosensitive; those that express the vanillinoid receptor 1 (VR1) ion channel are activated by capsaicin, the pungent ingredient in chili peppers, and also by noxious heat, leading to the burning sensation that both these stimuli evoke. These functional response properties are used to classify primary afferent neurons into three types: Aβ-, Aδ-, and C-fiber neurons (Figure 9-1). Aβ fibers detect small movements, light touch, hair movement, and vibrations; C-fiber peripheral terminals are bare nerve endings that are only activated by noxious mechanical, thermal, or chemical stimuli; Aδ fibers fall somewhere in between, sensing noxious mechanical stimuli and sub-noxious thermal stimuli (Figure 9-1).

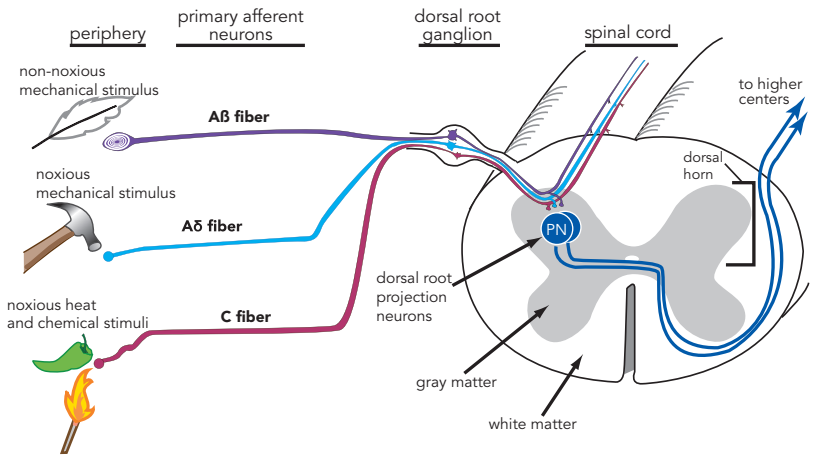


Figure 9-1 Activation of nociceptive nerve fibers. Detection of a noxious stimulus occurs at the peripheral terminals of primary afferent neurons and leads to generation of action potentials that propagate along the axon to the central terminals. Aβ fibers respond only to non-noxious stimuli, Aδ fibers respond to noxious mechanical stimuli and sub-noxious thermal stimuli, and C fibers respond only to noxious mechanical, heat, and chemical stimuli. Primary afferent neurons have their cell bodies in the dorsal root ganglion and send terminals into that spinal cord segment as well as sending less dense collaterals up the spinal cord for a short distance. Primary afferent neurons synapse onto several different classes of dorsal horn projection neurons (PN), which project via different tracts to higher centers.

Nociceptive input and pain can thus be caused by activating primary afferent neurons peripherally, such as from a sprained ankle or a tooth extraction. Nonsteroidal anti-inflammatory drugs (NSAIDs) can reduce painful input from these primary afferent neurons, presumably via their peripheral actions. Opiates can also reduce such pain, but from central actions as explained below.

Nociceptive Pathway from the Spinal Cord to the Brain

The central terminals of peripheral nociceptive neurons synapse in the dorsal horn of the spinal cord onto the next cells in the pathway – dorsal horn neurons, which receive input from many primary afferent neurons and then project to higher centers (Figures 9-2 and 9-3). For this reason, they are sometimes also called dorsal horn projection neurons (PN in Figures 9-1 through 9-3). Dorsal horn neurons are thus the first neurons of the nociceptive pathway that are located entirely within the central nervous system and thus a key site for modulation of nociceptive neuronal activity as it comes into the central nervous system. A vast number of neurotransmitters have been identified in the dorsal horn, some of which are shown in Figure 9-2.

Neurotransmitters in the dorsal horn are synthesized not only by primary afferent neurons, but also by the other neurons in the dorsal horn, including descending neurons and various interneurons (Figure 9-2). Some neurotransmitter systems in the dorsal horn are successfully targeted by known pain-relieving drugs, especially opiates, serotonin and norepinephrine boosting SNRIs, and $\alpha_2\delta$ ligands acting at VSCCs. All of the neurotransmitter systems acting in the dorsal horn are potential targets for novel pain-relieving drugs (Figure 9-2) and a plethora of such novel agents is currently in clinical and preclinical development.

There are several classes of dorsal horn neurons: some receive input directly from primary sensory neurons, some are interneurons, and some project up the spinal cord to higher centers (Figure 9-3). There are several different tracts in which these projection neurons can ascend, which can be crudely divided into two functions: the sensory/discriminatory pathway and the emotional/motivational pathway (Figure 9-3).

In the sensory/discriminatory pathway, dorsal horn neurons ascend in the spinothalamic tract; then, thalamic neurons project to the primary somatosensory cortex (Figure 9-3). This particular pain pathway is thought to convey the precise location of the nociceptive stimulus and its intensity. In the emotional/motivational pathway, other dorsal horn neurons project to brainstem nuclei, and from there to limbic regions (Figure 9-3). This second pain pathway is thought to convey the affective component that nociceptive stimuli evoke. Only when these two aspects of sensory discrimination and emotions come together and the final, subjective perception of pain is created, can we use the word "pain" to describe the modality (see "ouch" in Figure 9-3). Before this point, we are simply discussing activity in neural pathways, which should be described as noxious-evoked or nociceptive neuronal activity but not necessarily as pain.

NEUROPATHIC PAIN

The term *neuropathic pain* describes pain that arises from damage to, or dysfunction of, any part of the peripheral or central nervous system, whereas "normal" pain (so-called nociceptive pain just discussed in the section above) is caused by activation of nociceptive nerve fibers.

Peripheral Mechanisms in Neuropathic Pain

Normal transduction and conduction in peripheral afferent neurons can be hijacked in certain neuropathic pain states to maintain nociceptive signaling in the absence of a relevant noxious stimulus. Neuronal damage by disease or trauma can alter electrical activity of neurons, allow cross-talk between neurons, and initiate inflammatory processes to cause "peripheral sensitization." In this chapter, we will not emphasize peripheral sensitization disorders and mechanisms, but rather central sensitization disorders and mechanisms.

Central Mechanisms in Neuropathic Pain

At each major relay point in the pain pathway (Figure 9-3), the nociceptive pain signal is susceptible to modulation by endogenous processes to either dampen down the signal or to amplify it. This happens not only peripherally at primary afferent neurons, as has just been discussed, but also at central neurons in the dorsal horn of the spinal cord as well as in numerous brain regions. The events in the dorsal horn of the spinal cord are better understood than those in brain regions of nociceptive pathways, but pain processing in the brain may be the key to understanding the generation and amplification of pain centrally in disorders of chronic peripheral pain, such as osteoarthritis, low back pain, and diabetic peripheral neuropathic pain, as well as painful physical symptoms in affective and anxiety disorders and in fibromyalgia.

Multiple Neurotransmitters Modulate Pain Processing in the Spinal Cord

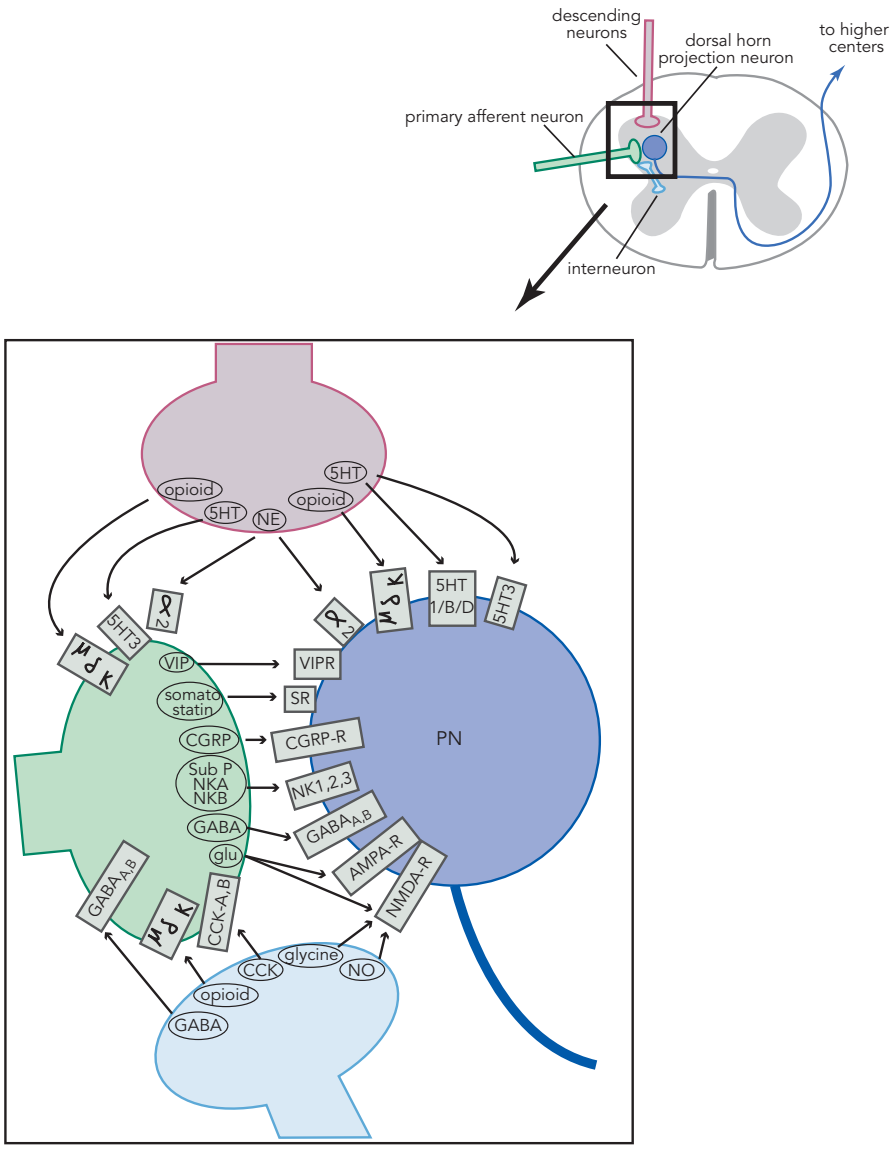


Figure 9-2 Multiple neurotransmitters modulate pain processing in the spinal cord. There are many neurotransmitters and their corresponding receptors in the dorsal horn. Neurotransmitters in the dorsal horn may be released by primary afferent neurons, by descending regulatory neurons, by dorsal horn projection neurons (PN), and by interneurons. Neurotransmitters present in the dorsal horn that have been best studied in terms of pain transmission include substance P (NK1, 2, and 3 receptors), endorphins (μ-opioid receptors), norepinephrine (α_2 adrenoceptors), and serotonin ($5HT_{1B/D}$ and $5HT_3$ receptors). Several other neurotransmitters are also represented, including vasopressin inhibitory protein (VIP) and its receptor VIPR; somatostatin and its receptor SR; calcitonin G-related peptide (CGRP) and its receptors CGRP-R; GABA and its receptors $GABA_A$ and $GABA_B$; glutamate and its receptors AMPA-R (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor) and NMDA-R (*N*-methyl-D-aspartate receptor); nitric oxide (NO); cholecystokinin (CCK) and its receptors CCK-A and CCK-B; and glycine and its receptor NMDA-R.

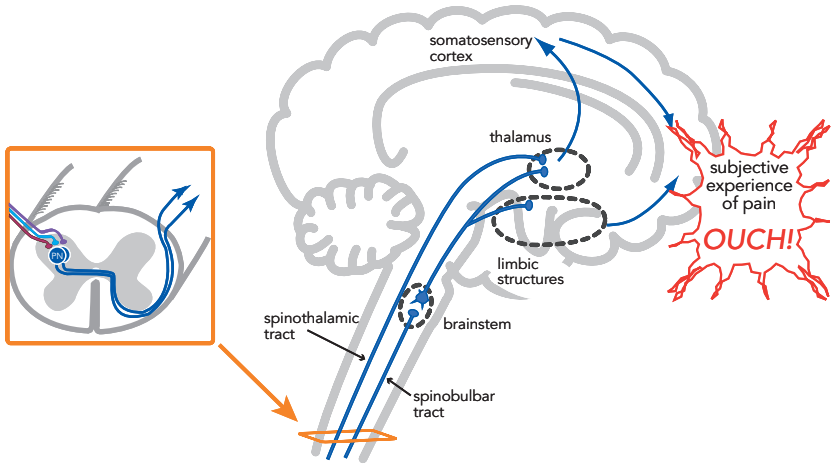


Figure 9-3 From nociception to pain. Dorsal horn neurons in the spinothalamic tract project to the thalamus and then to the primary somatosensory cortex. This pathway carries information about the intensity and location of the painful stimuli and is termed the sensory/discriminatory pathway. Neurons ascending in the spinobulbar tract project to brainstem nuclei and then to both the thalamus and limbic structures. These pathways convey the emotional and motivational aspects of the pain experience. Only when information from the sensory/discriminatory (thalamocortical) and emotional/motivational (limbic) pathways combine is the human subjective experience of pain formed ("ouch").

"Segmental" central sensitization is a process thought to be caused when plastic changes occur in the dorsal horn, classically in conditions such as phantom pain after limb amputation. Specifically, this type of neuronal plasticity in the dorsal horn is called activity-dependent or use-dependent because it requires constant firing of the pain pathway in the dorsal horn. The consequence of this constant input of pain is eventually to cause exaggerated (hyperalgesic) or prolonged responses to any noxious input – a phenomenon sometimes called "wind-up" – as well as painful responses to normally innocuous inputs (called allodynia). Phosphorylation of key membrane receptors and channels in the dorsal horn appears to increase synaptic efficiency and thus to trip a master switch opening the gate to the pain pathway and turning on central sensitization, which acts to amplify or create the perception of pain even if there is no pain input actually coming from the periphery. The gate can also close, as conceptualized in the classic "gate theory" of pain, in order to explain how innocuous stimulation (e.g., acupuncture, vibration, rubbing) away from the site of an injury can close the pain gate and reduce the perception of the injury pain.

In segmental central sensitization, a definite peripheral injury (Figure 9-4A) is combined with central sensitization at the spinal cord segment receiving nociceptive input from the damaged area of the body (Figure 9-4B). Segmental central sensitization syndromes are thus "mixed" states where the insult of central segmental changes (Figure 9-4B) are added to peripheral injuries such as low back pain, diabetic peripheral neuropathic pain, and painful cutaneous eruptions of herpes zoster (shingles) (Figure 9-4A).

"Suprasegmental" central sensitization is hypothesized to be linked to plastic changes that occur in brain sites within the nociceptive pathway, especially the thalamus and cortex, in the presence of known peripheral causes (Figure 9-5A) or even in the absence of identifiable triggering events (Figure 9-5B). In the case of peripherally activated suprasegmental central sensitization, it is as though the brain "learns" from its experience of pain, and decides not only to keep the process going, but also to enhance it and make it permanent. In the case of pain that originates centrally without peripheral input, it is as though the brain has figured out how to spontaneously activate its pain pathways. Interrupting this process of sensitized brain pathways for pain and getting the central nervous system to "forget" its molecular memories may be one of the greatest therapeutic opportunities in psychopharmacology today, not only because this may be a therapeutic strategy for various chronic neuropathic pain conditions as discussed here, but also because it may be a viable approach to treating the hypothesized molecular changes that may underlie disease progression in a wide variety of disorders, from schizophrenia, to stress-induced anxiety and affective disorders, to addictive disorders. Conditions hypothesized to be caused by suprasegmental central sensitization syndromes of pain originating in the brain without peripheral pain input include fibromyalgia, the syndrome of chronic widespread pain, and painful physical symptoms of depression and anxiety disorders, especially posttraumatic stress disorder (PTSD) (Figure 9-5B).

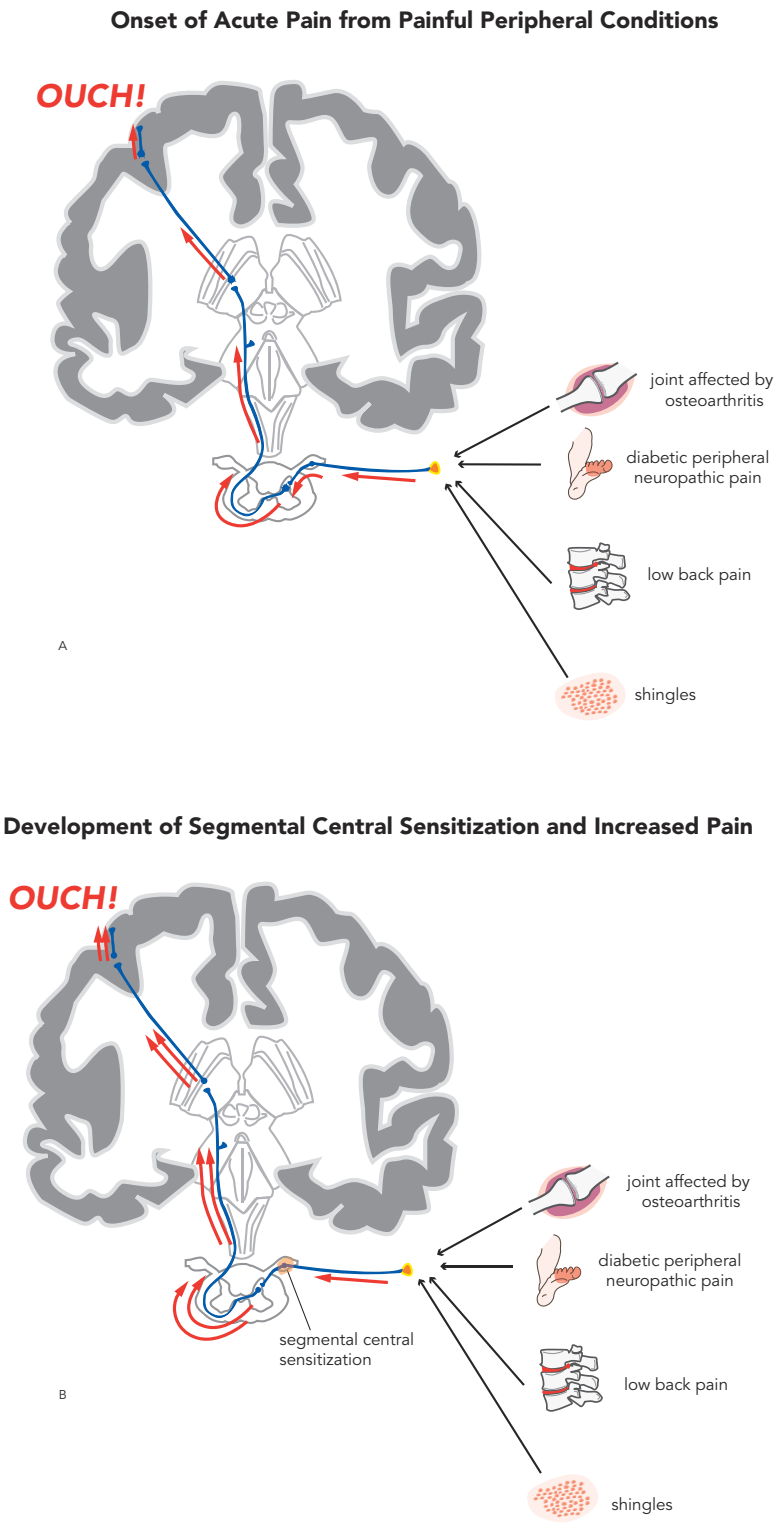
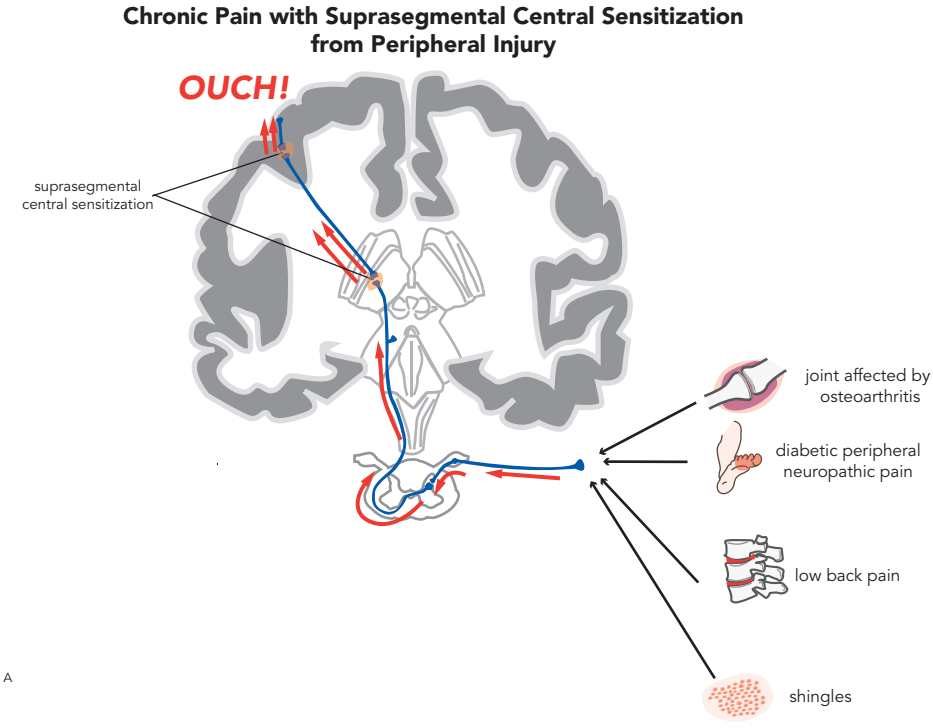


Figure 9-4 **Acute pain and development of segmental central sensitization.** (A) When peripheral injury occurs, nociceptive impulse flow from primary afferent neurons is transmitted via dorsal horn neurons to higher brain centers, where it can ultimately be interpreted as pain (represented by the "ouch"). (B) In some cases, injury or disease directly affecting the nervous system may result in plastic changes that lead to sensitization within the central nervous system, such that the experience of pain continues even after tissue damage is resolved. Impulses may be generated at abnormal locations either spontaneously or via mechanical forces. At the level of the spinal cord, this process is termed segmental central sensitization. This mechanism underlies conditions such as diabetic peripheral neuropathic pain and shingles.



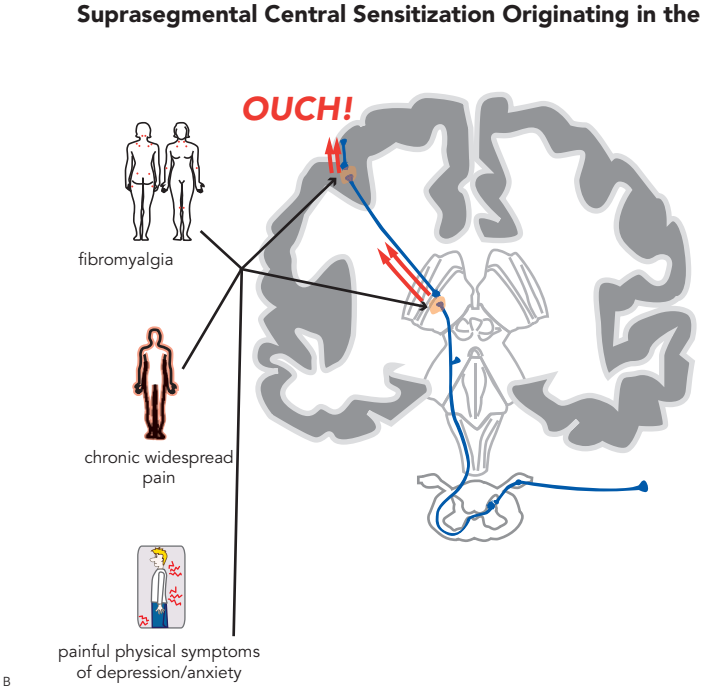


Figure 9-5 Suprasegmental central sensitization. Plastic changes in brain sites within the nociceptive pathway, especially the thalamus and cortex, can cause sensitization. This process within the brain is termed suprasegmental central sensitization. This can occur following peripheral injury (A) or even in the absence of identifiable triggering events (B). This mechanism is believed to underlie conditions such as fibromyalgia, chronic widespread pain, and painful symptoms in depression and anxiety disorders.

The Spectrum of Mood and Anxiety Disorders with Pain Disorders

A large group of overlapping disorders can have emotional symptoms, painful physical symptoms, or both (Figure 9-6). Although pain in the absence of emotional symptoms has long been seen as a neurological disorder, and pain in the presence of emotional symptoms as a psychiatric disorder, it is now clear that pain is a symptom that can be mapped onto inefficient information processing within the pain circuit, and is largely considered the same symptom with the same treatments, whether occurring by itself or as part of any number of syndromes (Figure 9-6). Thus, pain (Figure 9-6, right) can occur not only by itself, but also concomitantly with the emotional symptoms of depressed mood and anxiety (Figure 9-6, left), and with the physical symptoms of fatigue, insomnia, and problems concentrating (Figure 9-6, middle). No matter whether pain occurs by itself or with additional concomitant emotional or physical symptoms, or in the presence of full syndromal psychiatric disorders such as major depressive disorder, generalized anxiety disorder, or PTSD (Figure 9-6, left), it must be treated and the treatments are the same across the spectrum (Figure 9-6), namely SNRIs and $\alpha_2\delta$ ligands as will be explained below.

Fibromyalgia

Fibromyalgia has emerged as a diagnosable and treatable pain syndrome, with tenderness but no structural pathology in muscles, ligaments, or joints. Fibromyalgia is recognized as a chronic, widespread pain syndrome associated with fatigue and nonrestorative sleep. It is diagnosed based on the number of body areas in which the patient experiences pain (widespread pain index, or WPI) combined with the severity of associated symptoms (fatigue, waking unrefreshed, cognitive symptoms, and other somatic symptoms) (Figure 9-7). It is the second most common diagnosis in rheumatology clinics, and may affect 2–4% of the general population. Although symptoms of fibromyalgia are chronic and debilitating, they are not necessarily progressive. There is no known cause and there is no known pathology identifiable in the muscles or joints. This syndrome can be deconstructed into its component symptoms (Figure 9-8), and then matched with hypothetically malfunctioning brain circuits (Figure 9-9).

Decreased Gray Matter in Chronic Pain Syndromes?

Some very troubling preliminary reports suggest that chronic pain may even "shrink the brain" in the DLPFC (dorsolateral prefrontal cortex) (Figure 9-9) and thereby

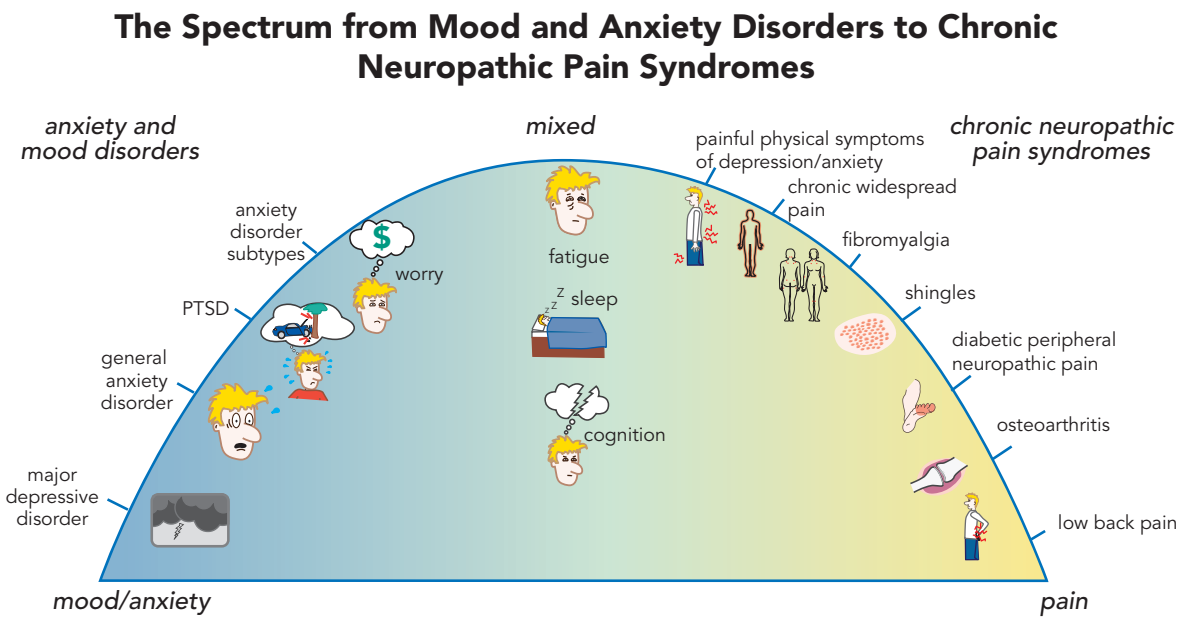


Figure 9-6 The spectrum from mood and anxiety disorders to chronic neuropathic pain syndromes. Pain, though not a formal diagnostic feature of depression or anxiety disorders, is nonetheless frequently present in patients with these disorders. Similarly, depressed mood, anxiety, and other symptoms identified as part of depression and anxiety disorders are now recognized as being common in pain disorders.

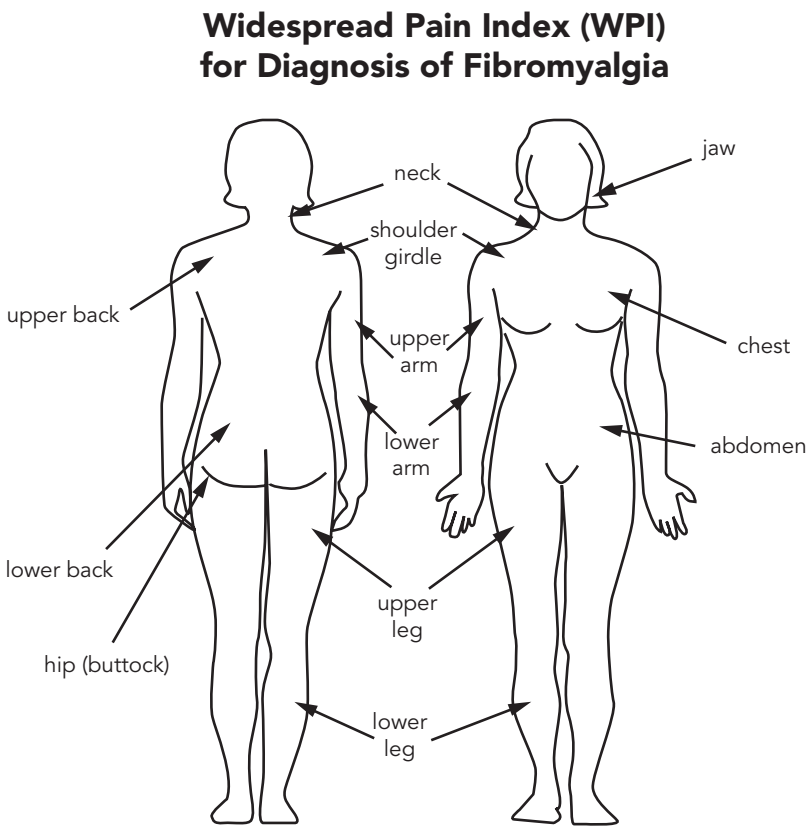


Figure 9-7 Widespread pain index (WPI). Fibromyalgia is a chronic widespread pain syndrome, formerly diagnosed based on the number of body areas in which the patient experiences pain (widespread pain index, or WPI) combined with the severity of associated symptoms (fatigue, waking unrefreshed, cognitive symptoms, and other somatic symptoms.

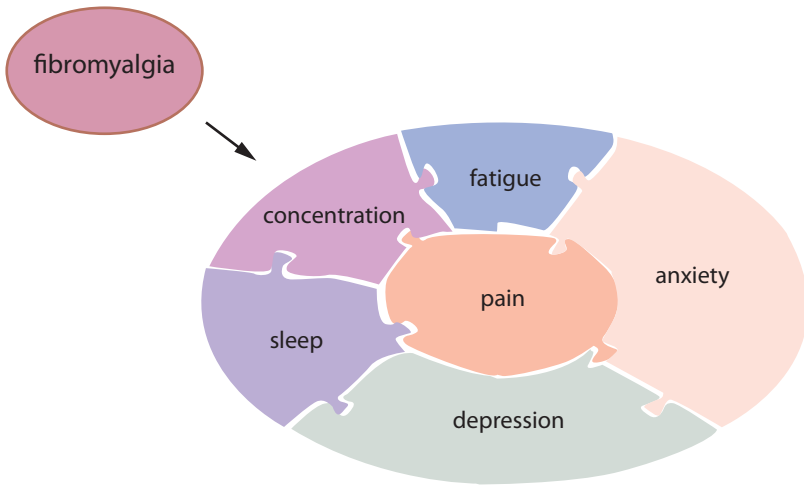


Figure 9-8 Symptoms of fibromyalgia. In addition to pain as a central feature of fibromyalgia, many patients experience fatigue, anxiety, depression, disturbed sleep, and problems concentrating.

contribute to cognitive dysfunction in certain pain states such as fibromyalgia (Figure 9-8) and low back pain. Brain atrophy is discussed in relationship to stress and anxiety disorders in Chapter 6 and illustrated in Figure 6-30. It would not be surprising if stressful conditions that cause pain, as well as pain that causes distress, may all be involved in causing brain atrophy and/or cognitive dysfunction in fibromyalgia and other chronic pain states. Chronic back pain, for example, has also been reported to be associated with decreased prefrontal and thalamic gray-matter density (Figure 9-10). Some experts have hypothesized that in fibromyalgia and other chronic

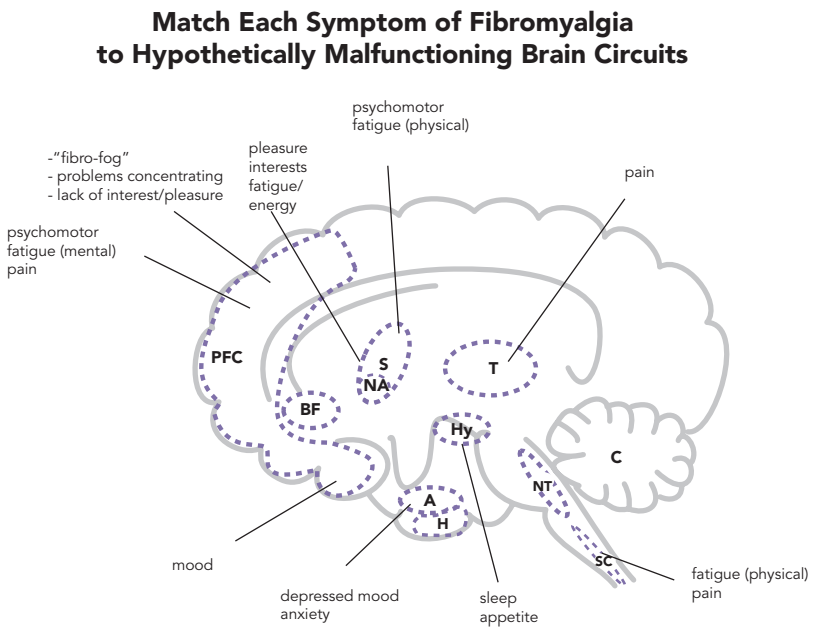


Figure 9-9 Symptom-based algorithm for fibromyalgia. A symptom-based approach to treatment selection for fibromyalgia follows the theory that each of a patient's symptoms can be matched with malfunctioning brain circuits and neurotransmitters that hypothetically mediate those symptoms; this information is then used to select a corresponding pharmacological mechanism for treatment. Pain is linked to transmission of information via the thalamus (T), while physical fatigue is linked to the striatum (S) and spinal cord (SC). Problems concentrating and lack of interest (termed "fibro-fog") as well as mental fatigue are linked to the prefrontal cortex (PFC), specifically the dorsolateral PFC. Fatigue, low energy, and lack of interest may all also be related to the nucleus accumbens (NA). Disturbances in sleep and appetite are associated with the hypothalamus (Hy), depressed mood with the amygdala (A) and orbital frontal cortex, and anxiety with the amygdala.

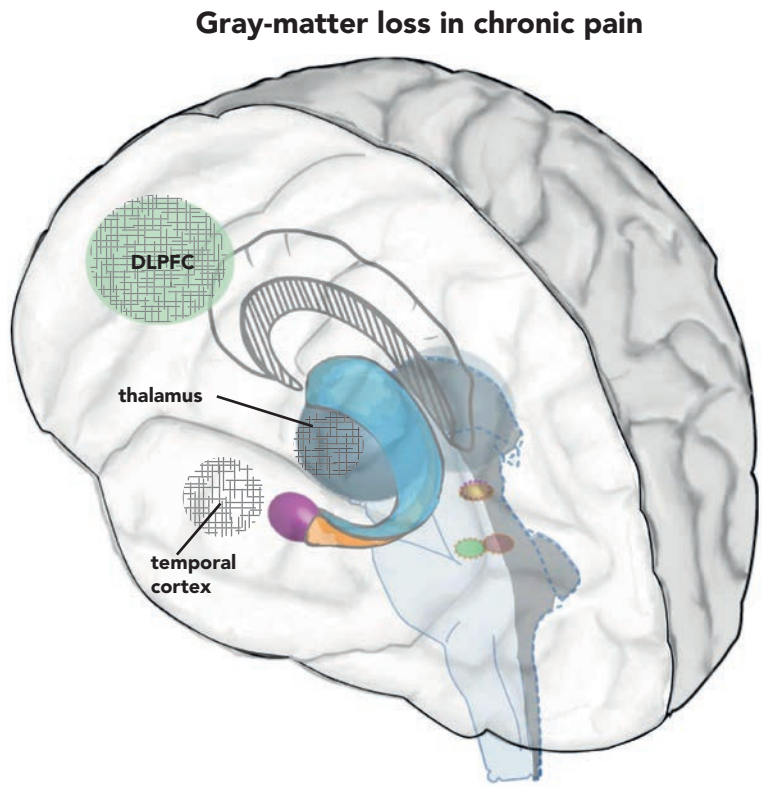


Figure 9-10 Gray-matter loss in chronic pain. Research suggests that chronic pain, like anxiety and stress-related disorders, may lead to brain atrophy. Specifically, there are data showing gray-matter loss in the dorsolateral prefrontal cortex (DLPFC), the thalamus, and the temporal cortex in patients with chronic pain conditions.

neuropathic pain syndromes, the persistent perception of pain could lead to overuse of DLPFC neurons, excitotoxic cell death in this brain region, and reduction of the cortico-thalamic "brake" on nociceptive pathways. Such an outcome could cause not only increased pain perception, but diminished executive functioning,

sometimes called "fibro-fog" in fibromyalgia. In Chapter 6 we discussed how stress-related HPA (hypothalamic-pituitary-adrenal) axis abnormalities in CRF–ACTH–cortisol regulation may be linked to hippocampal atrophy (see Figure 6-32), possibly linked to reduced availability of growth factors (Figures 6-27 and 6-29). Alterations in growth factors may be linked to the reports of reduction in gray-matter volume in chronic pain syndromes (fibromyalgia and low back pain), but in different brain regions (DLPFC, temporal cortex, and thalamus) (Figure 9-10) than reported for depression (Figure 6-30). Gray matter may actually be increased in other brain regions in chronic pain.

Although still preliminary, these findings suggest a possible structural consequence to suprasegmental central sensitization (Figure 9-10), not unlike that suspected for depression and stress (Figure 6-30). Abnormal pain processing, exaggerated pain responses, and perpetual pain could hypothetically be linked to deficiencies in the DLPFC circuit and its regulation by dopamine, and provide a potential explanation for the cognitive difficulties associated with chronic pain, especially fibro-fog in fibromyalgia (Figure 9-8). Thalamic abnormalities could hypothetically be linked to problems sleeping as well as nonrestorative sleep seen in chronic pain syndromes (Figure 9-8). Thus, chronic pain syndromes not only cause pain, but also problems with fatigue, mental concentration, sleep, depression, and anxiety (Figure 9-8). Structural brain abnormalities associated with inefficient information processing in brain areas that mediate these symptoms (Figure 9-9) may explain why these various symptoms (Figure 9-8) are frequently associated with chronic pain syndromes.

DESCENDING SPINAL SYNAPSES IN THE DORSAL HORN AND THE TREATMENT OF CHRONIC PAIN

The periaqueductal gray is the site of origin and regulation of much of the descending inhibition that projects down the spinal cord to the dorsal horn (Figure 9-2). The periaqueductal gray is discussed in relationship to its connections with the amygdala and the motor component of the fear response in Chapter 8 and illustrated in Figure 8-9. The periaqueductal gray also integrates inputs from nociceptive pathways and limbic structures such as the amygdala and limbic cortex, and sends outputs to brainstem nuclei and the rostroventromedial medulla to drive descending inhibitory pathways. Some of these descending pathways release endorphins, which act via mostly presynaptic μ-opioid receptors to inhibit neurotransmission from nociceptive primary afferent neurons (Figure 9-2). Spinal μ-opioid receptors are one target of opioid analgesics; so are μ-opioid receptors in the periaqueductal gray itself (Figure 9-11). Interestingly, since Aβ fibers (Figure 9-1) do not express μ-opioid receptors, this may explain why opioid analgesics spare normal sensory input. Enkephalins, which also act via δ-opioid receptors, are also antinociceptive, whereas dynorphins, acting at κ-opioid receptors, can be either anti- or pronociceptive. It is also interesting that opiates in general are no more effective for chronic neuropathic pain states than SNRIs or $\alpha_2\delta$ ligands, but in many cases, such as in fibromyalgia, opiates are not proven to be effective at all.

Two other important descending inhibitory pathways are also shown in Figure 9-2. One is the descending spinal norepinephrine pathway (Figure 9-12A), which originates in the locus coeruleus, and especially from noradrenergic cell bodies in the lower (caudal) parts of the brainstem neurotransmitter center (lateral tegmental norepinephrine cell system). The other important descending pathway is the descending spinal serotonergic pathway (Figure 9-13A), which originates in the nucleus raphe magnus of the rostroventromedial medulla and especially the lower (caudal) serotonin nuclei (raphe magnus, raphe pallidus, and raphe obscuris). Descending noradrenergic neurons inhibit neurotransmitter release from primary afferents directly via inhibitory α_2 adrenoceptors (Figure 9-2), explaining why direct-acting α_2 agonists such as clonidine can be useful in relieving pain in some patients. Serotonin inhibits primary afferent terminals via postsynaptic $5HT_{1B/D}$ receptors (Figure 9-2). These inhibitory receptors are G-protein-coupled, and indirectly influence ion channels to hyperpolarize the nerve terminal and inhibit nociceptive neurotransmitter release. However, serotonin is also a major transmitter in descending *facilitation* pathways to the spinal cord. Serotonin released onto some primary afferent neuron terminals in certain areas of the dorsal horn acts predominantly via excitatory $5HT_3$ receptors to enhance neurotransmitter release from these primary afferent neurons (Figure 9-2). The combination of both inhibitory and facilitatory actions of serotonin may explain why SSRIs (selective serotonin reuptake inhibitors), with actions that increase only serotonin levels, are not consistently useful in the treatment of pain, whereas SNRIs, with actions on both serotonin and norepinephrine, are now proven to be effective in various neuropathic pain states, including diabetic peripheral neuropathic pain and fibromyalgia.

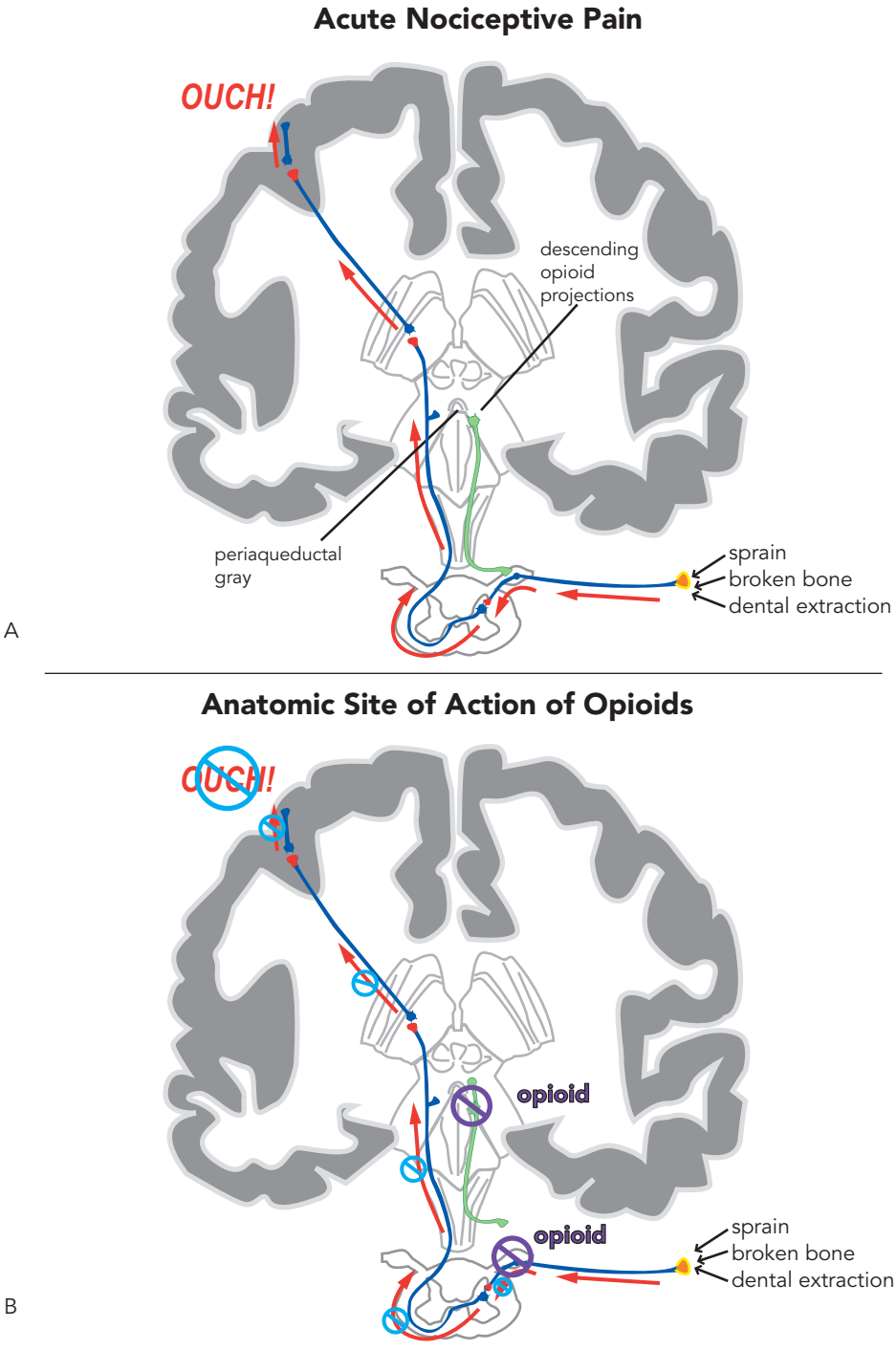


Figure 9-11 **Acute nociceptive pain and opioids.** The periaqueductal gray integrates inputs from nociceptive pathways and limbic structures and sends outputs to drive descending inhibitory pathways, including descending opioid projections. (A) Shown here is nociceptive input from a peripheral injury being transmitted to the brain and interpreted as pain. The descending opioid projection is not activated and thus is not inhibiting the nociceptive input. (B) Endogenous opioid release in the descending opioid projection, or exogenous administration of an opioid, can cause inhibition of nociceptive neurotransmission in the dorsal horn or in the periaqueductal gray and thus prevent or reduce the experience of pain.

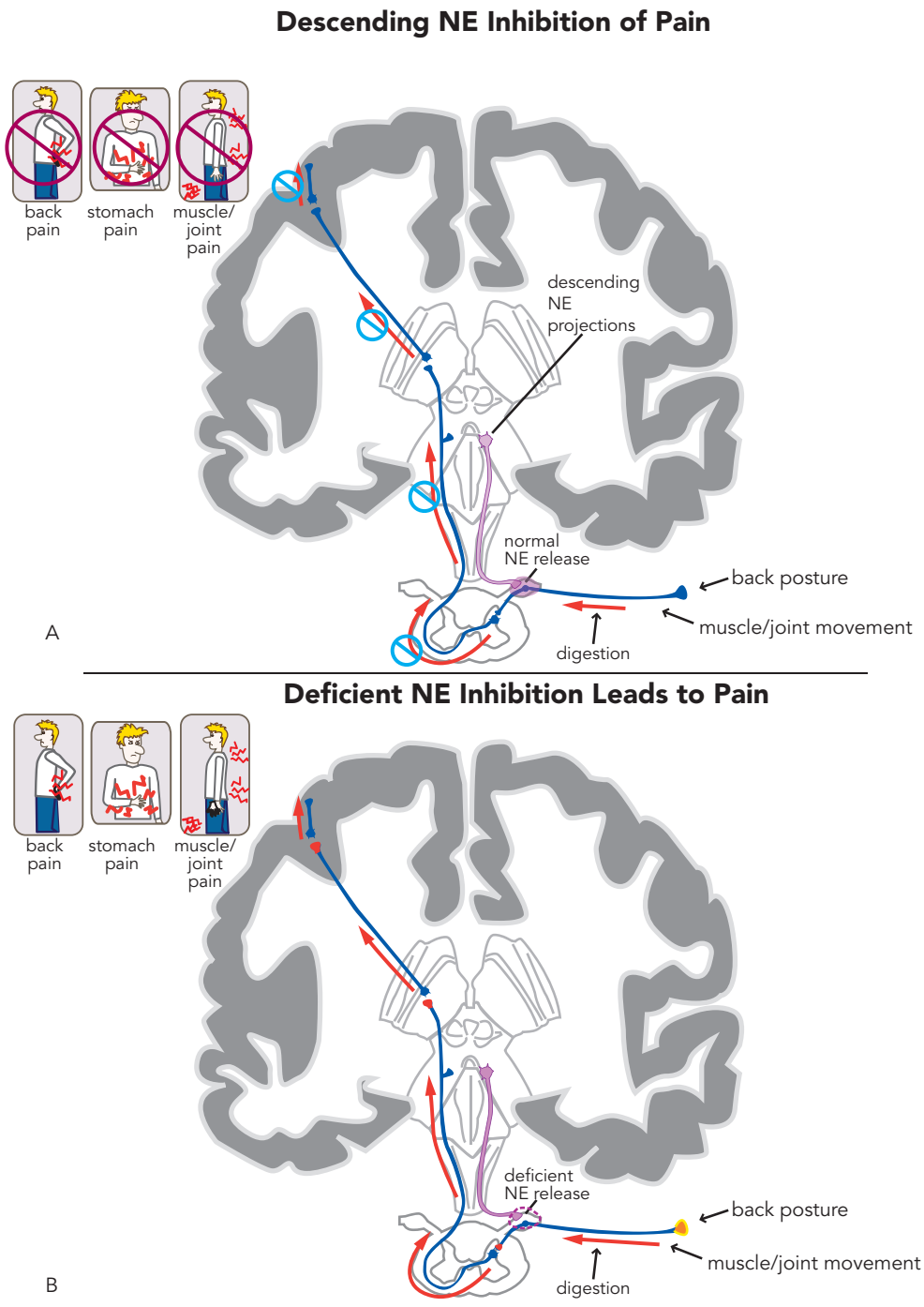


Figure 9-12A, B Descending noradrenergic neurons and pain. (A) The descending spinal norepinephrine (NE) pathway originates in the locus coeruleus. Descending NE neurons inhibit neurotransmitter release from primary afferent neurons via presynaptic α_2 adrenoceptors, and inhibit activity of dorsal horn neurons via postsynaptic α_2 adrenoceptors. This suppresses bodily input (e.g., regarding muscles/joints or digestion) from reaching the brain and thus prevents it from being interpreted as painful. (B) If descending NE inhibition is deficient, then it may not be sufficient to mask irrelevant nociceptive input, potentially leading to perception of pain from input that is normally ignored. This may be a contributing factor for painful somatic symptoms in fibromyalgia, depression, irritable bowel syndrome, and anxiety disorders.

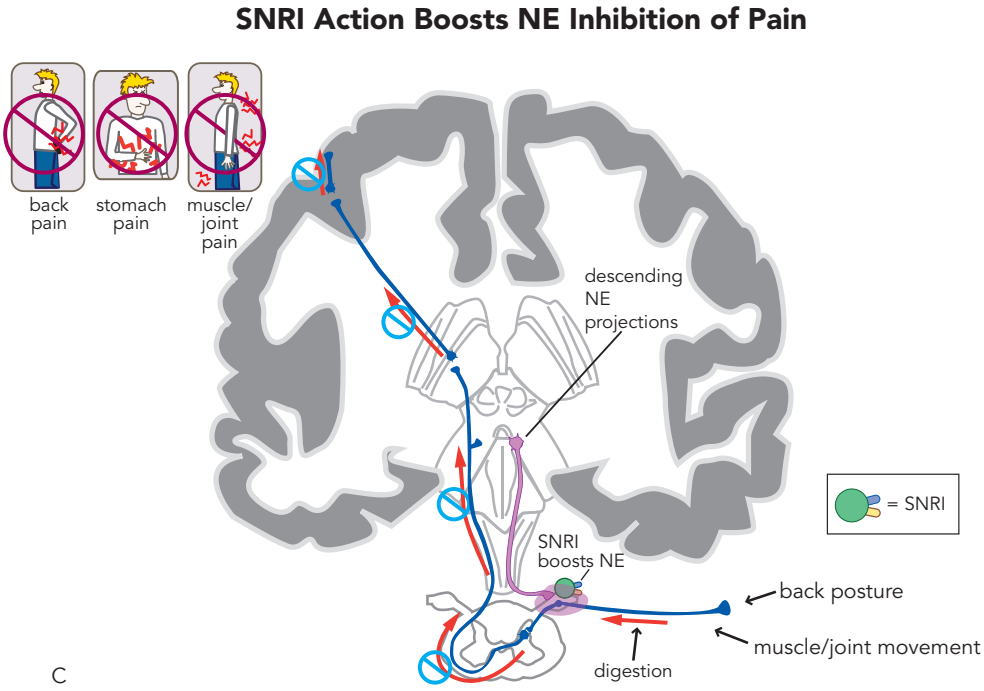


Figure 9-12C Enhancement of descending noradrenergic inhibition. A serotonin–norepinephrine reuptake inhibitor (SNRI) can increase noradrenergic neurotransmission in the descending spinal pathway to the dorsal horn, and thus may enhance inhibition of bodily input so that it does not reach the brain and get interpreted as pain.

Descending inhibition, mostly via serotonin and noradrenergic pathways, is normally active at rest and is thought to act physiologically to mask perception of irrelevant nociceptive input (e.g., from digestion, joint movement, etc.) (Figures 9-12A and 9-13A). One hypothesis for why patients with depression or fibromyalgia or related chronic pain disorders perceive pain when there is no obvious sign of peripheral trauma is that descending inhibition may not be acting adequately to mask irrelevant nociceptive input. This leads to the perception of pain from what is actually normal input that is ordinarily ignored (Figures 9-12B and 9-13B). If this descending monoaminergic inhibition is enhanced with an SNRI, irrelevant nociceptive inputs from joints, muscles, and the back in fibromyalgia and depression, and from digestion and the gastrointestinal tract in irritable bowel syndrome, depression, and anxiety disorders, are hypothetically once again ignored and thus are no longer perceived as painful (Figures 9-12C and 9-13C). SNRIs include duloxetine, milnacipran, levomilnacipran, venlafaxine, desvenlafaxine, and some tricyclic antidepressants (TCAs). SNRIs and TCAs are discussed extensively in Chapter 7.

Descending inhibition is also activated during severe injury by incoming nociceptive input, and in dangerous "conflict" situations via limbic structures, causing the release of endogenous opioid peptides (Figure 9-11B), serotonin (Figure 9-13A), and norepinephrine (Figure 9-12A). When this happens, this reduces not only the release of nociceptive neurotransmitters in the dorsal horn (Figure 9-2) but also the transmission of nociceptive impulses up the spinal cord into the brain (Figure 9-3), thereby reducing the perception of pain, dulling it to allow escape from the situation without the injury compromising physical performance in the short run (reduction of "ouch" in Figure 9-3). On return to safety, descending facilitation replaces the inhibition to redress the balance, increase awareness of the injury, and force rest of the injured part (lots of "ouch" in Figure 9-3).

The power of this system can be seen in humans persevering through severe injury on the sports field and on the battle field. The placebo effect may also involve endogenous opioid release from these descending inhibitory neurons (Figure 9-11B), since activation of a placebo response to pain is reversible by the μ-opioid antagonist naloxone. These are adaptive

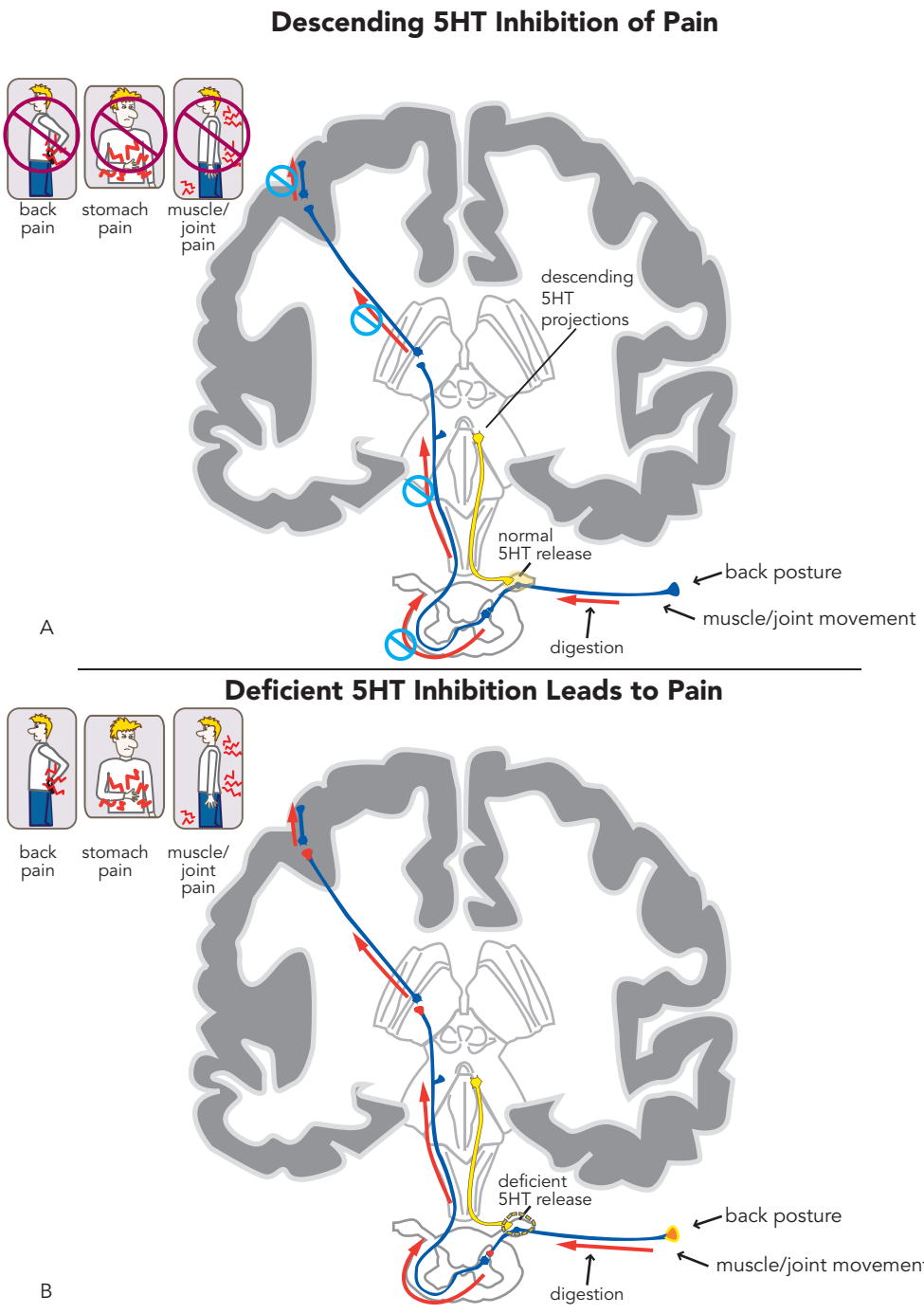


Figure 9-13A, B Descending serotonergic neurons and pain. (A) The descending spinal serotonin (5HT) pathway originates in the raphe nucleus. Descending serotonergic (5HT) neurons directly inhibit activity of dorsal horn neurons, predominantly via $5HT_{1B/D}$ receptors. This suppresses bodily input (e.g., regarding muscles/joints or digestion) from reaching the brain and thus prevents it from being interpreted as painful. (B) If descending 5HT inhibition is deficient, it may not be sufficient to mask irrelevant nociceptive input, potentially leading to perception of pain from input that is normally ignored. This may be a contributing factor for painful somatic symptoms in fibromyalgia, depression, irritable bowel syndrome, and anxiety disorders.

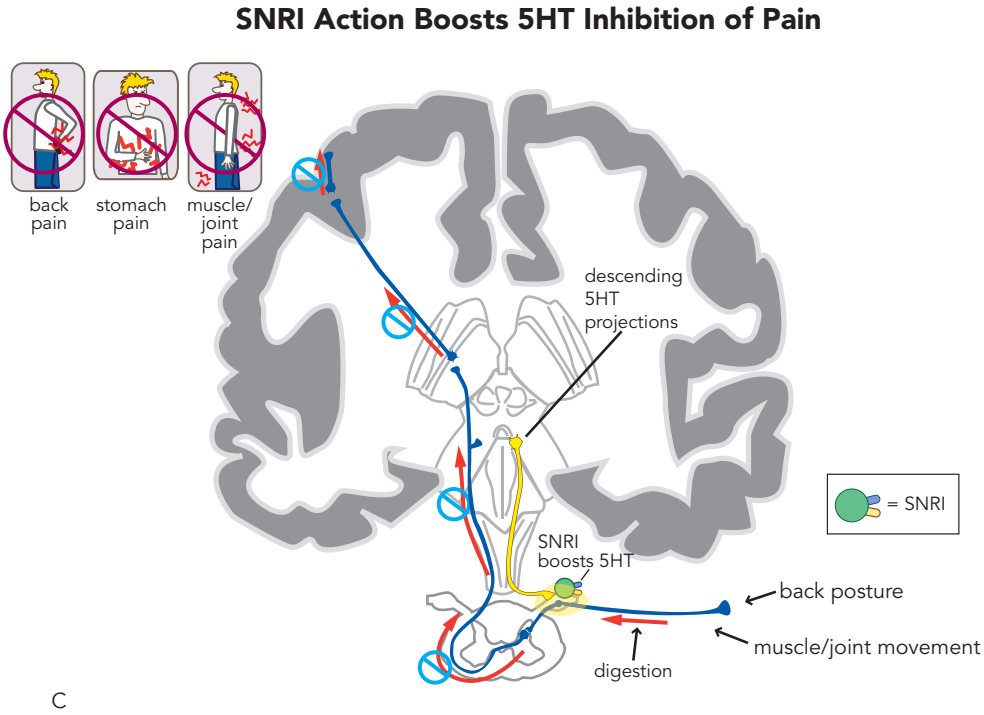


Figure 9-13C Enhancement of descending serotonergic inhibition. A serotonin–norepinephrine reuptake inhibitor (SNRI) can increase serotonergic neurotransmission in the descending spinal pathway to the dorsal horn, and thus may enhance inhibition of bodily input so that it does not reach the brain and get interpreted as pain. However, the noradrenergic effects of SNRIs may be more relevant to suppression of nociceptive input.

changes within the pain pathways that facilitate survival and enhance function for the individual. However, maladaptive changes can also hijack these same mechanisms to inappropriately maintain pain without relevant tissue injury, as may occur in various forms of neuropathic pain, ranging from diabetes to fibromyalgia and beyond.

TARGETING SENSITIZED CIRCUITS IN CHRONIC PAIN CONDITIONS

Chronic pain perpetuated as a marker of an irreversible sensitization process within the central nervous system has already been discussed as a disorder triggered by progressive molecular changes due to abnormal neuronal activity within the pain pathway, sometimes called central sensitization. When this occurs at the spinal or segmental level, it is likely linked to the multiple different neurotransmitters released there, with each neurotransmitter's release mechanism requiring presynaptic depolarization and activation of N-type and P/Q-type voltage-sensitive calcium channels (VSCCs; Figure 9-14), which is often coupled to the release of glutamate, but also to aspartate, substance P (SP), calcitonin-gene-related peptide (CGRP), and other neurotransmitters (Figure 9-2). When this occurs at suprasegmental levels in the thalamus and cortex, it is likely linked to release mostly of glutamate via the same N-type and P/Q-type VSCCs (Figures 9-14 and 9-15). The idea is that low release of neurotransmitter creates no pain response because there is insufficient neurotransmitter release to stimulate the postsynaptic receptors (Figure 9-14A). However, normal amounts of neurotransmitter release cause a full nociceptive pain response and acute pain (Figure 9-14B). Hypothetically, in states of central sensitization, there is excessive and unnecessary ongoing nociceptive activity causing neuropathic pain (Figure 9-15A). Blocking VSCCs with the $\alpha_2\delta$ ligands gabapentin or pregabalin (Figures 9-15B and 9-16) inhibits release of various neurotransmitters in the dorsal horn (Figures 9-2, 9-15B, and 9-17A) or in thalamus and cortex (Figures 9-15B and 9-17B) and has indeed proven to be an effective treatment for various disorders causing neuropathic pain. Gabapentin and pregabalin

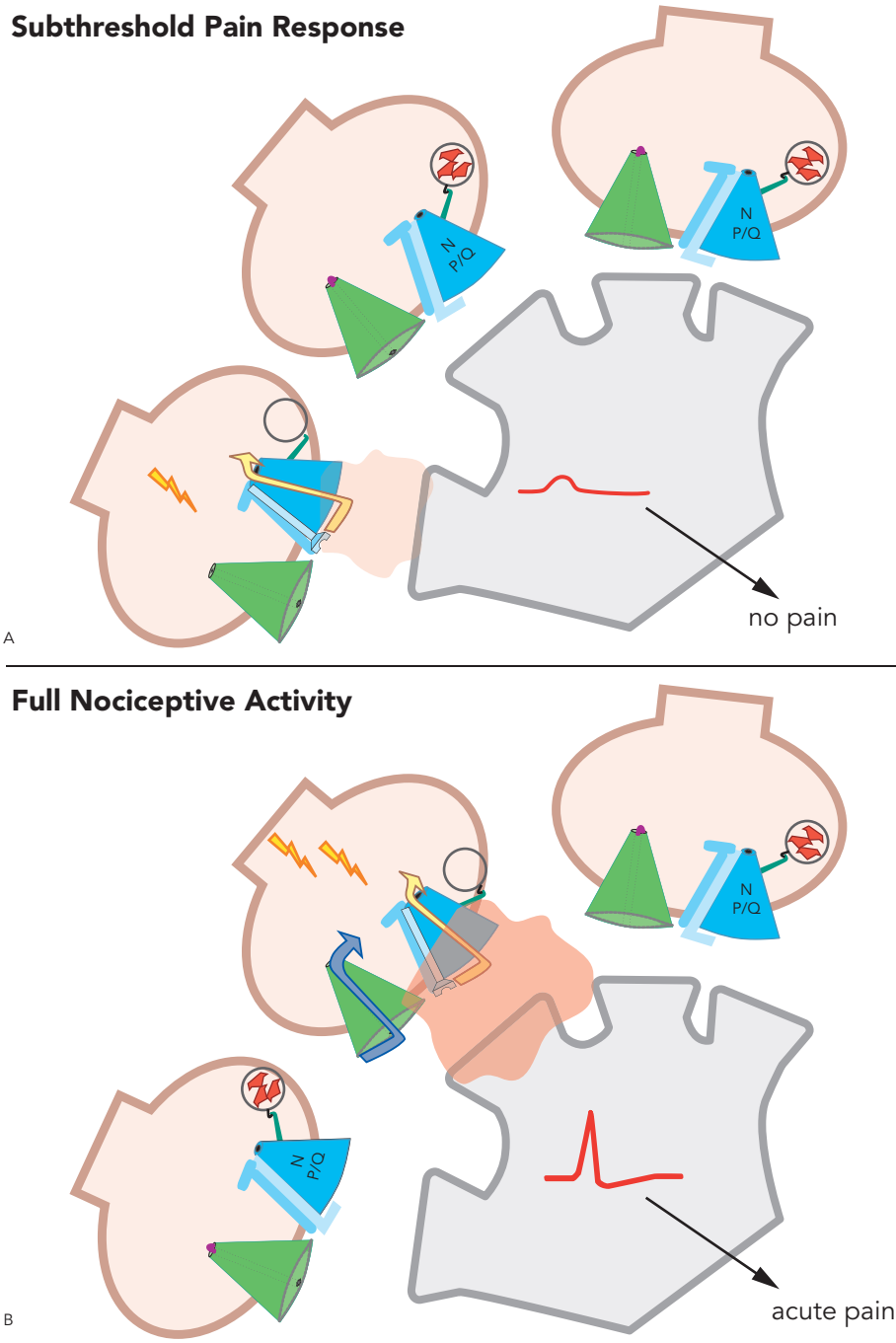


Figure 9-14 **Activity-dependent nociception in pain pathways, part 1: acute pain.** The degree of nociceptive neuronal activity in pain pathways determines whether one experiences acute pain. An action potential on a presynaptic neuron triggers sodium influx, which in turn leads to calcium influx, and ultimately release of neurotransmitter. (A) In some cases, the action potential generated at the presynaptic neuron causes minimal neurotransmitter release; thus the postsynaptic neuron is not notably stimulated and the nociceptive input does not reach the brain (in other words, there is no pain). (B) In other cases, a stronger action potential at the presynaptic neuron may cause voltage-sensitive calcium channels (VSCCs) to remain open longer, allowing more neurotransmitter release and more stimulation of the postsynaptic neuron. Thus, the nociceptive input is transmitted to the brain and acute pain occurs.

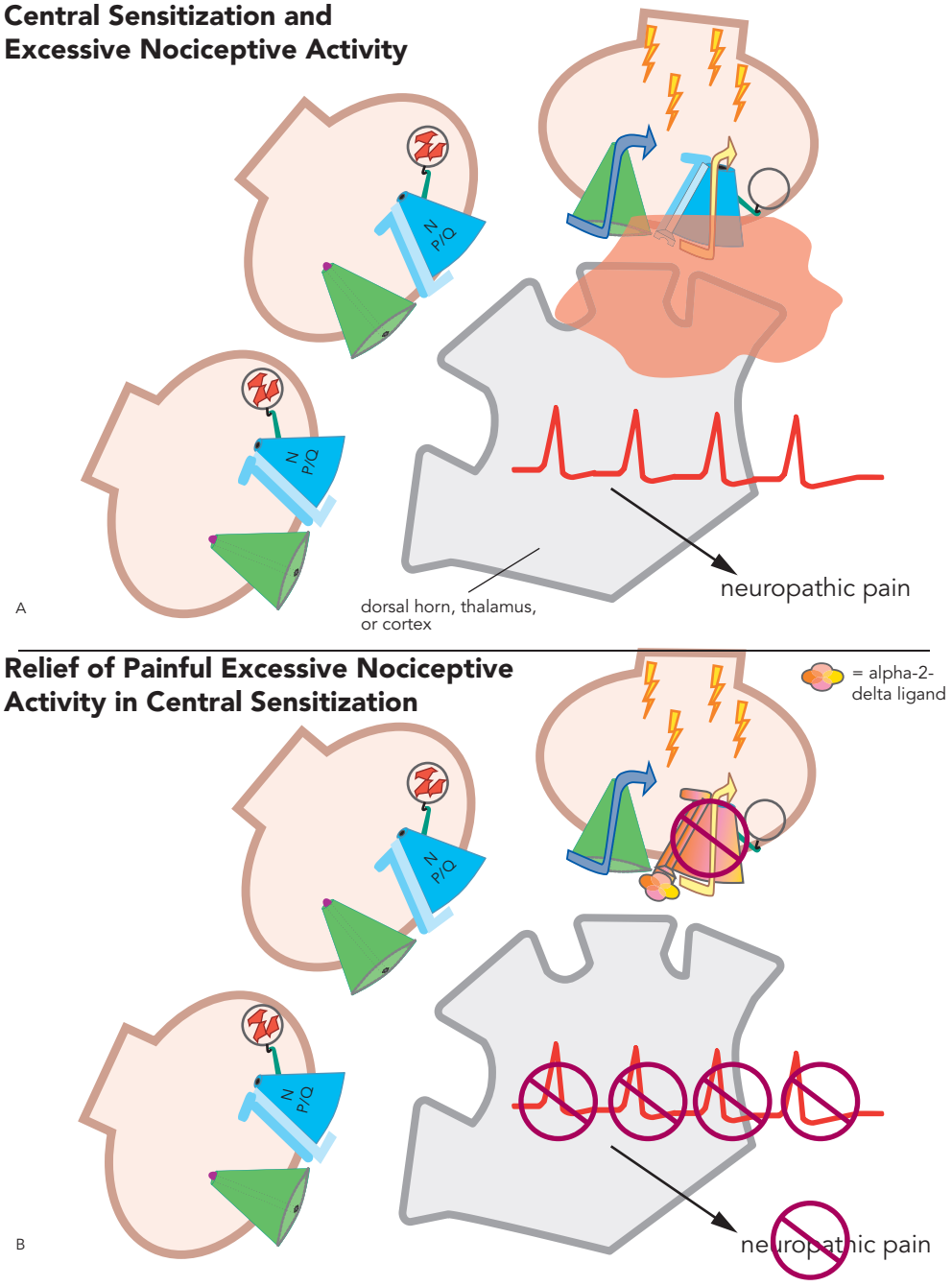


Figure 9-15 **Activity-dependent nociception in pain pathways, part 2: neuropathic pain.** The degree of nociceptive neuronal activity in pain pathways determines whether one experiences acute pain. An action potential on a presynaptic neuron triggers sodium influx, which in turn leads to calcium influx, and ultimately release of neurotransmitter. (A) Strong or repetitive action potentials can cause prolonged opening of calcium channels, which may lead to excessive release of neurotransmitter into the synaptic cleft, and consequently to excessive stimulation of postsynaptic neurons. Ultimately this may induce molecular, synaptic, and structural changes, including sprouting, which are the theoretical substrates for central sensitization syndromes. In other words, this can lead to neuropathic pain. (B) Alpha-2-delta ligands such as gabapentin or pregabalin bind to the $\alpha_2\delta$ subunit of voltage-sensitive calcium channels (VSCCs), changing their conformation to reduce calcium influx and therefore reduce excessive stimulation of postsynaptic receptors.

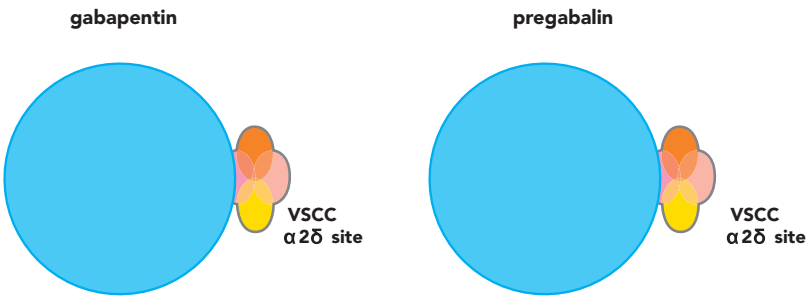


Figure 9-16 Gabapentin and pregabalin. Shown here are icons of the pharmacological actions of gabapentin and pregabalin. These agents bind to the $\alpha_2\delta$ subunit of voltage-sensitive calcium channels (VSCCs).

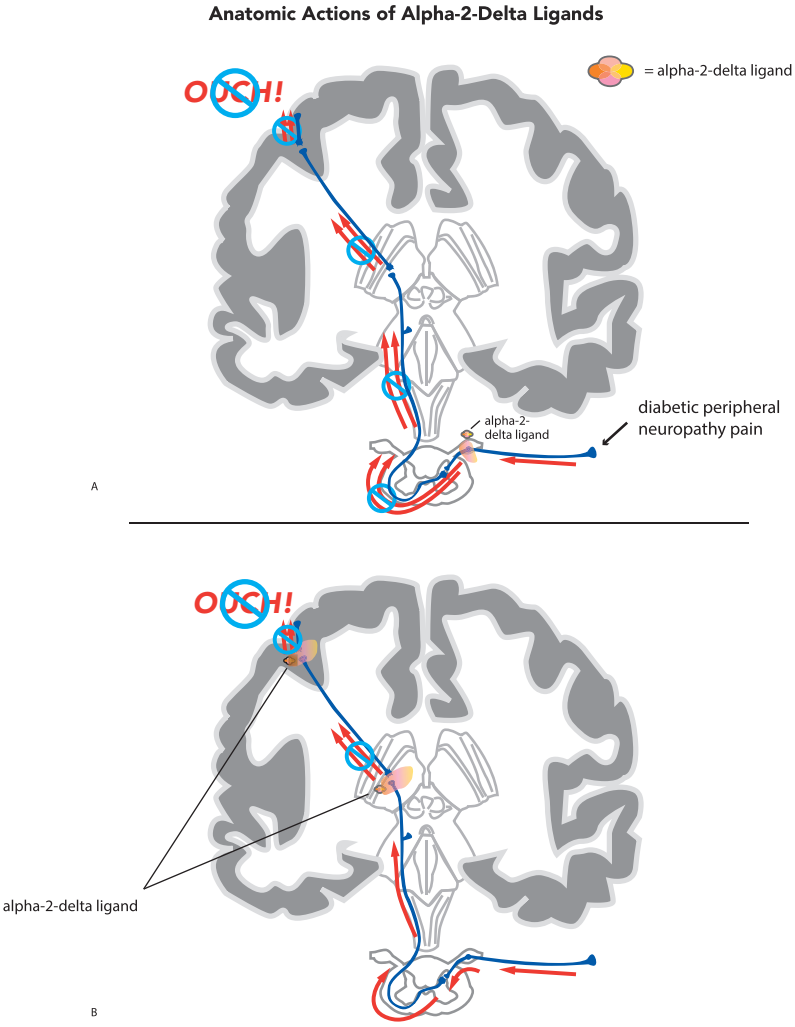


Figure 9-17 Anatomic actions of $\alpha_2\delta$ ligands. (A) Alpha-2-delta ligands may bind to voltage-sensitive calcium channels in the dorsal horn to reduce excitatory neurotransmission and alleviate pain. (B) Alpha-2-delta ligands may also bind to voltage-sensitive calcium channels in the thalamus and cortex to reduce excitatory neurotransmission and alleviate pain.

(Figure 9-16) may more selectively bind the "open-channel" conformation of VSCCs (Figures 9-17 and 9-18), and thus be particularly effective in blocking those channels that are the most active, with a "use-dependent" form of inhibition (Figures 9-17B and 9-18B). This molecular action predicts more affinity for centrally sensitized VSCCs that are actively conducting neuronal impulses within the pain pathway. Thus, they have a selective action on those VSCCs causing

Molecular Action of Alpha-2-Delta Ligands

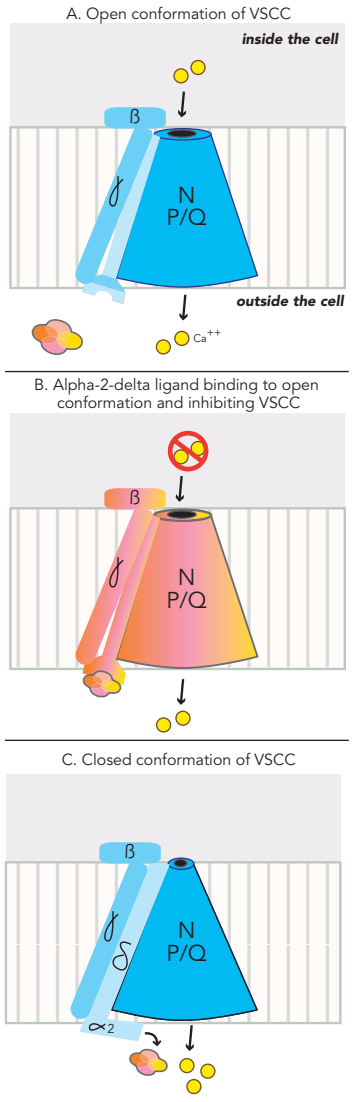


Figure 9-18 Binding of $\alpha_2\delta$ ligands. (A) Calcium influx occurs when voltage-sensitive calcium channels (VSCCs) are in the open-channel conformation. (B) Alpha-2-delta ligands such as gabapentin and pregabalin have greatest affinity for the open-channel conformation and thus block those channels that are most active. (C) When VSCCs are in the closed conformation $\alpha_2\delta$ ligands do not bind and thus do not disrupt normal neurotransmission.

neuropathic pain, ignoring other VSCCs that are not open, and thus not interfering with normal neurotransmission in central neurons uninvolved in mediating the pathological pain state.

Treatment of pain, including neuropathic pain conditions, may be less costly when you "pay" for it in advance, or at least early in the game. The hope is that early treatment of pain could interfere with the development of chronic persistent painful conditions by blocking the ability of painful experiences to imprint themselves upon the central nervous system by not allowing triggering of central sensitization. Thus, the mechanisms whereby symptomatic suffering of chronic neuropathic pain is relieved, such as with SNRIs or $\alpha_2\delta$ ligands, may also be the same mechanisms that could prevent disease progression to chronic persistent pain states. This notion calls for aggressive treatment of painful symptoms in these conditions that theoretically have their origin within the central nervous system, thus "intercepting" the central sensitization process before it is durably imprinted into angry circuits. Thus, major depression and anxiety disorders and fibromyalgia can all be treated with SNRIs and/or $\alpha_2\delta$ ligands to eliminate painful physical symptoms and thereby improve the chances of reaching full symptomatic remission. The opportunity to prevent permanent pain syndromes or progressive worsening of pain is one reason why pain is increasingly being considered a psychiatric "vital sign" that must be assessed routinely in the evaluation and treatment of psychiatric disorders by psychopharmacologists. Future testing of agents capable of reducing pain should be done to determine whether eliminating painful symptoms early in the course of psychiatric and functional somatic illnesses will improve outcomes, including preventing symptomatic relapses, the development of treatment resistance or even brain atrophy from stress in pain states (Figure 9-9), and hippocampal atrophy from stress in anxiety and affective disorders (Figure 6-30). Pre-emptively treating pain before it occurs, or at least rescuing centrally mediated and sensitizing pain by intercepting such pain before it becomes permanent, may be some of the most promising therapeutic applications of dual reuptake inhibitors and $\alpha_2\delta$ ligands and deserves careful clinical evaluation.

TARGETING ANCILLARY SYMPTOMS IN FIBROMYALGIA

We have repeatedly mentioned the proven usefulness of the $\alpha_2\delta$ ligands gabapentin and pregabalin and the SNRIs duloxetine, milnacipran, venlafaxine, and desvenlafaxine for treating the painful symptoms of fibromyalgia, yet these two classes have not been studied extensively in combination. Nevertheless, they are frequently used together in clinical practice on an empiric basis and anecdotally have been shown to give additive

improvement in relieving pain. Each class of drug may also help different ancillary symptoms in fibromyalgia, so the combination of $\alpha_2\delta$ ligands with SNRIs may lead to broader symptom relief than using either alone, although both are effective for pain in fibromyalgia. That is, $\alpha_2\delta$ ligands may reduce symptoms of anxiety in fibromyalgia (see discussion of $\alpha_2\delta$ ligands in anxiety in Chapter 8 and illustrated in Figures 8-17C and 8-18C) and for improving the slow-wave sleep disorder of fibromyalgia (sleep disorders and their treatment are discussed in further detail in Chapter 10). SNRIs can be useful in reducing symptoms of depression and anxiety in fibromyalgia (see Chapter 7 on treatment for mood disorders) and for treating fatigue as well as the cognitive symptoms associated with fibromyalgia, sometimes also called fibro-fog (see Figures 9-8 and 9-9). Problems with executive functioning in a wide variety of clinical conditions are generally linked to inefficient information processing in the dorsolateral prefrontal cortex (DLPFC) where dopamine neurotransmission is important in regulating brain circuits (see Chapter 4 on cognition in schizophrenia and Figure 4-17). This concept of dopaminergic regulation of cognition in the DLPFC and the role of boosting dopamine neurotransmission to improve executive dysfunction is also discussed in Chapter 11 on attention deficit hyperactivity disorder. Since SNRIs increase dopamine concentrations in the DLPFC (see Figure 7-33C), SNRI agents can also potentially improve symptoms of fibro-fog in fibromyalgia patients. This may be particularly so for the SNRIs milnacipran and levomilnacipran, which have potent norepinephrine reuptake binding properties at all clinically effective doses (Figures 7-30 and 7-31), or for higher doses of the SNRIs duloxetine (Figure 7-29), venlafaxine, and desvenlafaxine (Figure 7-28), which act to increase norepinephrine reuptake blocking properties of these agents and thus act to increase concentrations of dopamine in the DLPFC (Figure 7-33C). Other strategies for improving fibro-fog in fibromyalgia patients include the same ones used to treat cognitive dysfunction in depression, and include modafinil, armodafinil, selective norepinephrine reuptake inhibitors (NRIs) such as atomoxetine, norepinephrine–dopamine reuptake inhibitors (NDRIs) such as bupropion, and with caution, stimulants. SNRIs, sometimes augmented with modafinil, stimulants, or bupropion can also be useful for symptoms of physical fatigue as well as mental fatigue in fibromyalgia patients.

Second-line treatments for pain in fibromyalgia can include sedating drugs for depression including mirtazapine and tricyclic antidepressants, as well as the tricyclic muscle relaxant cyclobenzapine. Other sleep aids such as benzodiazepines, hypnotics, and trazodone can be helpful in relieving sleep disturbance in fibromyalgia. Evidence is also accumulating for the efficacy of γ-hydroxybutyrate (GHB or sodium oxybate) in fibromyalgia (use with extreme caution because of diversion and abuse potential). GHB is approved for narcolepsy, enhances slow-wave sleep, and is discussed in Chapter 10 on sleep (see Figures 10-67 and 10-68). In heroic cases the use of GHB by experts for the treatment of severe and treatment-resistant cases of fibromyalgia may be justified. A number of anticonvulsants other than the $\alpha_2\delta$ ligands (Figure 9-16) are also used second-line for chronic neuropathic pain states, including fibromyalgia. These agents are thought to target voltage-gated sodium channels rather than voltage-gated calcium channels and thus seem to have a different mechanism of action than $\alpha_2\delta$ ligands and may be effective in patients with inadequate response to $\alpha_2\delta$ ligands.

SUMMARY

This chapter has defined pain, and has explained the processing of nociceptive neuronal activity into the perception of pain by pathways that lead to the spinal cord, and then up the spinal cord to the brain. Neuropathic pain is discussed extensively, including both peripheral and central mechanisms, and the concept of central sensitization. The key role of descending inhibitory pathways that reduce the activity of nociceptive pain neurons with the release of serotonin and norepinephrine is explained, and shown to be the basis for the actions of serotonin–norepinephrine reuptake inhibitors (SNRIs) as agents that reduce the perception of pain in conditions ranging from major depression to fibromyalgia to diabetic peripheral neuropathic pain, low back pain, osteoarthritis, and related conditions. The critical role of voltage-sensitive calcium channels (VSCCs) is also explained, providing the basis for the actions of $\alpha_2\delta$ ligands as agents that also reduce the perception of pain in diabetic peripheral neuropathic pain, fibromyalgia, painful physical symptoms of depression and anxiety disorders, shingles, and other neuropathic pain conditions. Finally, the spectrum of conditions from affective disorders to chronic neuropathic pain disorders is introduced, with emphasis on the condition of fibromyalgia and its newly evolving psychopharmacological treatments.

10 Disorders of Sleep and Wakefulness and Their Treatment: Neurotransmitter Networks for Histamine and Orexin

Neurobiology of Sleep and Wakefulness 402
The Arousal Spectrum 402
Histamine 402
Orexins/Hypocretins 406
Pathways of Arousal and Sleep for the Sleep/Wake Cycle 408
Ultradian Cycles 413
Neurotransmitters and the Ultradian Sleep Cycle 414
Why Do We Sleep? Can't I Sleep When I Die? 414
Insomnia 418
What Is Insomnia? 418
Diagnosis and Comorbidities 418
Treating Insomnia: Drugs with Hypnotic Actions 421
Benzodiazepines ($GABA_A$ Positive Allosteric Modulators) 421
Z Drugs ($GABA_A$ Positive Allosteric Modulators) 422
Dual Orexin Receptor Antagonists (DORAs) 423
Serotonergic Hypnotics 424
Histamine 1 Antagonists as Hypnotics 425
Anticonvulsants as Hypnotics 426
Hypnotic Actions and Pharmacokinetics: Your Sleep Is at the Mercy of Your Drug Levels! 426
Behavioral Treatments of Insomnia 430
Excessive Daytime Sleepiness 430
What Is Sleepiness? 430
Causes of Hypersomnia 431
Circadian Rhythm Disorders 435
Wake-Promoting Agents and Treatment of Excessive Daytime Sleepiness 440
Caffeine 440
Amphetamine and Methylphenidate 441
Modafinil/Armodafinil 442
Solriamfetol, a Wake-Promoting NDRI 444
Pitolisant, H_3 Presynaptic Antagonist 444
Sodium Oxybate and Narcolepsy/Cataplexy 446
Summary 448

This chapter will provide a brief overview of the psychopharmacology of disorders of sleep and wakefulness. Included here are short discussions of the symptoms, diagnostic criteria, and treatments for disorders that cause insomnia, excessive daytime sleepiness, or both. Clinical descriptions and formal criteria for how to diagnose sleep disorders are mentioned here only in passing. The reader should consult standard reference sources for this material. The discussion here will emphasize the links between various brain circuits and their neurotransmitters with disorders that cause insomnia or sleepiness. The goal of this chapter is to acquaint the reader with ideas about the clinical and biological aspects of sleep and wakefulness, how various disorders can alter sleep and wakefulness, and how many new and evolving treatments can resolve the symptoms of insomnia and sleepiness.

The detection, assessment, and treatment of sleep/wake disorders are rapidly becoming standardized parts of a psychiatric evaluation. Modern psychopharmacologists increasingly consider sleep to be a psychiatric "vital sign," thus requiring routine evaluation and symptomatic treatment whenever encountered. This is similar to the earlier discussion in Chapter 9, where pain is also increasingly being considered as another psychiatric "vital sign." That is, disorders of sleep (and pain) are so important, so pervasive, and cut across so many psychiatric conditions that the elimination of these symptoms – no matter what psychiatric disorder may be present – is increasingly recognized as necessary in order to achieve full symptomatic and functional remission for the patient.

Many of the treatments discussed in this chapter are covered in previous chapters. For details of mechanisms of insomnia treatments that are also used for the treatment of depression, the reader is referred to Chapter 7; for those insomnia treatments that are benzodiazepines, the reader is also referred to Chapter 7. For various hypersomnia treatments, especially stimulants, the reader is referred to Chapter 11 on attention deficit hyperactivity disorder (ADHD) and to Chapter 13 on impulsivity, compulsivity, and addiction

for additional information. The discussion in this chapter is at the conceptual level, and not at the pragmatic level. The reader should consult standard drug handbooks (such as *Stahl's Essential Psychopharmacology: the Prescriber's Guide*) for details of doses, side effects, drug interactions, and other issues relevant to the prescribing of these drugs in clinical practice.

NEUROBIOLOGY OF SLEEP AND WAKEFULNESS

The Arousal Spectrum

Although many experts approach insomnia and sleepiness by emphasizing the separate and distinct *disorders* that cause them, many pragmatic psychopharmacologists approach insomnia or excessive daytime sleepiness as important *symptoms* that cut across many conditions and that occur along a spectrum from deficient arousal to excessive arousal (Figure 10-1). In this conceptualization, an awake, alert, creative, and problem-solving person has the right balance between too much and too little arousal (baseline brain functioning in the middle of the spectrum in Figure 10-1). As arousal increases beyond normal, during the day there is hypervigilance (Figure 10-1); if this increased arousal occurs at night, there is insomnia (Figure 10-1, overactivation of the brain). From a treatment perspective, insomnia can be conceptualized as a disorder of excessive arousal, with drugs having hypnotic actions moving the patient from too much arousal to sleep (specific drugs with hypnotic actions discussed below).

On the other hand, as arousal diminishes, symptoms crescendo from mere inattentiveness to more severe forms of cognitive disturbances until the patient has excessive daytime sleepiness with sleep attacks (Figure 10-1, hypoactivation of the brain). From a treatment perspective, sleepiness can be conceptualized as a disorder of deficient arousal, with wake-promoting agents moving the patient from too little arousal to awake with normal alertness (specific wake-promoting agents are discussed below).

Note in Figure 10-1 that cognitive disturbance is the product of both too little as well as too much arousal, consistent with the need for cortical pyramidal neurons to be optimally "tuned," with too much activity making them just as out of tune as too little. Note also in Figure 10-1 that the arousal spectrum is linked to the actions of several neurotransmitters that will be explained in detail in the following paragraphs (i.e., histamine, orexin, dopamine, norepinephrine, serotonin, acetylcholine, and γ-aminobutyric acid [GABA]). Several of these neurotransmitter circuits as a group are called the ascending reticular activating system, because they are known to work together to regulate arousal. This was discussed in Chapter 5 and illustrated for histamine, dopamine, and norepinephrine in Figure 5-14. This same ascending neurotransmitter system is blocked at several sites by many agents that cause sedation (see Chapter 5 and Figures 5-8 and 5-13). Figure 10-1 also shows that excessive arousal can extend past insomnia to panic, hallucinations, and all the way to frank psychosis (far right-hand side of the spectrum).

Histamine

Histamine is one of the key neurotransmitters regulating wakefulness, and is the ultimate target of many wake-promoting drugs (via enhancement of histamine release) and sleep-promoting drugs (antihistamines that block histamine at H_1 receptors). Histamine is produced from the amino acid histidine, which is taken up into histamine neurons and converted into histamine by the enzyme histidine decarboxylase (Figure 10-2). Histamine's action is terminated by two enzymes working in sequence: histamine *N*-methyltransferase, which converts histamine to *N*-methylhistamine, and monoamine oxidase B (MAO-B), which converts *N*-methylhistamine into *N*-MIAA (*N*-methylindoleacetic acid), an inactive substance (Figure 10-3). Additional enzymes such as diamine oxidase can also terminate histamine action outside the brain. Note that there is no apparent reuptake pump for histamine. Thus, histamine is likely to diffuse widely away from its synapse, just like dopamine does in the prefrontal cortex.

There are a number of histamine receptors (Figures 10-4 through 10-7). The postsynaptic histamine 1 (H_1) receptor is best known (Figure 10-5) because it is the target of "antihistamines" (i.e., H_1 antagonists) (see below). When histamine itself acts at H_1 receptors, it activates a G-protein-linked second-messenger system that activates phosphatidylinositol, and the transcription factor cFOS, and results in wakefulness, normal alertness, and pro-cognitive actions (Figure 10-5). When these H_1 receptors are blocked in the brain, this interferes with the wake-promoting actions of histamine, and thus can cause sedation, drowsiness, or sleep (see below).

Histamine 2 (H_2) receptors, best known for their actions in gastric acid secretion and the target of a number of anti-ulcer drugs, also exist in the brain (Figure 10-6). These postsynaptic receptors also activate a G-protein second-messenger system with cyclic adenosine monophosphate (cAMP), phosphokinase A (PKA), and the gene product CREB. The function of H_2

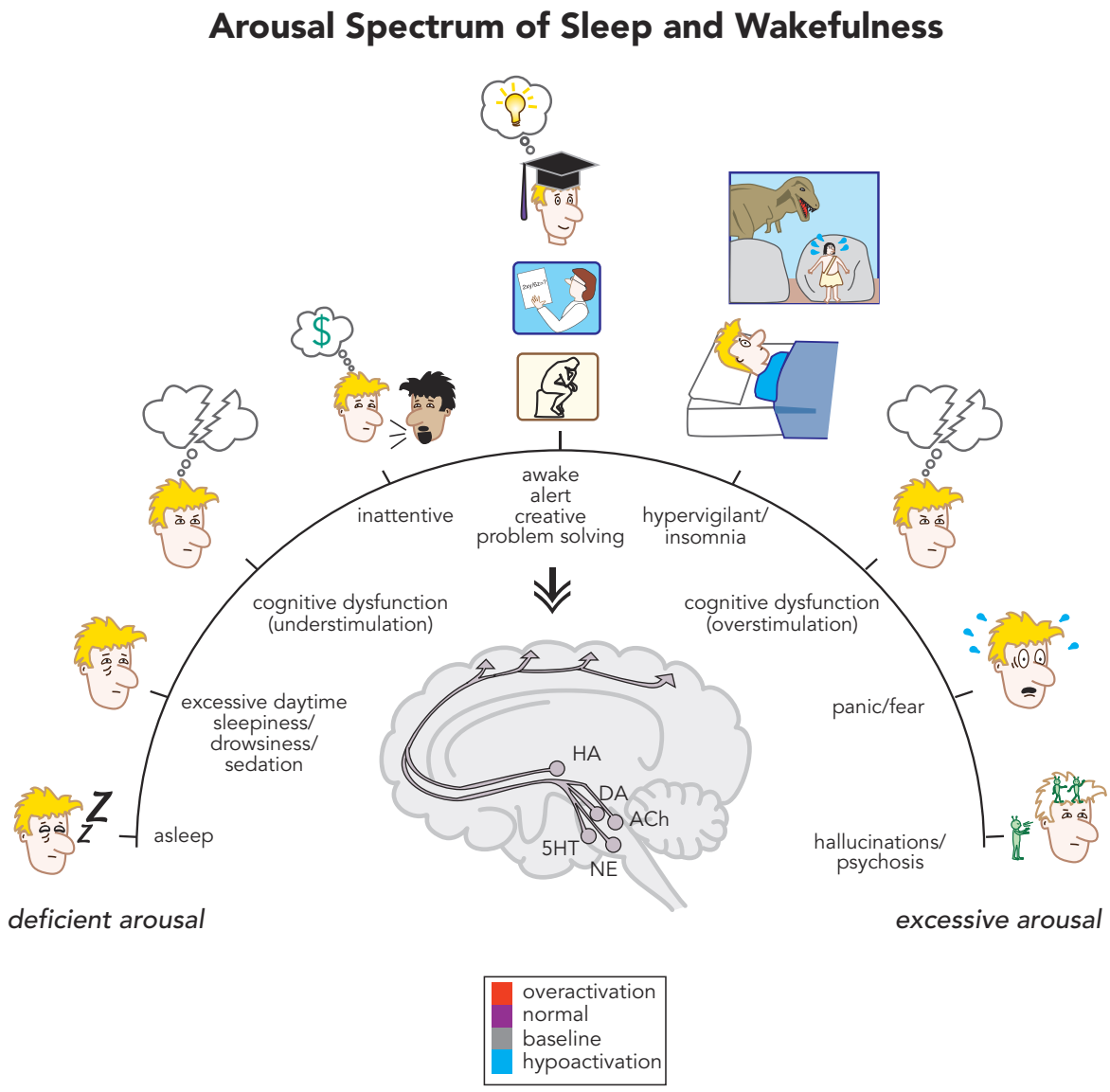


Figure 10-1 **Arousal spectrum of sleep and wakefulness.** One's state of arousal is more complicated than simply being "awake" or "asleep." Rather, arousal exists as if on a dimmer switch, with many phases along the spectrum. Where on the spectrum one lies is influenced by several key neurotransmitters: histamine (HA), dopamine (DA), norepinephrine (NE), serotonin (5HT), and acetylcholine (ACh) (all shown) as well as GABA (γ-aminobutyric acid) and orexin (not shown). When there is good balance between too much and too little arousal – depicted by the gray (baseline) color of the brain – one is awake, alert, and able to function well. As the dial shifts to the right there is too much arousal, which may cause hypervigilance and consequently insomnia at night. As arousal further increases this can cause cognitive dysfunction, panic, and in extreme cases perhaps even hallucinations. On the other hand, as arousal diminishes individuals may experience inattentiveness, cognitive dysfunction, sleepiness, and ultimately sleep.

receptors in brain is still being clarified, but apparently is not linked directly to wakefulness.

A third histamine receptor is present in brain, namely the H_3 receptor (Figure 10-7). Histamine H_3 receptors are presynaptic (Figure 10-7A) and function as autoreceptors (Figure 10-7B). That is, when histamine binds to these receptors, it turns off further release of histamine (Figure 10-7B). One novel approach to new wake-promoting and pro-cognitive drugs is to block these receptors, thus facilitating the release of histamine, allowing histamine to act at H_1 receptors to produce the desired effects (see below).

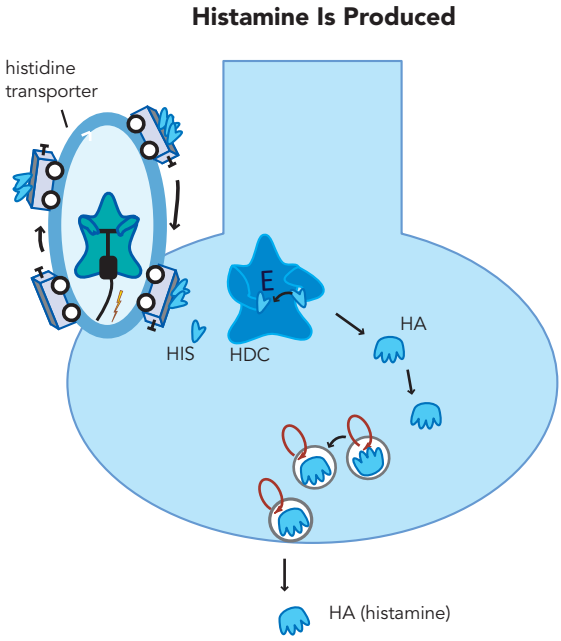


Figure 10-2 Histamine is produced. Histidine (HIS), a precursor to histamine, is taken up into histamine nerve terminals via a histidine transporter and converted into histamine by the enzyme histidine decarboxylase (HDC). After synthesis, histamine (HA) is packaged into synaptic vesicles and stored until its release into the synapse during neurotransmission.

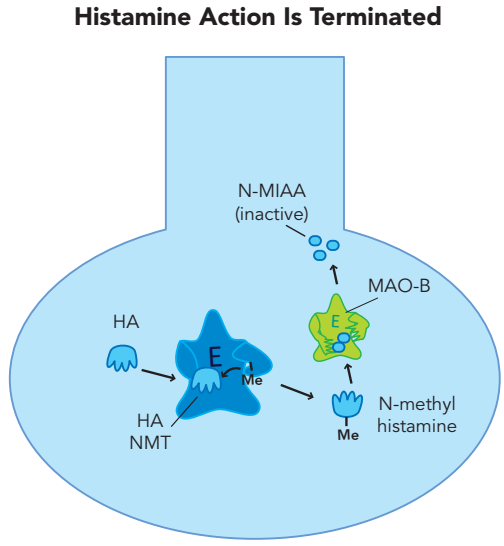


Figure 10-3 Histamine's action is terminated. Histamine can be broken down intracellularly by two enzymes. Histamine *N*-methyltransferase (HA NMT) converts histamine into *N*-methylhistamine, which is then converted by monoamine oxidase B (MAO-B) into the inactive substance *N*-methylindoleacetic acid (*N*-MIAA). Note that there is no apparent reuptake transporter for histamine; thus, histamine that is released into the synapse can diffuse widely.

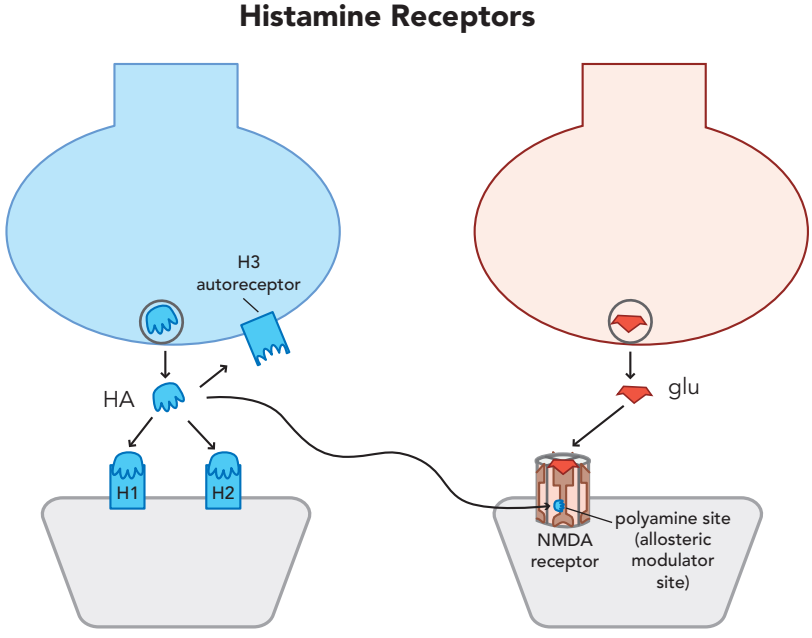


Figure 10-4 Histamine receptors. Shown here are receptors for histamine that regulate its neurotransmission. Histamine 1 and histamine 2 receptors are postsynaptic, while histamine 3 receptors are presynaptic autoreceptors. There is also a binding site for histamine on glutamatergic NMDA (*N*-methyl-D-aspartate) receptors – it can act at the polyamine site, which is an allosteric modulatory site.

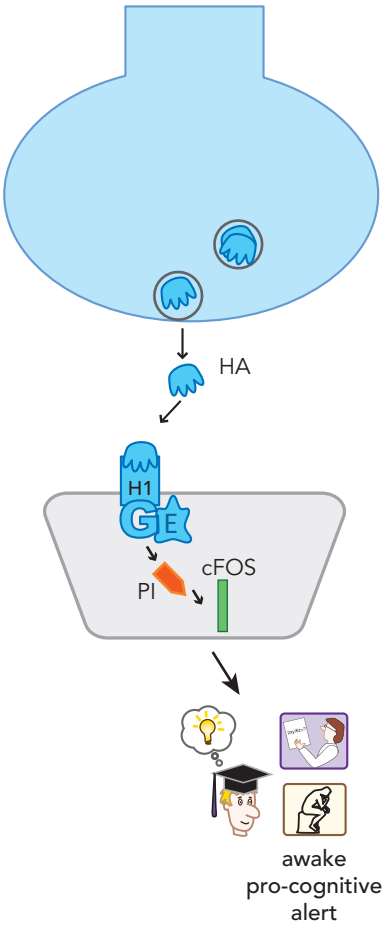


Figure 10-5 Histamine 1 receptors. When histamine binds to postsynaptic histamine 1 (H_1) receptors, it activates a G-protein-linked second-messenger system that activates phosphatidylinositol (PI) and the transcription factor cFOS. This results in wakefulness and normal alertness.

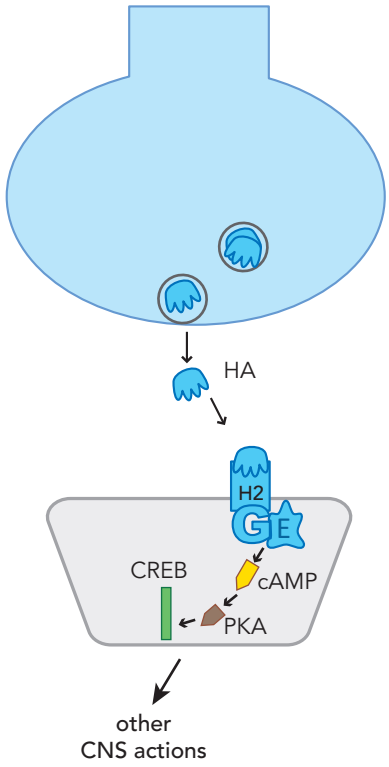


Figure 10-6 Histamine 2 receptors. Histamine 2 (H_2) receptors are present both in the body and in the brain. When histamine binds to postsynaptic H_2 receptors it activates a G-protein-linked second-messenger system with cyclic adenosine monophosphate (cAMP), phosphokinase A (PKA), and the gene product CREB. The function of H_2 receptors in the brain is not yet elucidated but does not appear to be directly linked to wakefulness.

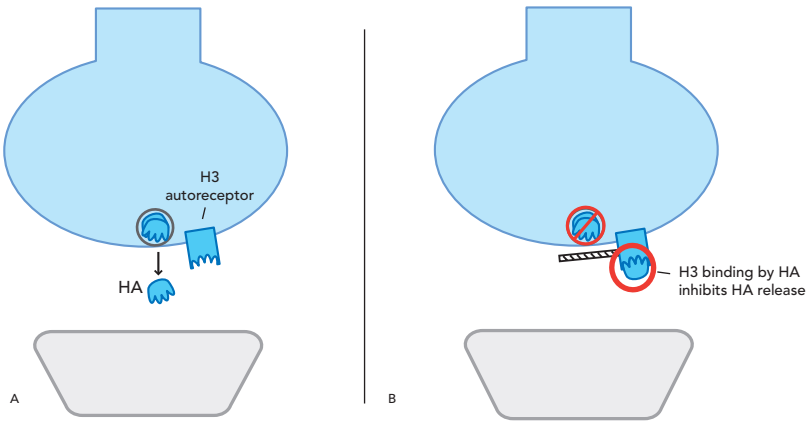


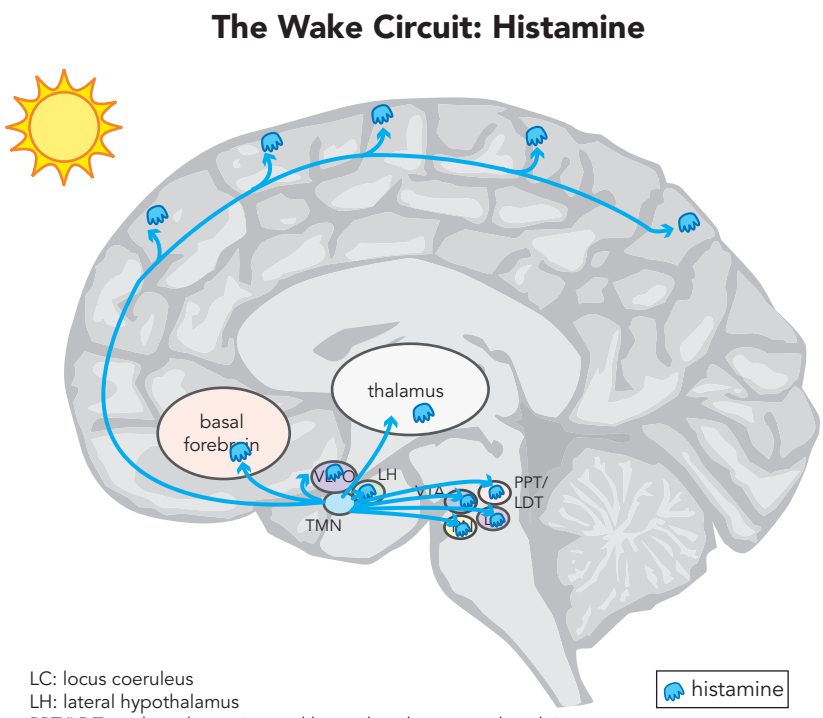
Figure 10-7 Histamine 3 receptors. Histamine 3 (H_3) receptors are presynaptic autoreceptors and function as gatekeepers for histamine. (A) When H_3 receptors are not bound by histamine, the molecular gate is open and allows histamine release. (B) When histamine binds to the H_3 receptor, the molecular gate closes and prevents histamine from being released.

There is a fourth type of histamine receptor, H_4, but these are not known to occur in the brain. Finally, histamine acts also at NMDA (*N*-methyl-D-aspartate) receptors (Figure 10-4). Interestingly, when histamine diffuses away from its synapse to a glutamate synapse containing NMDA receptors, it can act at an allosteric modulatory site called the polyamine site, to alter the actions of glutamate at NMDA receptors (Figure 10-4). The role of histamine and function of this action are not well clarified.

Histamine neurons all arise from a single small area of the hypothalamus known as the tuberomammillary nucleus (TMN) (Figure 10-8), which regulates arousal. Thus, histamine plays an important role in arousal, wakefulness, and sleep. The TMN is a small bilateral nucleus that provides histaminergic input to most brain regions and to the spinal cord (Figure 10-8).

Orexins/Hypocretins

These are peptide neurotransmitters with two names because two different groups of scientists simultaneously discovered them, and named them differently. One group reported the discovery of neurotransmitters in the lateral hypothalamus that were oddly similar to the gut hormone secretin, a member of the incretin family, so they named it "hypocretin" to stand for a hypothalamic member of the incretin family. At the same time, another group reported the discovery of the "orexins" to reflect the orexigenic (appetite-simulating) activity of these neurotransmitter peptides. Soon it was realized that these were the same neurotransmitters: excitatory neuropeptides with approximately 50% sequence identity produced by cleavage of a single precursor protein to form orexin A with 33 amino acids and orexin B with 28 amino acids. This nomenclature can certainly be confusing but many now recognize the history of the discovery of hypocretin by using "hypocretin" to refer to the gene or genetic products and "orexins" to refer to the peptide neurotransmitters themselves. The use of both terms remains a practical necessity because "HCRT" is the standard gene symbol in databases and "OX" is used to refer to the pharmacology of the peptide system by international societies.



LC: locus coeruleus
LH: lateral hypothalamus
PPT/LDT: pedunculopontine and laterodorsal tegmental nuclei
RN: raphe nuclei
TMN: tuberomammillary nucleus
VLPO: ventrolateral preoptic area
VTA: ventral tegmental area

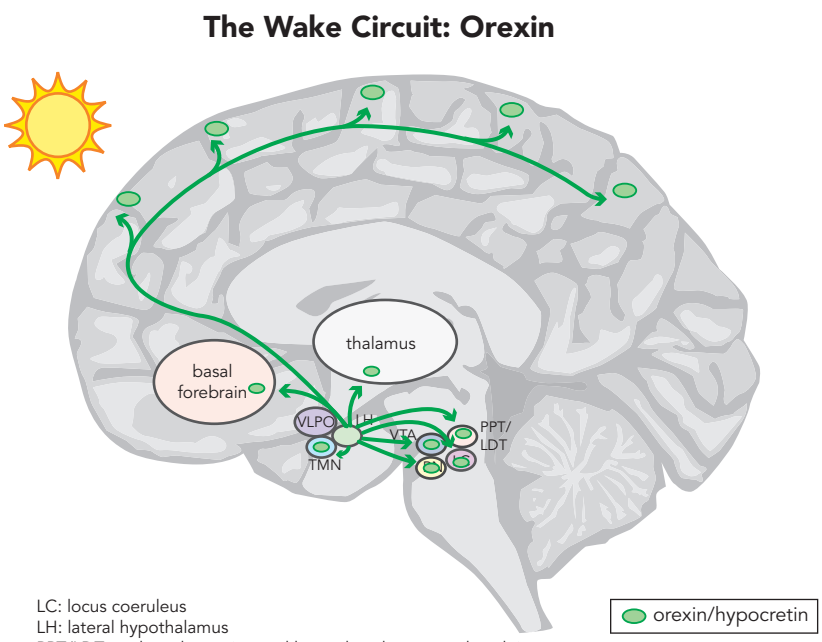
Figure 10-8 Histamine projections and wakefulness. In the brain, histamine is produced solely by cells in the tuberomamillary nucleus (TMN) of the hypothalamus. From the TMN, histaminergic neurons project to most brain regions; those relevant for wakefulness include the prefrontal cortex, the basal forebrain, the thalamus, and brainstem neurotransmitter centers, as well as the ventrolateral preoptic area and lateral hypothalamus.

Orexin/hypocretin neurons are localized exclusively in certain hypothalamic areas (lateral hypothalamic area, perifornical area, and posterior hypothalamus) (Figure 10-9). These hypothalamic neurons degenerate in a condition called narcolepsy, characterized by the inability to stabilize wakefulness and thus sleep attacks in the daytime. Loss of these neurons causes the inability of orexin to be produced and released downstream on wake-promoting neurotransmitter centers and thus lack of stabilizing wakefulness. Treatment of narcolepsy is discussed below.

Orexin/hypocretin neurons in the hypothalamus make two neurotransmitters: orexin A and orexin B, which are released from their neuronal projections all over the brain (Figures 10-9 and 10-10), but especially in the monoamine neurotransmitter centers in the brainstem (Figure 10-9). The postsynaptic actions of the orexins are mediated by two receptors called orexin 1 and orexin 2 (Figure 10-11). Orexin A is capable of interacting with both receptors, whereas the neurotransmitter orexin B binds selectively to the orexin 2 receptor (Figure 10-11). The binding of orexin A to the orexin 1 receptor leads to increased intracellular calcium as well as activation of the sodium/calcium exchanger (Figure 10-11). The binding of orexin A or B to orexin 2 receptors leads to increased expression of *N*-methyl-D-aspartate (NMDA) glutamate receptors as well as inactivation of G-protein-regulated inwardly rectifying potassium (GIRK) channels (Figure 10-11).

In addition to their role in stabilizing wakefulness, orexins also are thought to regulate feeding behavior, reward, and other behaviors (Figure 10-12). During periods of wakefulness, orexin/hypocretin neurons are active and fire with tonic frequency to maintain arousal, but when presented with a stimulus – either external, such as an escapable stressor, or internal, such as elevated blood CO_2 levels – orexin neurons exhibit a more rapid phasic burst firing pattern (Figure 10-12). This excitement of hypocretin/orexin neurons leads to increased activation not only of orexin but of all the other brain areas that orexin stimulates, hypothetically leading in turn to execution of appropriate behavioral responses such as attainment of reward or the avoidance of potential danger. In this way, the hypocretin/orexin system not only mediates wakefulness, but also allows for the facilitation of goal-directed, motivated behaviors, including increased food intake in response to hunger (Figure 10-12).

Orexin 1 receptors are highly expressed in the noradrenergic locus coeruleus, whereas orexin 2



LC: locus coeruleus
LH: lateral hypothalamus
PPT/LDT: pedunculopontine and laterodorsal tegmental nuclei
RN: raphe nuclei
TMN: tuberomammillary nucleus
VLPO: ventrolateral preoptic area
VTA: ventral tegmental area

Figure 10-9 Orexin/hypocretin projections and wakefulness. The neurotransmitter orexin (also called hypocretin) is made by cells located in the hypothalamus, specifically in the lateral hypothalamic area as well as the perifornical and posterior hypothalamus. From the hypothalamus, orexinergic neurons project to various brain areas, including the hypothalamic tuberomammillary nucleus (TMN), the basal forebrain, the thalamus, and brainstem neurotransmitter centers.

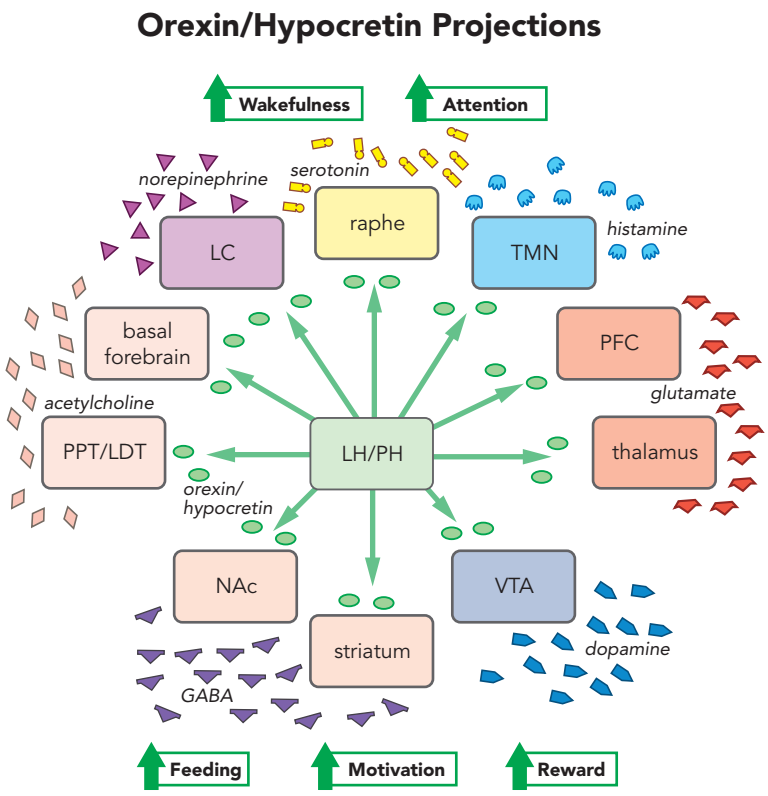


Figure 10-10 Orexin/hypocretin projections interact with arousal neurotransmitters. Orexin/hypocretin is released widely in the brain, interacting with all the arousal neurotransmitters to stabilize wakefulness and regulate attention. Orexin is also involved in other behaviors, including feeding, motivation, and reward. LH/PH, lateral hypothalamus/posterior hypothalamus; PPT/LDT, pedunculopontine and laterodorsal tegmental nuclei; LC, locus coeruleus; TMN, tuberomammillary nucleus; PFC, prefrontal cortex; VTA, ventral tegmental area; NAc, nucleus accumbens.

receptors are highly expressed in the histaminergic tuberomammillary nucleus (TMN). It is believed that the effect of orexin/hypocretins on wakefulness is largely mediated by activation of the TMN histaminergic neurons that express orexin 2 receptors. However, orexin receptors and orexin projections to all the arousal neurotransmitter centers make orexins ideally situated to regulate wakefulness indirectly by effects on the multitude of arousal neurotransmitters (see Figures 10-13 through 10-16). Thus, orexins may be not so much arousal neurotransmitters themselves to *cause* wakefulness, but rather serve to *stabilize* wakefulness by interacting with all the arousal neurotransmitters (Figures 10-10 and 10-13 through 10-16). For example, orexin's actions to maintain wakefulness and attention may be mediated by stimulation of *acetylcholine* from the basal forebrain and the pedunculopontine and laterodorsal tegmental (PPT/LDT) nuclei (Figure 10-13); *dopamine* release from the ventral tegmental area (VTA) (Figure 10-14); *norepinephrine* release from the locus coeruleus (LC) (Figure 10-15); *serotonin* release from the raphe nuclei (RN) (Figure 10-16) and *histamine* release from the tuberomammillary nucleus (TMN) (Figure 10-8). Wow!

When circadian drives, homeostatic drives, and darkness all act together at the end of the day and in the dark, orexin levels are low, wakefulness is no longer stabilized, and sleep is promoted from the ventrolateral preoptic area (VLPO) with GABA (γ-aminobutryric acid) neurotransmission enhanced (Figure 10-17), thus inhibiting *all* the wake-promoting neurotransmitter centers (Figures 10-8, 10-13 through 10-16).

Pathways of Arousal and Sleep for the Sleep/Wake Cycle

We have indicated that a multitude of neurotransmitters are involved in the regulation of arousal and have illustrated their pathways in Figures 10-8, 10-9, and 10-13 through 10-17. This regulation results in a daily cycle of sleep and wakefulness mediated by two opposing drives: the *homeostatic sleep drive* and the *circadian wake drive* (Figure 10-18). The homeostatic sleep drive accumulates throughout periods of wakefulness and light and is opposed by the circadian wake drive.

The longer an individual is awake, the greater the homeostatic drive to sleep. The homeostatic sleep drive is dependent upon the accumulation of adenosine, which

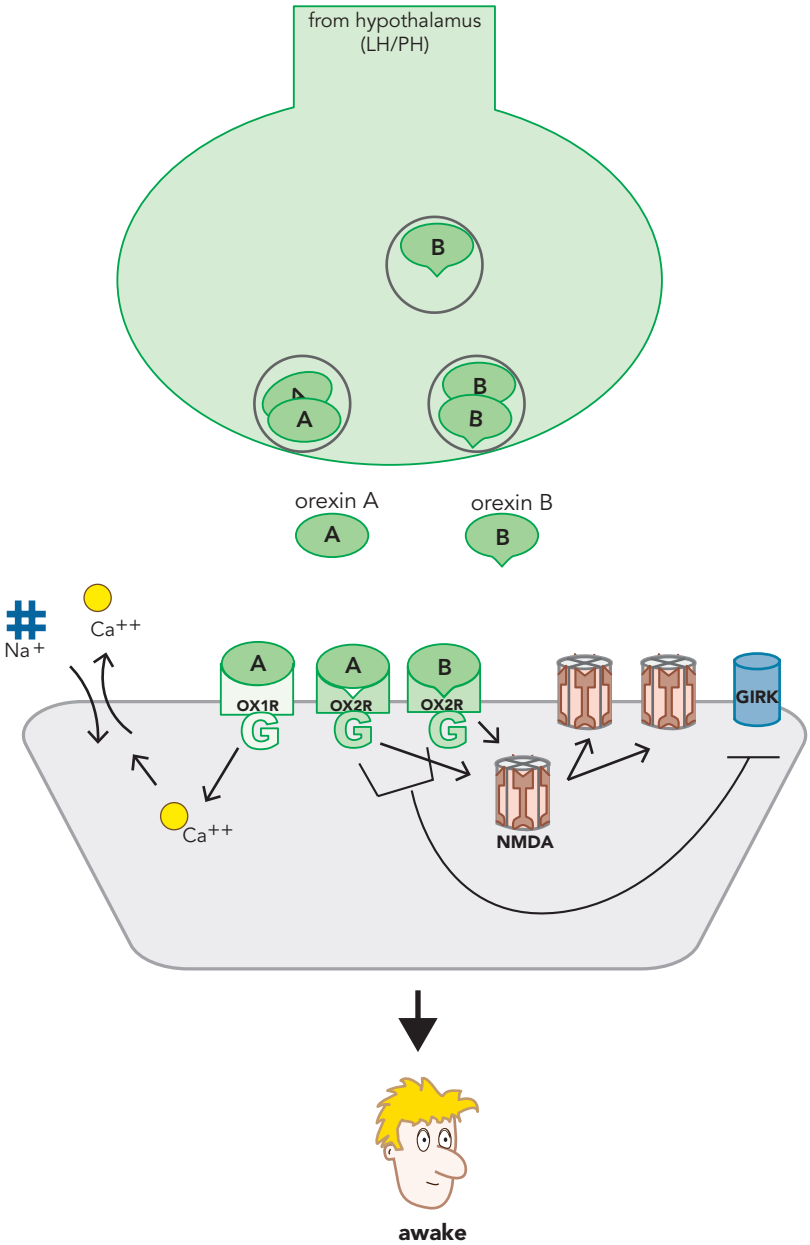


Figure 10-11 Orexin/hypocretin receptors. Orexin/hypocretin neurons make two neurotransmitters: orexin A and orexin B. Orexin neurotransmission is mediated by two types of postsynaptic G-protein-coupled receptors, orexin 1 (OX1R) and orexin 2 (OX2R). Orexin A is capable of interacting with both OX1R and OX2R, whereas orexin B binds selectively to OX2R. Binding of orexin A to OX1R leads to increased intracellular calcium as well as activation of the sodium/calcium exchanger. Binding of orexin A and B to OX2R leads to increased expression of NMDA (*N*-methyl-D-aspartate) glutamate receptors as well as inactivation of G-protein-regulated inward rectifying potassium channels (GIRK). OX1R are particularly expressed in the noradrenergic locus coeruleus whereas OX2R are highly expressed in the histaminergic tuberomammillary nucleus (TMN).

increases as the person tires with fatigue throughout the day, and ultimately leads to the disinhibition of the ventrolateral preoptic (VLPO) nucleus and the release of GABA in the sleep circuit (Figure 10-17), facilitating onset of sleep.

The circadian wake drive, mediated by light acting upon the suprachiasmatic nucleus, stimulates the release of orexin as part of the wake circuit to stabilize wakefulness by enhancing the release of several other wake-promoting neurotransmitters. During periods of light, histamine is released from the tuberomammillary nucleus onto neurons throughout the cortex and in the ventrolateral preoptic area, inhibiting the release of GABA (Figure 10-8). Histamine from the tuberomammillary nucleus also stimulates the release of orexin from the lateral hypothalamus as well as the perifornical area and

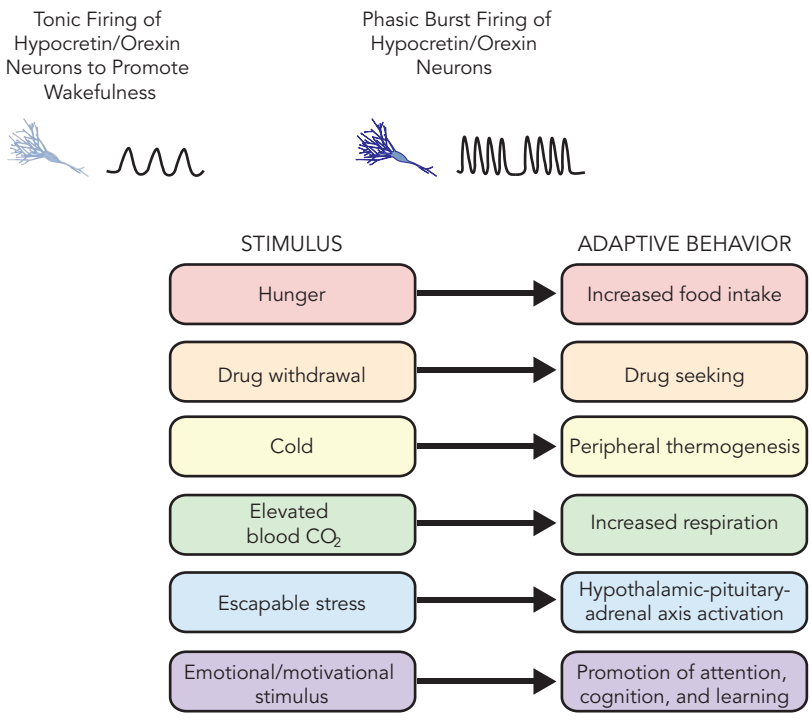


Figure 10-12 **Orexin/hypocretin regulation of adaptive behavior.** During periods of wakefulness, orexin/hypocretin neurons fire with tonic frequency to maintain arousal. When presented with a stimulus, whether internal (e.g., hunger) or external (e.g., an escapable stressor), orexin neurons exhibit a phasic pattern of firing, which leads not only to increased orexin neurotransmission but also to increased activation in brain areas that orexin stimulates. Thus orexin not only mediates wakefulness but also allows for the facilitation of goal-directed behaviors.

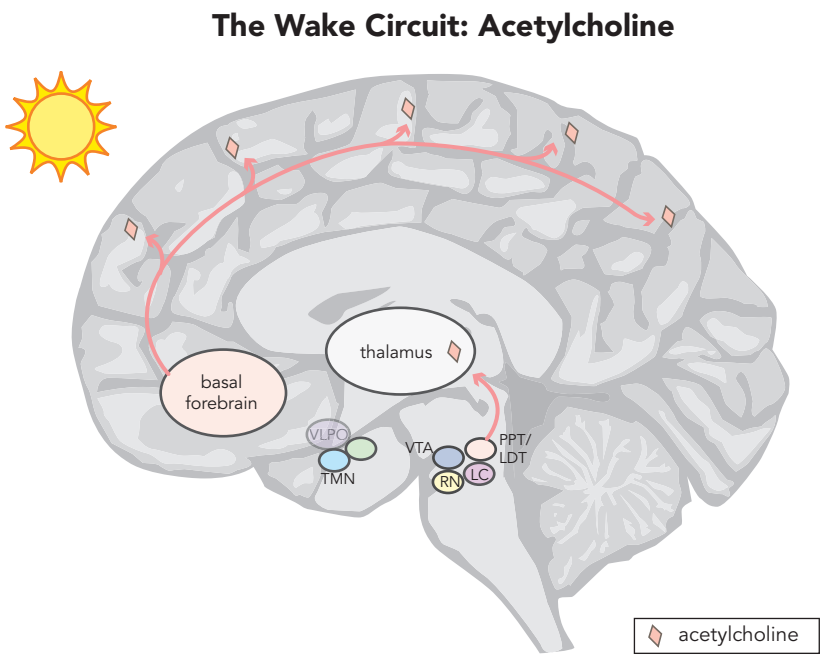


Figure 10-13 **Acetylcholine projections and wakefulness.** Release of acetylcholine from the basal forebrain into cortical areas and from the pedunculopontine and laterodorsal tegmental nuclei (PPT/LDT) onto the thalamus are associated with wakefulness. Orexin/hypocretin may thus stabilize wakefulness through its regulation of acetylcholine (and other arousal neurotransmitters).

LC: locus coeruleus
PPT/LDT: pedunculopontine and laterodorsal tegmental nuclei
RN: raphe nuclei
TMN: tuberomammillary nucleus
VLPO: ventrolateral preoptic area
VTA: ventral tegmental area

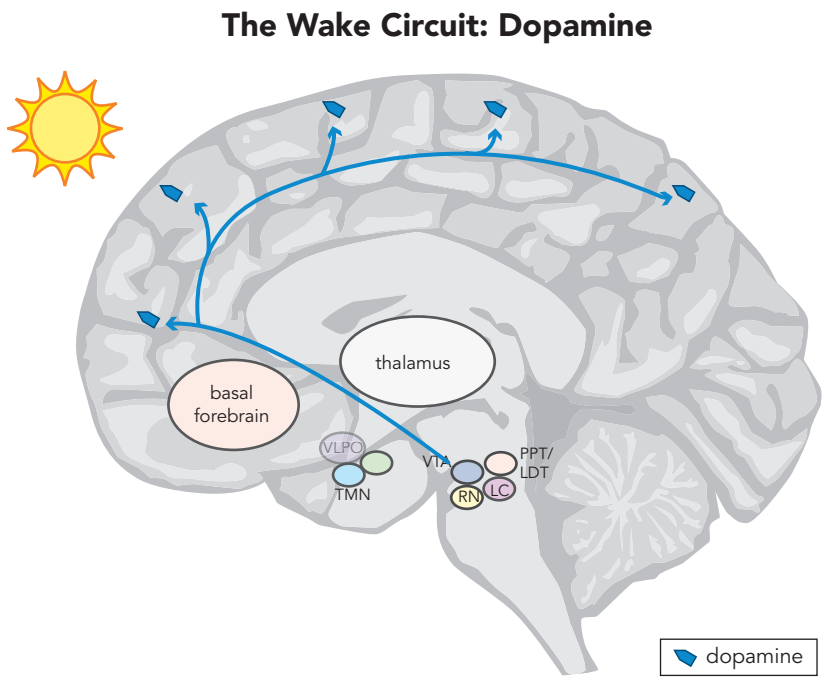


Figure 10-14 Dopamine projections and wakefulness. Release of dopamine from the ventral tegmental area (VTA) into cortical areas is associated with wakefulness. Orexin/hypocretin may thus stabilize wakefulness through its regulation of dopamine (and other arousal neurotransmitters).

LC: locus coeruleus
PPT/LDT: pedunculopontine and laterodorsal tegmental nuclei
RN: raphe nuclei
TMN: tuberomammillary nucleus
VLPO: ventrolateral preoptic area
VTA: ventral tegmental area

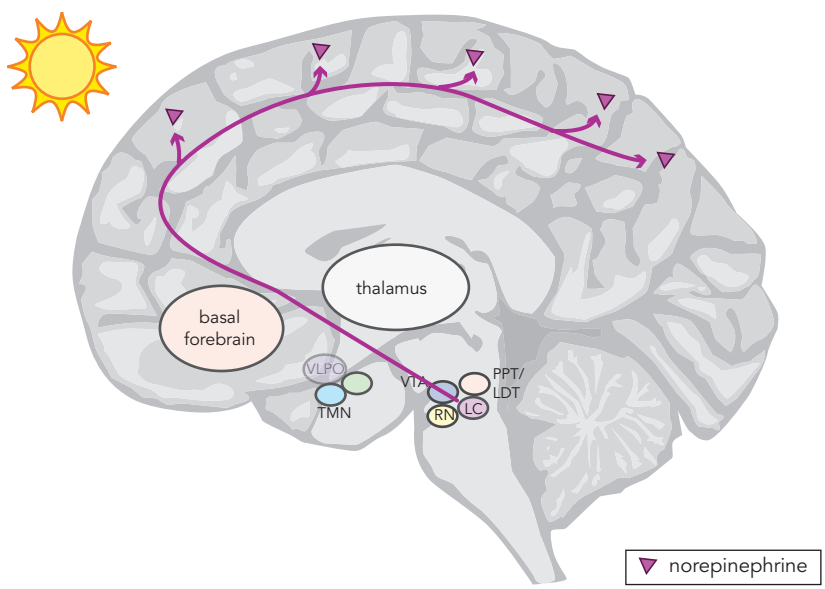
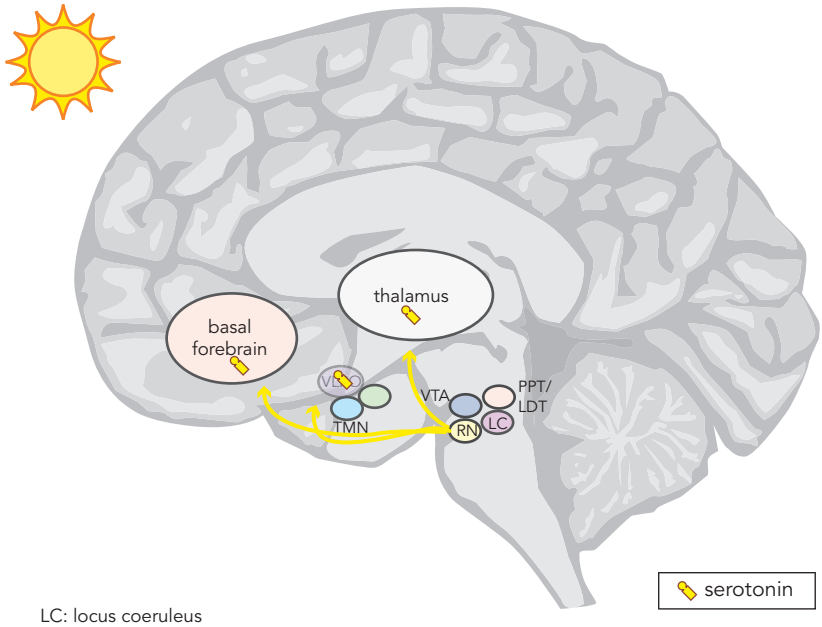


Figure 10-15 Norepinephrine projections and wakefulness. Release of norepinephrine from the locus coeruleus (LC) into cortical areas is associated with wakefulness. Orexin/hypocretin may thus stabilize wakefulness through its regulation of norepinephrine (and other arousal neurotransmitters).

LC: locus coeruleus
PPT/LDT: pedunculopontine and laterodorsal tegmental nuclei
RN: raphe nuclei
TMN: tuberomammillary nucleus
VLPO: ventrolateral preoptic area
VTA: ventral tegmental area

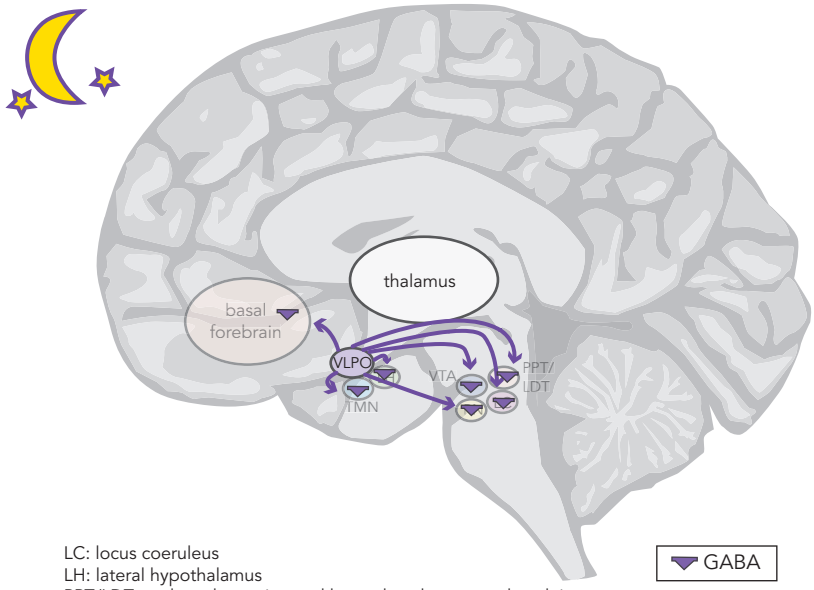
The Wake Circuit: Serotonin



LC: locus coeruleus
PPT/LDT: pedunculopontine and laterodorsal tegmental nuclei
RN: raphe nuclei
TMN: tuberomammillary nucleus
VLPO: ventrolateral preoptic area
VTA: ventral tegmental area

Figure 10-16 Serotonin projections and wakefulness. Release of serotonin from the raphe nucleus (RN) onto the basal forebrain and the thalamus is associated with wakefulness. Orexin/hypocretin may thus stabilize wakefulness through its regulation of serotonin (and other arousal neurotransmitters).

The Sleep Circuit



LC: locus coeruleus
LH: lateral hypothalamus
PPT/LDT: pedunculopontine and laterodorsal tegmental nuclei
RN: raphe nuclei
TMN: tuberomammillary nucleus
VLPO: ventrolateral preoptic area
VTA: ventral tegmental area

Figure 10-17 GABA projections and sleep. GABA (γ-aminobutyric acid) is released from the ventrolateral preoptic nucleus (VLPO) of the hypothalamus onto the tuberomammillary nucleus (TMN), the lateral hypothalamus (LH), the basal forebrain, and neurotransmitter centers. By inhibiting activity in these wake-promoting brain regions, GABA can induce sleep.

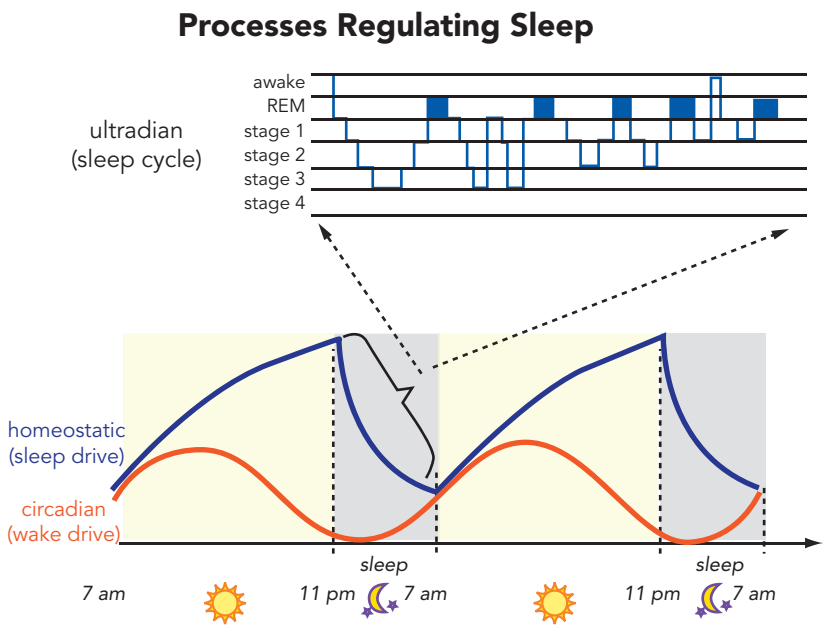


Figure 10-18 **Processes regulating sleep.** The sleep/wake cycle is mediated by two opposing drives: homeostatic sleep drive and circadian wake drive. The circadian wake drive is a result of input (light, melatonin, activity) to the suprachiasmatic nucleus of the hypothalamus, which stimulates the release of orexin to stabilize wakefulness. Homeostatic sleep drive is dependent on the accumulation of adenosine, which increases the longer one is awake and decreases with sleep. Accumulated adenosine leads to disinhibition of the ventrolateral preoptic nucleus and thus the release of GABA in the tuberomammillary nucleus to inhibit wakefulness. As the day progresses, circadian wake drive diminishes and homeostatic sleep drive increases until a tipping point is reached. Sleep itself consists of multiple phases that recur in a cyclical manner; this process is known as the ultradian cycle and depicted at the top of this figure.

the posterior hypothalamus. Then, orexin has a number of knock-on effects:

- Orexin induces the release of acetylcholine from the basal forebrain in cortical areas and from the pedunculopontine and laterodorsal tegmental nuclei onto the thalamus (Figure 10-13)
- Orexin also causes the release of dopamine from the ventral tegmental area onto cortical areas (Figure 10-14)
- Orexin stimulates the release of norepinephrine from the locus coeruleus onto cortical areas (Figure 10-15)
- Finally, orexin also instigates the release of serotonin from the raphe nuclei onto both the basal forebrain and the thalamus (Figure 10-16)

Then, as light fades, norepinephrine from the locus coeruleus and serotonin from the raphe nuclei build up and are released onto neurons in the lateral hypothalamus, causing negative feedback *inhibiting the release of orexin.* Without orexin, wakefulness is no longer stabilized, and the VLPO and GABA take charge and suppress all the arousal neurotransmitters (Figure 10-17). Thus, sleep is facilitated and melatonin is secreted at night in the dark. Then the cycle repeats itself as rest restores homeostatic sleep drive and light initiates wakefulness neurotransmitters.

Ultradian Cycles

In addition to the daily sleep/wake cycle (Figure 10-18), there is also an ultradian sleep cycle (see inset of Figure 10-18; this cycle occurs faster [ultra] than a day [dian] and is thus called ultradian). A complete ultradian sleep cycle (non-REM [rapid eye movement] and REM) lasts approximately 90 minutes and occurs four to five times a night (Figure 10-18, inset). Stages 1 and 2 of sleep make up non-REM sleep, whereas stages 3 and 4 of the sleep cycle are part of deeper, slow-wave sleep. During the normal sleep period, the duration of non-REM sleep is gradually reduced during the night while the duration of REM sleep is increased. REM sleep is characterized by faster activity on an electroencephalogram (EEG) – similar to that seen during periods of wakefulness – as well as distinct eye movements, and peripheral muscle paralysis and loss of muscle tone called atonia. It is during REM sleep that dreaming occurs, and positron emission tomography (PET) studies have shown activation of

the thalamus, the visual cortex, and limbic regions accompanied by reduced metabolism in other regions, such as the dorsolateral prefrontal cortex and the parietal cortex during REM sleep. In contrast, there is overall reduced brain activity during non-REM sleep.

Neurotransmitters and the Ultradian Sleep Cycle

Neurotransmitters (Figures 10-8, 10-9, and 10-13 through 10-17) not only have a role in regulating the daily sleep/wake cycle (Figure 10-18), but also in regulating the various phases of sleep with the ultradian sleep cycle (see inset of Figure 10-18). Thus, neurotransmitters fluctuate not only on a circadian (24-hour) basis, but also throughout the various phases of the sleep cycle every night (Figures 10-19 through 10-22). Not surprisingly, GABA is "on" all night, rising steadily during the first few hours of sleep, plateaus, and then steadily declines before one wakens (Figure 10-19). Also, not surprisingly, the pattern for orexin is exactly the opposite: namely, orexin levels steadily decrease during the first few hours of sleep, plateau, and then steadily increase before one wakens (Figure 10-20). The pattern of the other neurotransmitters is sleep-phase dependent (Figures 10-21 and 10-22). That is, acetylcholine levels fluctuate throughout the sleep cycle, reaching their lowest levels during stage 4 sleep and peaking during REM sleep, tracing the ups and downs between stage 4 and REM every cycle (Figure 10-21). On the other hand, dopamine, norepinephrine, serotonin, and histamine levels demonstrate a different trend. They all act together to peak during stage 2 sleep and are at their lowest during REM sleep (Figure 10-22).

Why Do We Sleep? Can't I Sleep When I Die?

There is still much debate over the purpose of sleep. Some propose that sleep is essential for synaptic growth, while others argue that sleep is necessary for synaptic pruning (Figure 10-23). Regardless of which hypothesis – or some combination of both – is more accurate, it has become increasingly evident that disturbances of the sleep/wake cycle have a detrimental effect on a myriad of physiological and psychiatric functions. Aside from the economic costs of sleep/wake disorders, the risk of cardiometabolic disease, cancer, mental illness, and overall poorer quality of life are all increased when the sleep/wake cycle is disturbed (Figure 10-23). Disturbances in the sleep/wake cycle can have profound effects on cognitive functioning, including impairments in attention, memory deficits, and an inability to process new information (Figure 10-24). In fact, 24 hours of sleep deprivation or chronic short sleep duration (i.e., 4–5 hours per night) results in cognitive impairments equivalent to those seen when legally intoxicated with alcohol. Both REM and non-REM sleep appear to be essential for optimal cognitive functioning, with REM sleep modulating affective memory consolidation and non-REM sleep being critical for declarative and procedural memory. At the neurobiological level, there is evidence that disruption of the sleep/wake cycle impairs hippocampal neurogenesis,

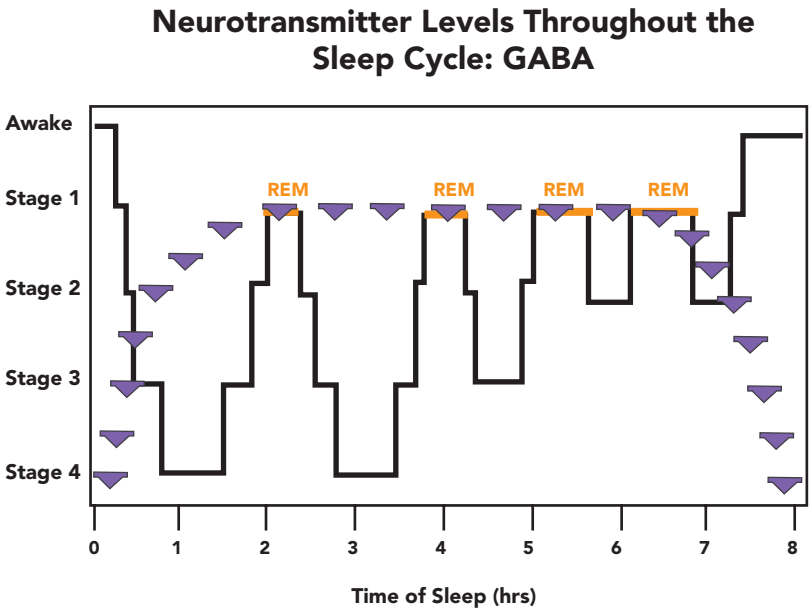


Figure 10-19 GABA levels throughout the sleep cycle. Neurotransmitter levels fluctuate throughout the sleep cycle. GABA levels rise steadily during the first couple of hours of sleep, plateau, and then steadily decline before one wakes.

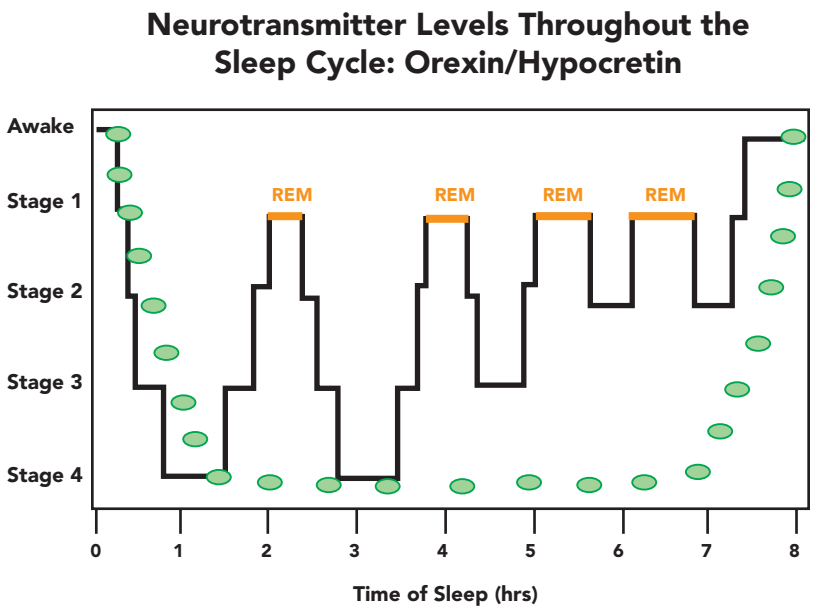


Figure 10-20 Orexin/hypocretin levels throughout the sleep cycle. Neurotransmitter levels fluctuate throughout the sleep cycle. Orexin/hypocretin levels drop rapidly during the first hour of sleep, plateau, and then steadily rise before one wakes.

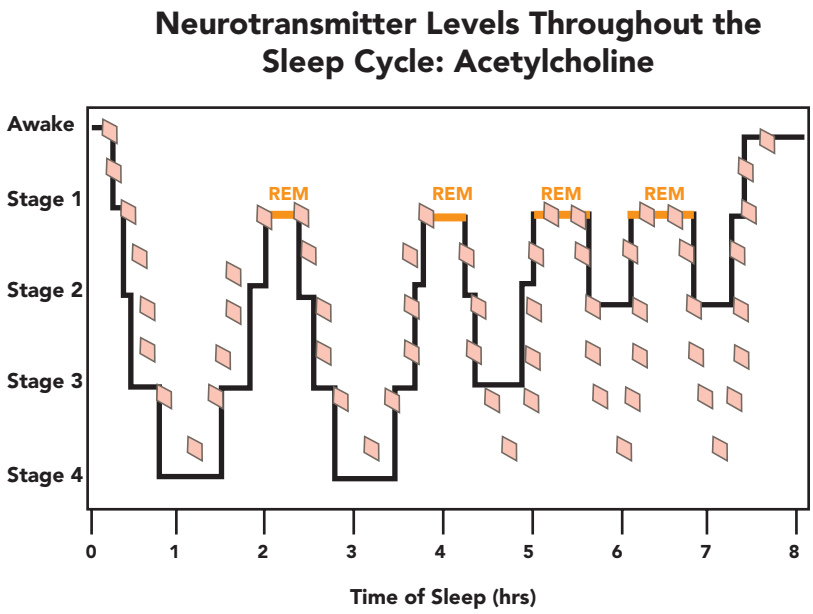


Figure 10-21 Acetylcholine levels throughout the sleep cycle. Neurotransmitter levels fluctuate throughout the sleep cycle. Acetylcholine levels are sleep-phase dependent: they are lowest during stage 4 sleep and at their peak during rapid eye movement (REM) sleep.

which may partly explain the behavioral effects of sleep/wake cycle disturbances on cognition.

In recent years, much interest in the relationship between sleep and cardiometabolic issues such as type 2 diabetes and obesity has been expressed (Figure 10-25). Although much remains unknown, an impaired sleep/wake cycle has been shown to disrupt the circulating levels of both the anorectic (appetite-inhibiting) hormone leptin and the orexigenic (appetite-stimulating) hormone ghrelin (Figure 10-25). These changes lead to dysfunctional insulin, glucose, and lipid metabolism; in turn, this may increase the risk of obesity, type 2 diabetes, and cardiovascular disease. Additionally, an altered sleep/wake cycle has been shown to disturb the natural fluctuations in gut microbiota, perhaps further promoting glucose intolerance and obesity.

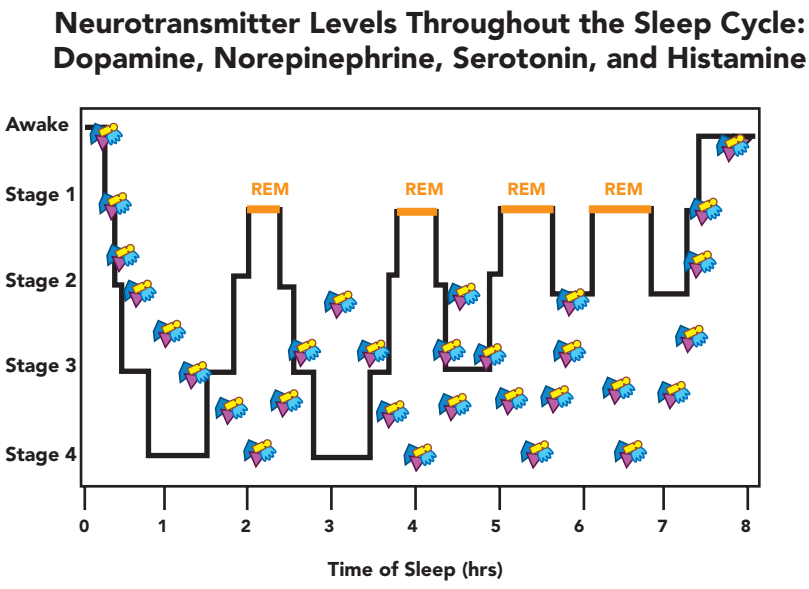


Figure 10-22 **Monoamine levels throughout the sleep cycle.** Neurotransmitter levels fluctuate throughout the sleep cycle. The monoamines dopamine, norepinephrine, serotonin, and histamine are at their lowest levels during rapid eye movement (REM) sleep and peak during Stage 2 sleep.

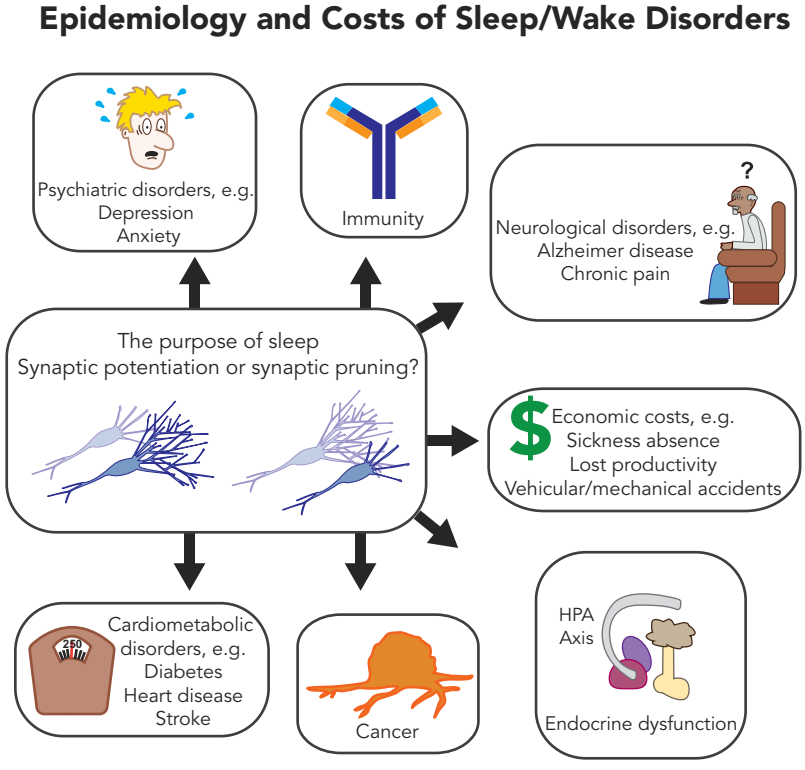


Figure 10-23 **Costs of sleep/wake disorders.** Disturbances in the sleep/wake cycle can have profound influences on both physical and mental health. From a neuropathological perspective, disruption in sleep may affect synaptic potentiation and/or synaptic pruning. Chronically disturbed sleep can increase the risk of mental illness, cardiometabolic disorders, and cancer, as well as disrupt immune and endocrine function. HPA Axis: hypothalamic-pituitary-adrenal axis.

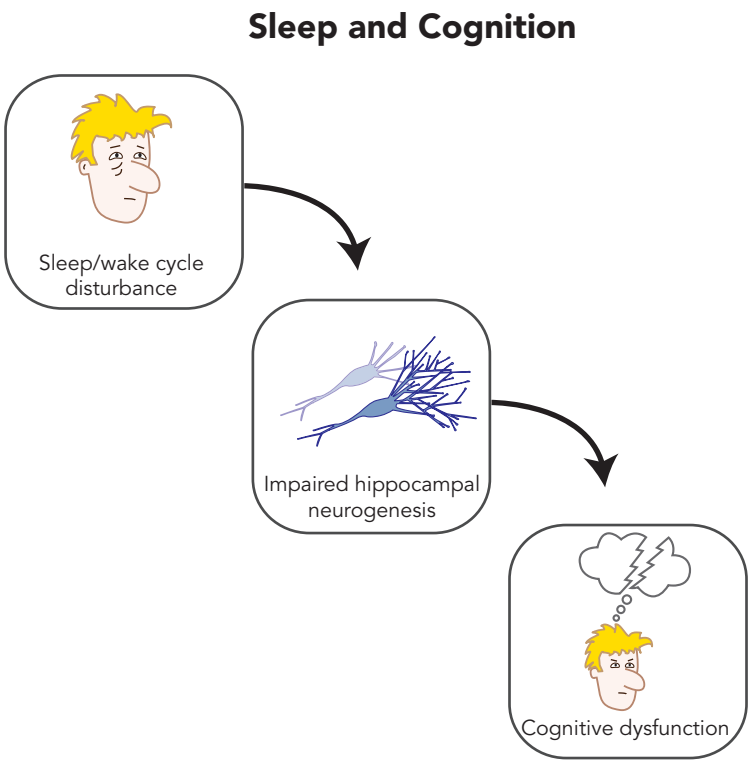


Figure 10-24 Sleep and cognition. Disturbances in the sleep/wake cycle have been shown to impair hippocampal neurogenesis, which may partially explain the profound effects of sleep deprivation on cognitive functioning, including impairments in attention, memory deficits, and an inability to process new information.

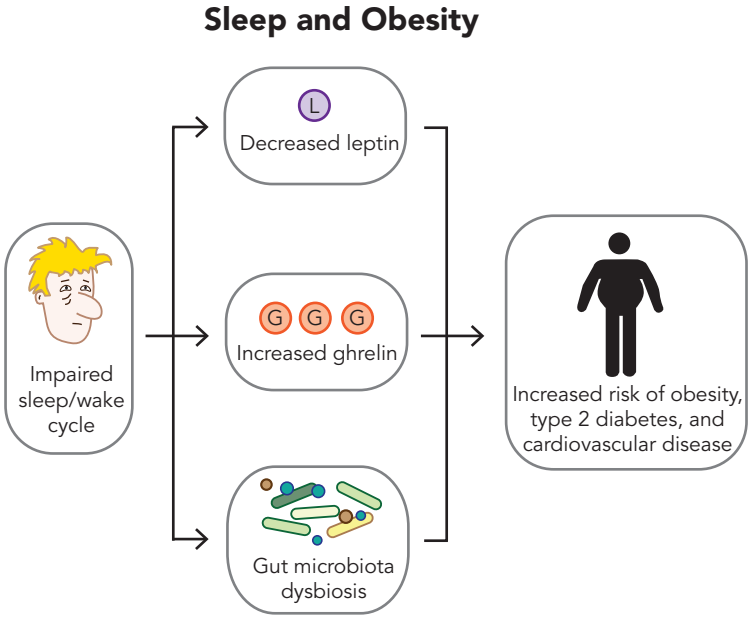


Figure 10-25 Sleep and obesity. Disturbances in the sleep/wake cycle can decrease circulating levels of the appetite-inhibiting hormone leptin and increase circulating levels of the appetite-stimulating hormone ghrelin, as well as contribute to gut microbiota dysbiosis. These changes may lead to increased risk of obesity, type 2 diabetes, and cardiovascular disease.

INSOMNIA

What Is Insomnia?

One way to conceptualize insomnia is being hyperaroused at night (Figure 10-26). It is not well established why some of those with insomnia have hyperarousal at night or how it is mediated, but the most recent evidence from human neuroimaging studies suggests that in insomnia there is not so much an inability of the brain to switch on sleep-related circuits from the VLPO (shown in Figure 10-17) but instead, the inability to switch off arousal-related circuits (shown in Figures 10-8, 10-9, 10-13 through 10-16). Some patients with insomnia at night are also hyperaroused and even anxious in the daytime and despite poor sleep do not necessarily feel sleepy in the daytime. Whatever causes this hyperarousal, whether it is cortical hyperactivity keeping the wake-promoting arousal neurotransmitters from dimming at night, or even an excess of wake-stabilizing orexin keeping them awake, is still under active investigation.

Diagnosis and Comorbidities

Approximately 40 million individuals in the United States suffer from chronic insomnia, and an additional 20 million suffer from episodic insomnia. However, as many as 70% of individuals with insomnia may not report it to their clinician. Many conditions are associated with insomnia, including improper sleep hygiene; medical illness; other sleep/wake disorders, including circadian rhythm disorders, restless legs syndrome, and sleep apnea; effects from medications or substances of abuse; and psychiatric disorders (Figure 10-27). Insomnia may be self-perpetuating in that repeated episodes of wakefulness in bed may become associated with anxiety and sleeplessness. Several biological factors have been associated with insomnia, including increased activation of the autonomic nervous system, abnormal glucose metabolism, decreased GABA levels, reduced nocturnal melatonin secretion, systemic inflammation, and reduced brain volume (Figure 10-28). There are also several genetic factors that have been linked to an increased risk for insomnia (Figure 10-28). Insomnia may be a risk factor for, or a prodromal symptom of, various psychiatric disorders, including depression, anxiety, and substance use disorders (Figure 10-29). Additionally, insomnia due to psychiatric illness, especially depression, may be more likely to persist than insomnia due to other causes. Conversely, patients with depression who complain

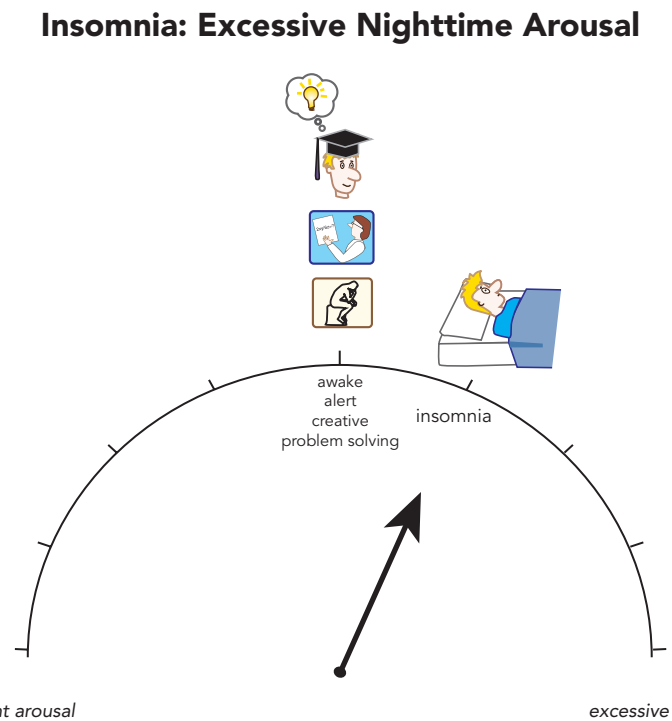


Figure 10-26 Insomnia: excessive nighttime arousal? Insomnia is conceptualized as being related to hyperarousal at night. Recent neuroimaging data suggest that insomnia is the result of an inability to switch off arousal-related circuits, rather than an inability to switch on sleep-related circuits. Some patients with insomnia experience hyperarousal during the day as well.

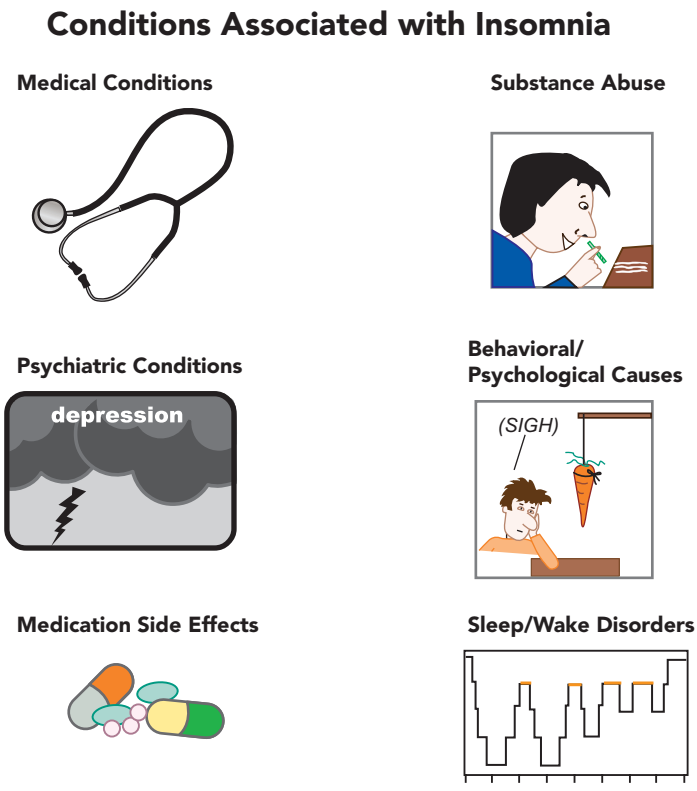


Figure 10-27 **Conditions associated with insomnia.** Numerous conditions are associated with insomnia, including medical conditions, psychiatric disorders, other sleep/wake disorders, and substance use. Insomnia may also be related to medication side effects.

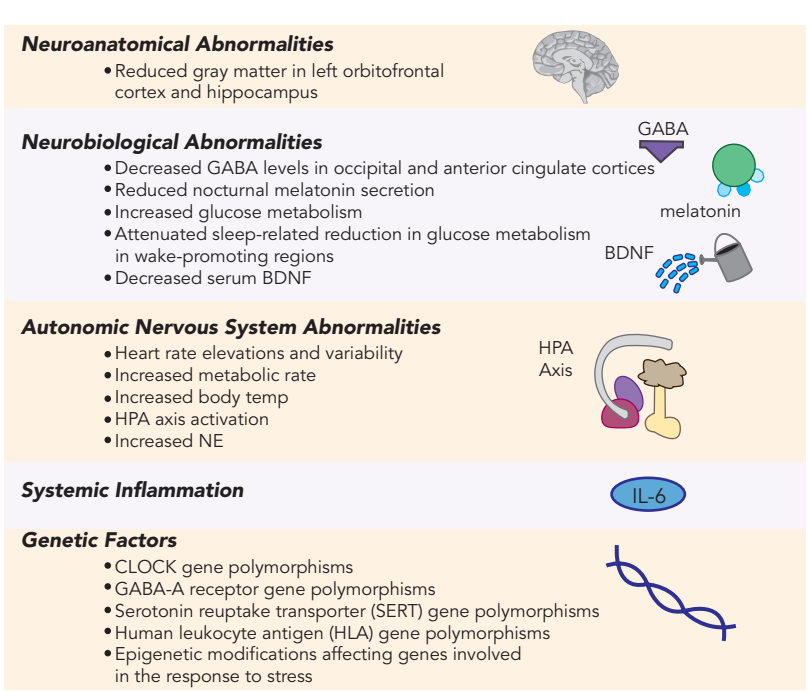


Figure 10-28 **Biology of insomnia.** Numerous neuroanatomical, neurobiological, and autonomic abnormalities have been associated with insomnia. There are also several genetic factors that have been linked to an increased risk for insomnia.

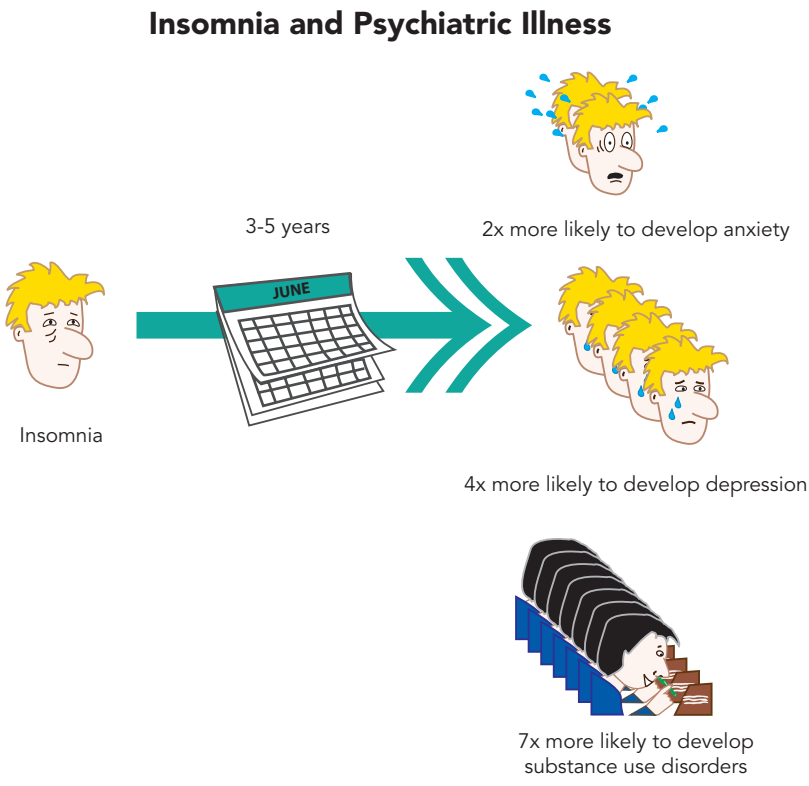


Figure 10-29 **Insomnia and psychiatric illness.** Individuals with insomnia are at increased risk of developing anxiety, depression, and substance use disorders. Whether this reflects insomnia as a risk factor or as a prodromal symptom is unknown.

of insomnia (approximately 70% of individuals with depression) show worse treatment response, increased depressive episodes, and a worse overall long-term outcome.

Insomnia has traditionally been categorized as either "secondary" (i.e., a symptom of a psychiatric or medical illness) or "primary" (i.e., neither associated with a psychiatric or medical illness nor a result of substance abuse or withdrawal) (Figure 10-30). However, it is now more fully understood that insomnia is often a comorbidity rather than a symptom of psychiatric and medical illnesses. The most recent revised DSM-5 diagnostic criteria for insomnia seek to do away with the concepts of secondary and primary insomnia and instead recognize the intricate two-way, perpetuating relationship between insomnia and psychiatric and medical conditions (Figure 10-30). Patients with insomnia often complain of poor sleep quality or duration, difficulty falling asleep, nighttime awakenings, or wake times that are earlier than desired (Figure 10-31). Many patients also report poor restoration from their sleep and thus daytime fatigue, cognitive impairments, and mood disturbances.

Polysomnography is not generally indicated for the diagnosis of insomnia but may be useful for ruling out narcolepsy, restless legs syndrome (RLS), or obstructive sleep apnea (OSA). Although subjective measures of sleep duration often do not correlate with objective measures, subjective assessments of sleep are nevertheless important since complaints of short sleep duration are strongly associated with persistent insomnia and can be quite difficult to treat (Figure 10-31). Thus, insomnia can be treated both as a subjective symptom and as an objective disorder of arousal for best outcomes as well as patient satisfaction.

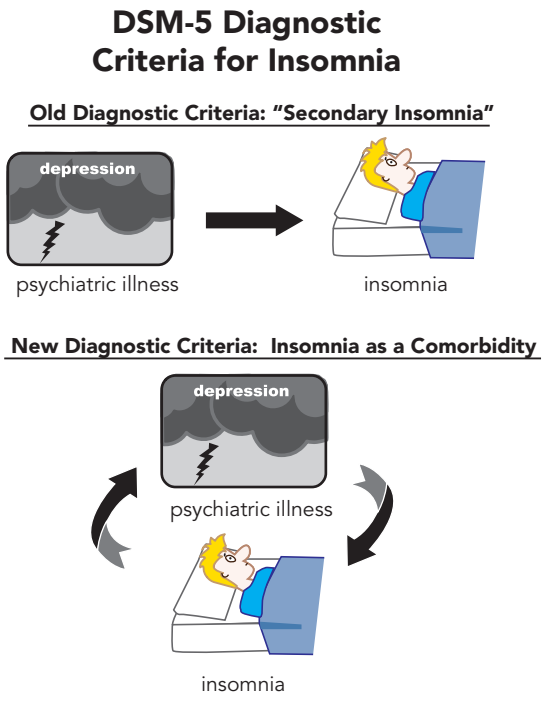


Figure 10-30 **DSM-5 criteria for insomnia.** Insomnia has previously been conceptualized as primary (not related to another condition) or secondary (a symptom of another condition). However, insomnia may more often be comorbid with rather than a symptom of another disorder, a concept that is recognized in the DSM-5.

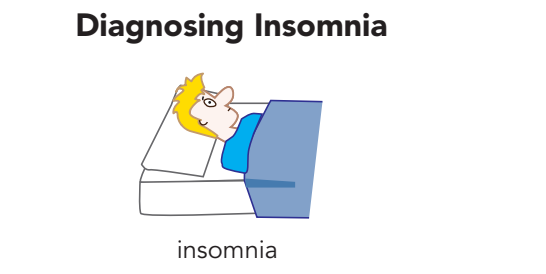


Figure 10-31 **Suggested criteria for identifying insomnia.** Most often, insomnia is diagnosed using subjective measures. This may reflect difficulty falling asleep (sleep latency), wakefulness after sleep onset, poor quality of sleep, and overall reduced duration of sleep.

TREATING INSOMNIA: DRUGS WITH HYPNOTIC ACTIONS

Agents that treat insomnia come in two categories. The first are drugs that reduce brain activation by *enhancing sleep drive* via activation of GABA in the hypothalamic sleep center (VLPO illustrated in Figure 10-17). All drugs in this category are positive allosteric modulators (PAMs) of $GABA_A$ receptors ($GABA_A$ PAMs), i.e., the benzodiazepines and the "Z drugs".

If insomnia is too much arousal drive rather than not enough sleep drive, one wonders if enhancing the sleep drive with the popular benzodiazepine and Z drugs is the best way to go for the treatment of insomnia. Thus, one can also treat insomnia by *reducing arousal*; drugs that do this form the second category of agents for insomnia. Arousal can be reduced by many mechanisms with drugs from this category: namely, by blocking orexins (with dual orexin receptor antagonists or DORAs), by blocking histamine (with H_1 antagonists), by blocking serotonin (with $5HT_{2A}$ antagonists), and by blocking norepinephrine (with α_1 antagonists). No matter what strategy is taken to treat insomnia, the idea is to shift one's abnormal and unwanted arousal state at bedtime from hyperactive to asleep (Figure 10-32).

Benzodiazepines ($GABA_A$ Positive Allosteric Modulators)

There are at least five benzodiazepines approved specifically for insomnia in the US (Figure 10-33), although there are several others approved in different countries. Various benzodiazepines approved for the treatment of anxiety disorders are also frequently used to treat insomnia. Use of benzodiazepines for the treatment of anxiety is discussed in Chapter 8 on anxiety disorders. The mechanism of action of benzodiazepines at $GABA_A$ receptors as positive allosteric modulators (PAMs) is discussed in Chapter 6 and illustrated in Figures 6-17 through 6-23. These drugs presumably act to treat insomnia by facilitating GABA neurotransmission in inhibitory sleep circuits arising from the hypothalamic VLPO (Figure 10-17).

Benzodiazepines bind to only some $GABA_A$ receptors. $GABA_A$ receptors are classified by the specific isoform subunits that they contain, by their sensitivity or insensitivity to benzodiazepines, by whether they mediate tonic or phasic inhibitory neurotransmission, and by whether they are synaptic or extrasynaptic (see Chapter 6 and Figures 6-17 through 6-23). Benzodiazepines,

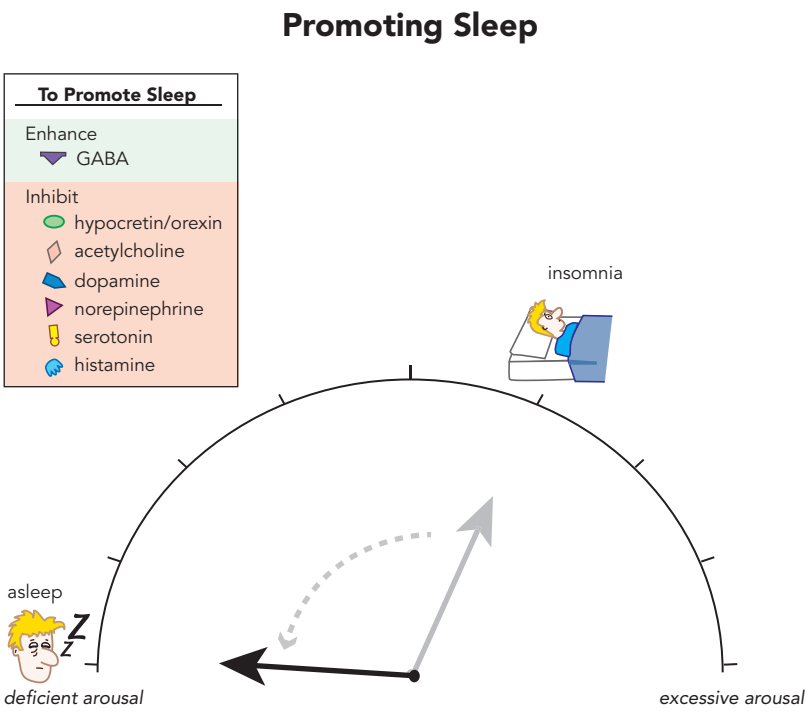


Figure 10-32 **Promoting sleep.** To treat insomnia, one can administer medications that enhance the sleep drive, such as the GABAergic benzodiazepines or Z drugs. Alternatively, one can administer medications that reduce arousal by inhibiting neurotransmission involved in wakefulness; notably, with antagonists at orexin, histamine, serotonin, or norepinephrine receptors.

as well as the related Z drugs discussed below, target those $GABA_A$ receptors that contain a γ subunit, are localized in postsynaptic areas, and mediate phasic inhibitory neurotransmission. For a $GABA_A$ receptor to be sensitive to benzodiazepines or to a Z drug, there must be two β units plus a γ unit of either the γ_2 or γ_3 subtype, plus two α units of either the α_1, α_2, or α_3 subtype (see Chapter 6 and Figure 6-20C). Benzodiazepines and Z drugs bind to a molecular site on the $GABA_A$ receptor that is different from where GABA itself binds (thus allosteric or "other site"). Currently available benzodiazepines are nonselective for $GABA_A$ receptors with different α subunits (Figure 10-33). As discussed in Chapter 6, $GABA_A$ receptors containing a δ subunit are extrasynaptic, mediate tonic neurotransmission, and are insensitive to benzodiazepines and Z drugs.

Because benzodiazepines can cause long-term problems such as loss of efficacy over time (tolerance) and withdrawal effects, including rebound insomnia in some patients that is worse than their original insomnia, they are generally considered second-line agents for use as hypnotic drugs. However, when first-line hypnotic agents (either Z drugs or blockers of various other neurotransmitter receptors) fail to work, benzodiazepines still have a place in the treatment of insomnia, particularly for severe and treatment-resistant insomnia associated with various psychiatric and medical illnesses.

Z Drugs ($GABA_A$ Positive Allosteric Modulators)

Another group of $GABA_A$ positive allosteric modulating drugs, sometimes called "Z drugs" (because they all start with the letter Z: zaleplon, zolpidem, zopiclone), are also prescribed for their hypnotic effects (Figure 10-34). There is debate as to whether Z drugs bind to an allosteric site different from that of benzodiazepines, or whether they bind to the same site but perhaps in a different molecular manner that might produce less tolerance and dependence. Whether or not Z-drug binding differs from benzodiazepine binding at the allosteric site of so-called benzodiazepine-sensitive $GABA_A$ receptors, some Z drugs do bind selectively to α_1 subunits of benzodiazepine-sensitive $GABA_A$ receptors (e.g., zaleplon and zolpidem) (Figure 10-34). By contrast, benzodiazepines (and zopiclone/eszopiclone) bind to four α subunits (α_1, α_2, α_3, and α_5) (Figures 10-33 and 10-34). The functional significance of α_1 selectivity is not yet proven, but may contribute to lower risk of tolerance and dependence. The α_1 subtype is known to be critical for producing sedation and thus is targeted by every effective $GABA_A$ PAM hypnotic, both benzodiazepines

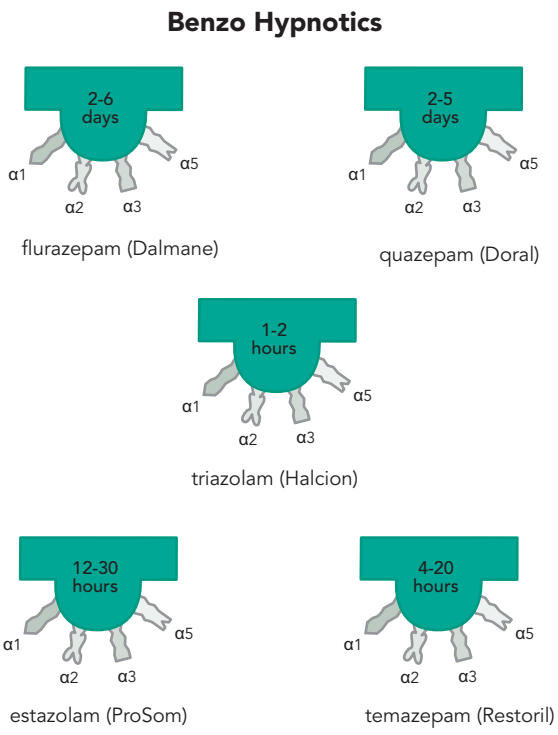


Figure 10-33 **Benzodiazepine hypnotics.** Five benzodiazepines that are approved in the United States for insomnia are shown here. These include flurazepam and quazepam, which have ultra-long half-lives; triazolam, which has an ultra-short half-life; and estazolam and temazepam, which have moderate half-lives. These benzodiazepines are nonselective for $GABA_A$ receptors with different α subunits.

and Z drugs. The α_1 subtype is also linked to daytime sedation, anticonvulsant actions, and possibly to amnesia. Adaptations of this receptor with chronic hypnotic treatments that target it are thought to lead to tolerance and withdrawal. The α_2 receptor and α_3 receptor subtypes are linked to anti-anxiety, muscle relaxant, and alcohol-potentiating actions. Finally, the α_5 subtype, mostly in the hippocampus, may be linked to cognition and other functions.

Multiple versions for two of the Z drugs, zolpidem and zopiclone, are available for clinical use. For zolpidem, a controlled-release formulation known as zolpidem CR (Figure 10-34) extends the duration of action of zolpidem immediate release from about 2–4 hours to a more optimized duration of 6–8 hours, improving sleep maintenance. An alternative dosage formulation of zolpidem for sublingual administration with faster onset and given at a fraction of the usual nighttime dose is also available for middle-of-the-night administration for patients who have middle insomnia. For zopiclone, there is a racemic mixture of both R- and S-zopiclone, available outside the US, and the single S enantiomer, eszopiclone, available in the US (Figure 10-34). Clinically meaningful differences between the active enantiomer and the racemic mixture are debated.

Dual Orexin Receptor Antagonists (DORAs)

Orexins/hypocretins, their receptors, and their pathways have been discussed above and are illustrated in Figures 10-9 through 10-12. Pharmacological blockade of orexin receptors has hypnotic actions but not by enhancing inhibitory GABA action in the sleep-promoting center (VLPO) as do the benzodiazepines and Z drugs (Figure 10-17). Instead, dual orexin receptor antagonists (DORAs) (at both orexin 1 and 2 receptors) block the wake-stabilizing effects of the orexins, especially at orexin 2 receptors (Figures 10-35, 10-36). DORAs inhibit the ability of naturally occurring orexins from promoting the release of other wake-promoting neurotransmitters such as histamine, acetylcholine, norepinephrine, dopamine, and serotonin (as shown in Figure 10-37). After administration of a DORA, arousal is no longer enhanced and wakefulness is no longer stabilized by orexins, and the patient goes to sleep. Both suvorexant and lemborexant (Figure 10-35) improve not only the initiation but also the maintenance of sleep and do so without the side effects expected of a benzodiazepine or Z-drug hypnotic, namely lacking dependence, withdrawal, rebound, unsteady gait, falls, confusion, amnesia, or respiratory depression.

Both suvorexant and lemborexant (Figure 10-35) are reversible inhibitors, which means that as endogenous orexins build up in the morning, the inhibitory action of the DORAs are reversed. Thus, at night, DORAs have more effect since there is a higher ratio of drug to orexin. As daylight begins, orexin levels rise just as DORA levels are falling, and there is less drug relative to the amount of orexin present, (i.e., lower ratio of drug to orexin). When a threshold of blockade of orexin receptors is no longer present, the patient awakens. Suvorexant has comparable affinity for orexin 1 and orexin 2 receptors, and lemborexant has higher affinity for orexin 2 receptors than orexin 1 receptors (Figure 10-35). Lemborexant reportedly exhibits much faster association and dissociation kinetics at orexin 2 receptors than suvorexant. The clinical significance of this is uncertain but may imply a faster reversibility of lemborexant than suvorexant in the morning as endogenous orexin levels rise to compete for binding at orexin receptors.

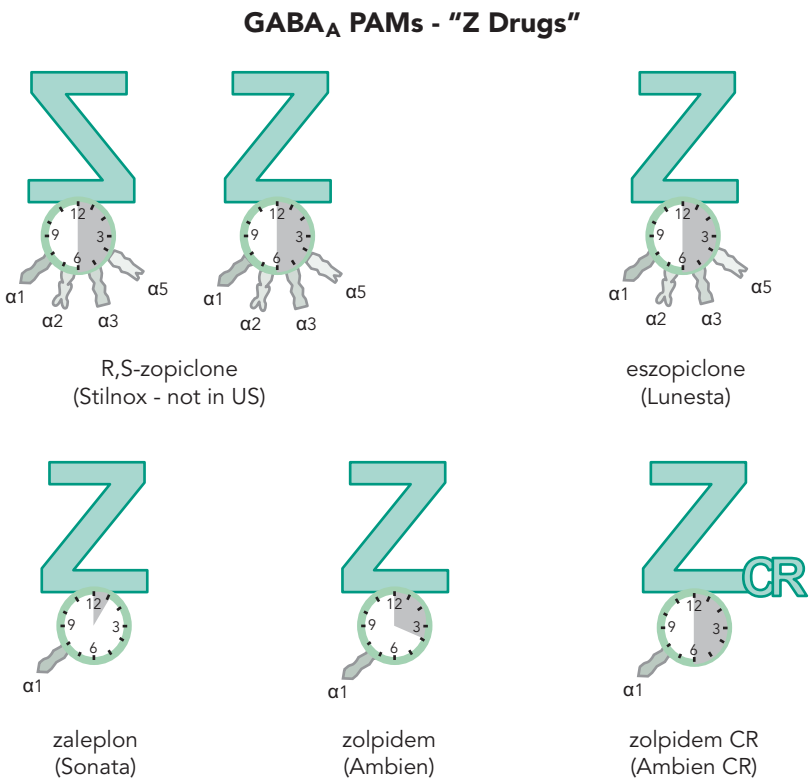


Figure 10-34 **Z drugs: GABA$_A$ positive allosteric modulators (PAMs).** Several Z drugs are shown here. These include racemic zopiclone (not available in the United States), eszopiclone, zaleplon, zolpidem, and zolpidem CR. Zaleplon, zolpidem, and zolpidem CR are selective for GABA$_A$ receptors that contain the α_1 subunit; however, it does not appear that zopiclone or eszopiclone have this same selectivity.

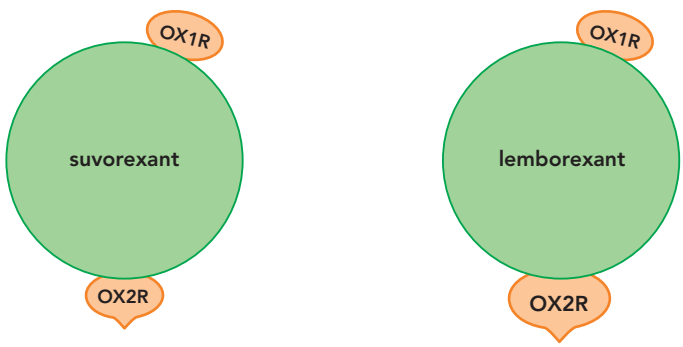


Figure 10-35 **Orexin receptor antagonists.** The dual orexin receptor antagonists suvorexant and lemborexant are shown here. Suvorexant has comparable affinity for orexin 1 (OX1R) and orexin 2 (OX2R) receptors, while lemborexant has higher affinity for OX2R than for OX1R.

Other DORAs (such as daridorexant) and also selective orexin 2 and selective orexin 1 antagonists are currently in development as well. Competition of endogenous neurotransmitter with drug for the same receptor is a concept also discussed in Chapter 7 regarding D_3 antagonists/partial agonists and dopamine itself at the D_3 receptor (see Figure 7-72).

Serotonergic Hypnotics

One of the most popular hypnotics is the $5HT_{2A}$/ α_1/H_1 antagonist trazodone (Figure 7-46), even though this agent is not specifically approved for the treatment of insomnia (see Chapter 7 for discussion of trazodone's use in depression and Figures 7-45 through 7-47). Trazodone, like the DORAs, is another agent that works to reduce arousal in insomnia rather than by enhancing sleep drive. Trazodone's hypnotic mechanism is via blockade of the arousal neurotransmitters serotonin, norepinephrine, and histamine (Figure 7-46). Blockade of α_1-adrenergic and H_1 histaminergic pathways is discussed as a side effect of some drugs for psychosis in Chapter 5 and illustrated in Figures 5-13 and 5-14. Indeed, one does not want blockade of all these arousal neurotransmitters in the daytime. However, when α_1 blockade is combined

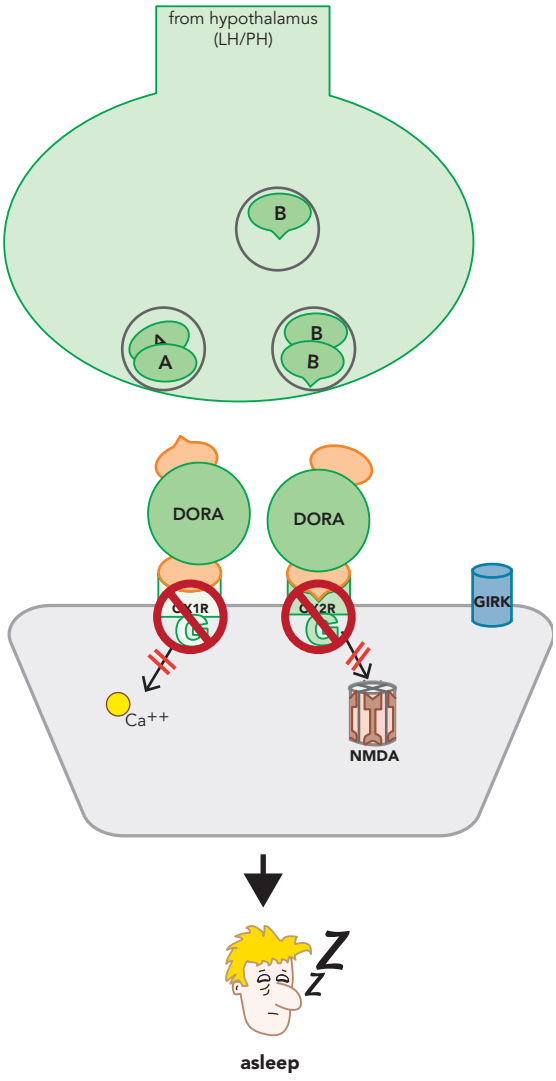


Figure 10-36 **Blockade of orexin receptors.** Orexin neurotransmission is mediated by two types of postsynaptic G-protein-coupled receptors, orexin 1 (OX1R) and orexin 2 (OX2R). OX1R are particularly expressed in the noradrenergic locus coeruleus whereas OX2R are highly expressed in the histaminergic tuberomammillary nucleus (TMN). Blockade of orexin receptors by dual orexin receptor antagonists (DORAs) prevents the excitatory effects of orexin neurotransmitters. In particular, blockade of OX2R leads to decreased expression of NMDA (*N*-methyl-D-aspartate) glutamate receptors and prevents inactivation of G-protein-regulated inward rectifying potassium channels (GIRK). LH/PH: lateral hypothalamus/posterior hypothalamus.

with H_1 blockade (described below and illustrated in Figures 10-38 through 10-40), and these actions are further combined with $5HT_{2A}$ antagonism, a powerful hypnotic effect results. $5HT_{2A}$ antagonism (Figures 7-45 and 7-46) specifically enhances slow-wave sleep/deep sleep, which can correlate with restorative sleep and even improvement in daytime pain and fatigue.

Trazodone was initially studied for depression at high doses that also block serotonin reuptake (Figure 7-45), and given in a short-acting immediate-release formulation two or three times a day. Although effective as an antidepressant, it also caused daytime sedation. It was serendipitously discovered that lowering the dose of immediate-release trazodone and giving it at night made for a very effective hypnotic, which wore off before morning, and thus a new hypnotic agent was born and has continued to be the most commonly prescribed agent for sleep in the world. In order for trazodone to have optimum antidepressant actions, the dose has to be increased, and for it to be tolerated, it has to be given in a once-daily controlled-release formulation that generates blood levels above those needed for antidepressant action yet below those needed for sedative hypnotic action (Figure 7-47). Trazodone has not been associated with tolerance, withdrawal, dependence, or rebound.

Histamine 1 Antagonists as Hypnotics

It is widely appreciated that antihistamines are sedating. Antihistamines are popular as over-the-counter sleep aids (especially those containing diphenhydramine/Benadryl or doxylamine) (Figure 10-38). Because antihistamines have been widely used for many years not only as hypnotic agents but also for the treatment of allergies, there is the common misperception that the properties of classic agents such as diphenhydramine apply to any drug with antihistaminic properties. This includes the idea that all antihistamines have "anticholinergic" side effects such as blurred vision, constipation, memory problems, dry mouth; that they cause next-day hangover effects when used as hypnotics at night; that tolerance develops to their hypnotic actions; and that they cause weight gain. It now seems that some of these ideas about antihistamines are due to the fact that most agents with potent antihistamine properties have anticholinergic actions as well (Figures 10-38 and 10-39). This applies not only to antihistamines used for allergy, but also to drugs approved for use in psychosis (e.g., chlorpromazine Figure 5-27 and quetiapine Figure 5-45) and depression (such as doxepin Figure 10-39 and other tricyclic antidepressants Figure 7-67) but also used at low doses as hypnotic agents.

The tricyclic antidepressant doxepin is an interesting case because of its very high affinity for the H_1 receptor. At low to very low doses, far lower than needed for the treatment of depression, it is a relatively selective H_1

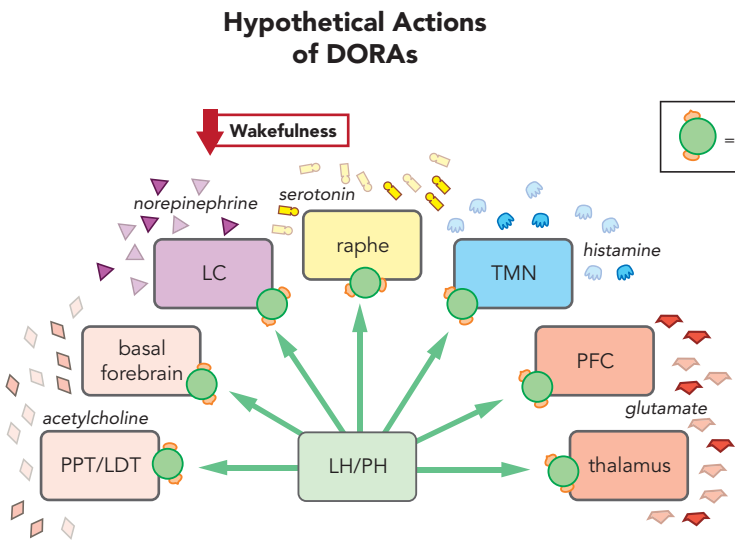


Figure 10-37 **Hypothetical actions of dual orexin receptor antagonists (DORAs).** By blocking orexin receptors, and particularly orexin 2 receptors, DORAs prevent orexin from promoting the release of other wake-promoting neurotransmitters.

What Is Diphenhydramine's (Benadryl's) Mechanism as a Hypnotic?

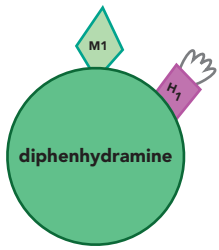


Figure 10-38 **Diphenhydramine.** Diphenhydramine is a histamine 1 (H_1) receptor antagonist commonly used as a hypnotic. However, this agent is not selective for H_1 receptors and thus can also have additional effects. Specifically, diphenhydramine is also a muscarinic 1 (M_1) receptor antagonist and thus can have anticholinergic effects (blurred vision, constipation, memory problems, dry mouth).

antagonist (Figure 10-39), without either unwanted anticholinergic properties, or the serotonin and norepinephrine reuptake blocking properties that make it a drug for depression at high doses (Figure 10-39). In fact, doxepin is so selective at low doses that it is even being used in trace doses as a PET ligand to label central nervous system H_1 receptors selectively. At clinical doses much smaller than those necessary for its antidepressant actions, doxepin occupies a substantial number of central nervous system H_1 receptors (Figures 10-39 and 10-40) and has proven hypnotic actions. Blocking one of the most important arousal neurotransmitters histamine and its actions at H_1 receptors is clearly an effective way to induce sleep.

H_1 antagonists have only been anecdotally associated with tolerance, but not with withdrawal, dependence, or rebound.

Anticonvulsants as Hypnotics

Anticonvulsants are not approved for the treatment of insomnia but some are prescribed off-label in order to promote sleep, especially gabapentin and pregabalin. The mechanism of action of these agents as open-channel, N and P/Q voltage-gated ion-channel inhibitors, also called $\alpha_2\delta$ ligands, is explained in Chapter 9 on pain and illustrated in Figures 9-15 through 9-18. These $\alpha_2\delta$ ligands are approved not only for pain and epilepsy, but in some countries for anxiety, and their anxiolytic actions are explained in Chapter 8 on anxiety and illustrated in Figures 8-17 and 8-18. Although not particularly sedating, the $\alpha_2\delta$ ligands pregabalin and gabapentin can enhance slow-wave sleep, restorative sleep, and assist in the improvement of pain.

Hypnotic Actions and Pharmacokinetics: Your Sleep Is at the Mercy of Your Drug Levels!

So far in this chapter, we have discussed the pharmacodynamic properties of drugs to treat insomnia; that is, their pharmacological mechanism of action. Many areas of psychopharmacology involve drugs classified by their immediate molecular actions, but that have important delayed molecular events that are more clearly linked to their therapeutic effects, which are also often delayed. This is not so for drugs with hypnotic actions. For sleep-inducing agents, their immediate pharmacological

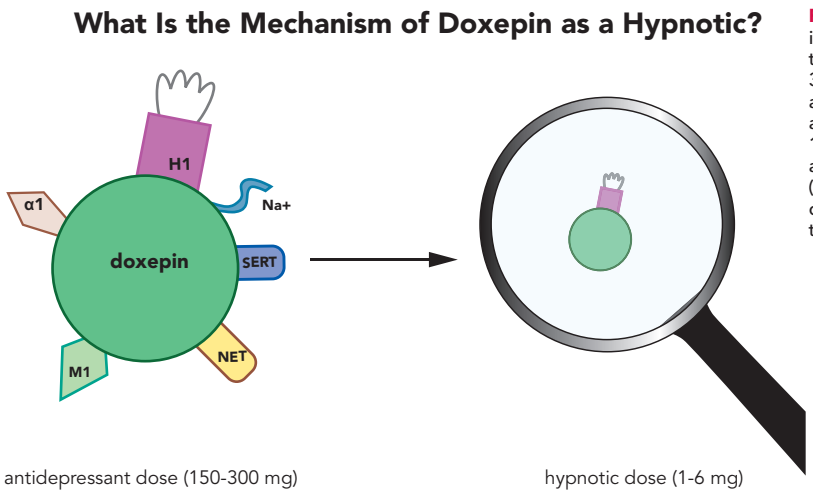


Figure 10-39 Doxepin. Doxepin is a tricyclic antidepressant (TCA) that, at antidepressant doses (150–300 mg/day), inhibits serotonin and norepinephrine reuptake and is an antagonist at histamine 1 (H_1), muscarinic 1 (M_1), and α_1-adrenergic receptors. At low doses (1–6 mg/day), however, doxepin is quite selective for H_1 receptors and thus may be used as a hypnotic.

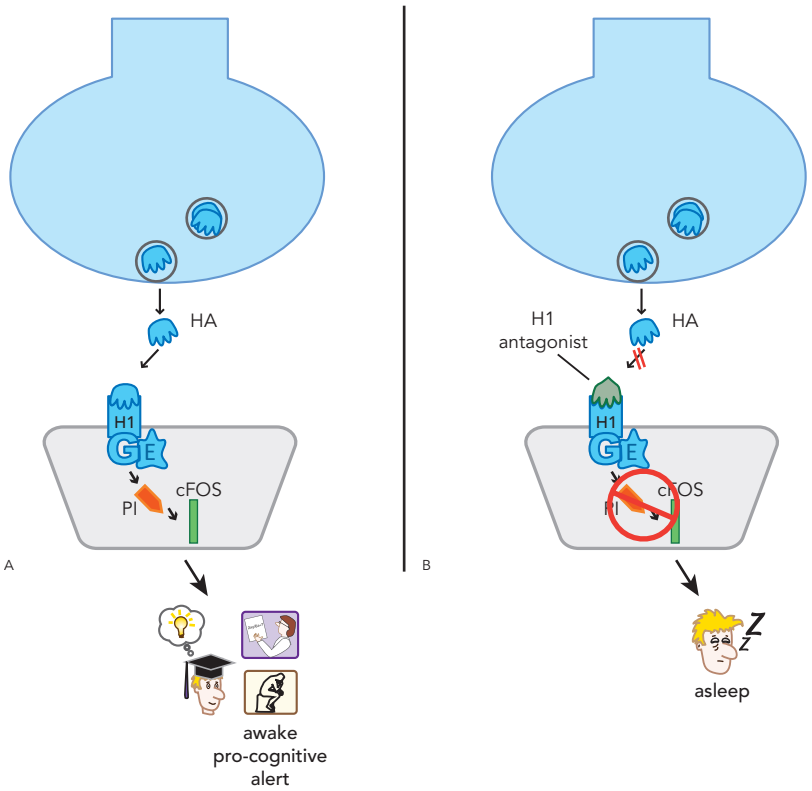
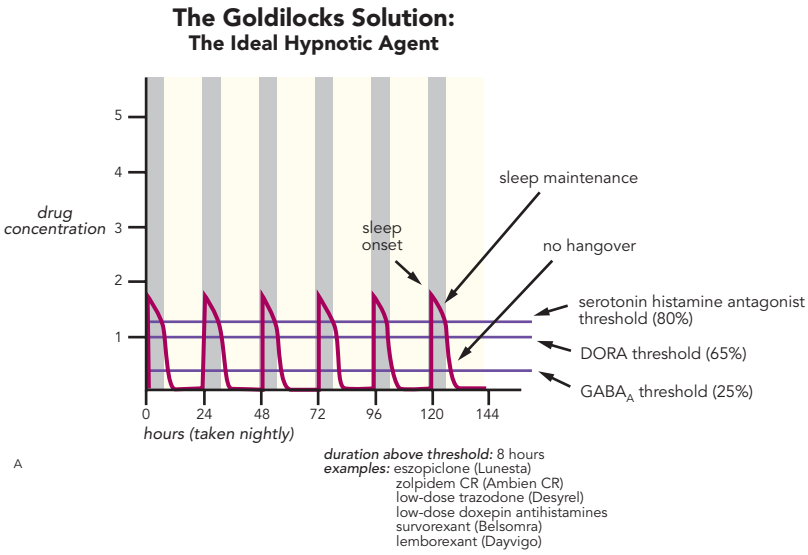


Figure 10-40 Histamine 1 antagonism. (A) When histamine (HA) binds to postsynaptic histamine 1 (H_1) receptors, it activates a G-protein-linked second-messenger system that activates phosphatidyl inositol (PI) and the transcription factor cFOS. This results in wakefulness and normal alertness. (B) H_1 antagonists prevent activation of this second messenger and thus can cause sleepiness.

action causes their immediate therapeutic actions. In fact, your sleep induction is theoretically at the "mercy" of your drug being above a critical threshold of receptor occupancy! For $GABA_A$ drugs, that threshold based on preclinical studies is around 25–30% receptor occupancy (Figure 10-41A). For DORAs, it is around 65% (Figure 10-41A). For antagonists of serotonin and histamine, the threshold is not as well investigated but is likely to be around 80% for a single receptor blocked, or less if more than one receptor is simultaneously blocked. Whatever the exact thresholds, the concept is clear: as soon as a hypnotic drug rises above its sleep-inducing threshold,

you go to sleep, and as soon as the drug falls below this threshold, you awaken. In practice, these effects may not be immediate, and being near the threshold may mean sleepiness but not sleep. Nevertheless, this is an important concept because it is not so much the pharmacokinetic half-life that is important for a hypnotic drug (i.e., how long until half the drug is gone), it is its duration of time above the sleep threshold. These concepts are illustrated in Figure 10-41A–D; the ideal profile for a hypnotic is shown in Figure 10-41A: neither too short a time above the threshold nor too long a time, but "just right": the Goldilocks solution. In Figure 10-41B and 10-41C, the concept of too long a half-life, but more importantly too long above the threshold, is shown: "too hot" and the result is next-day residual effects. Finally, the concept of too short a half-life, but more importantly not long enough above the threshold, is shown (Figure 10-41D): "too cold" and the result is early morning awakenings before the desired time of rising. These same concepts of a drug needing to pierce a threshold, and sustain its level above that threshold to be effective, apply to another area of psychopharmacology: namely, the use of stimulants for the treatment of ADHD (attention deficit hyperactivity disorder). This will be discussed in Chapter 11 on ADHD.



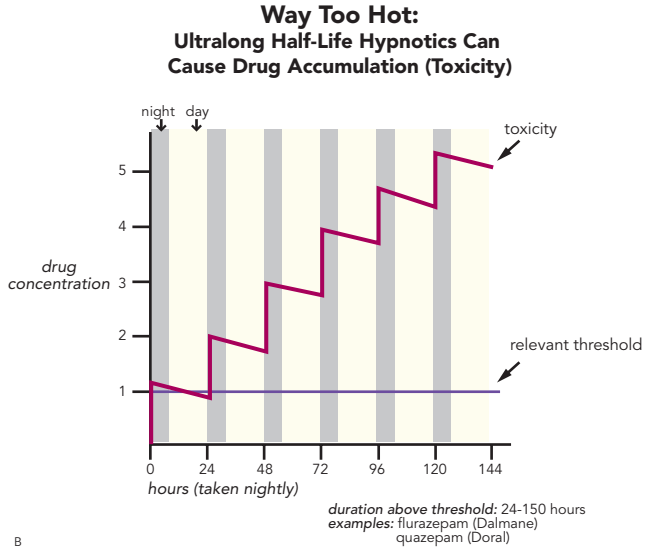
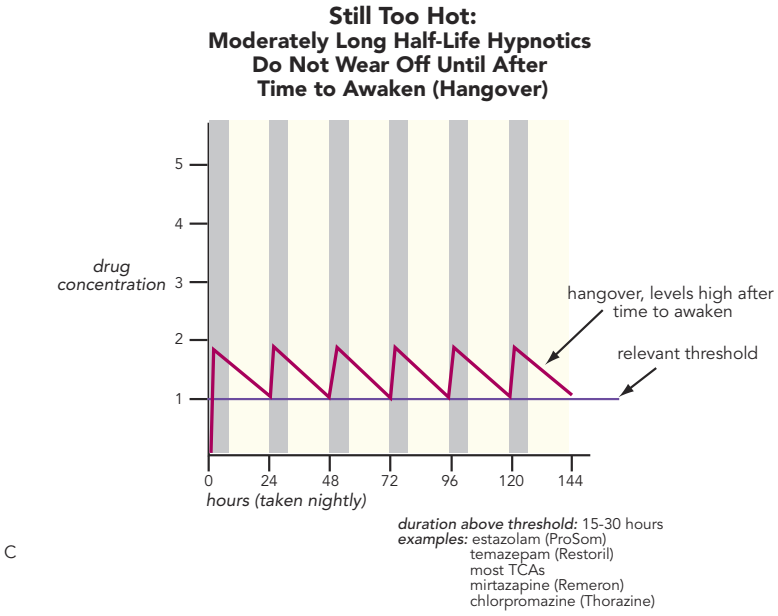


Figure 10-41A, B Pharmacokinetics of hypnotics, part 1. (A) For GABA$_A$ medications, the critical threshold of receptor occupancy for onset of hypnotic effects is 25–30%, for dual orexin receptor antagonists (DORAs) it is 65%, and for serotonin and histamine antagonists it is thought to be 80%. Both the onset to achieving the threshold, and the duration of time above the sleep threshold, are important for efficacy. The ideal hypnotic agent would have a duration above the threshold of approximately 8 hours. (B) Hypnotics with ultra-long half-lives (greater than 24 hours; for example, flurazepam and quazepam) can cause drug accumulation with chronic use. This can result in too long a duration of time above the sleep threshold, and can cause impairment that has been associated with increased risk of falls, particularly in the elderly.



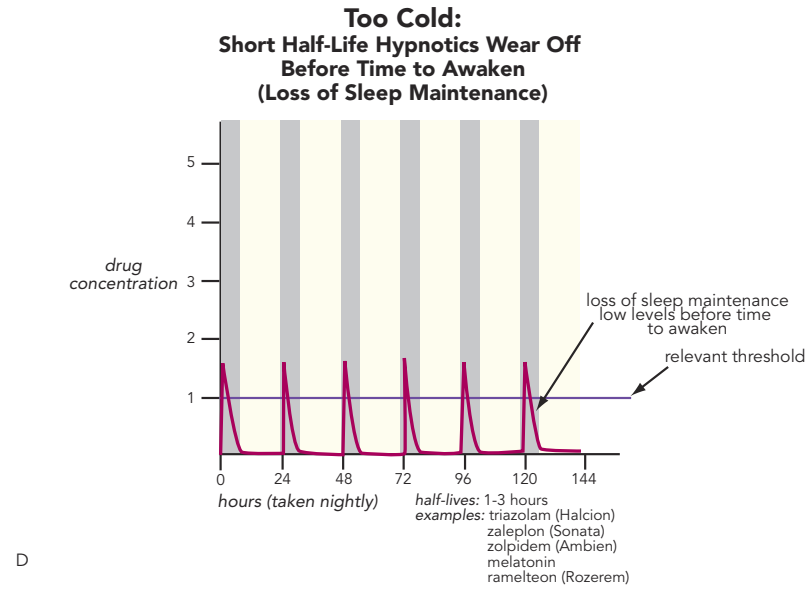


Figure 10-41C, D Pharmacokinetics of hypnotics, part 2. (C) For hypnotics with moderately long half-lives (15–30 hours), receptor occupancies above the sleep threshold may not wear off until after the individual needs to awaken, potentially leading to "hangover" effects (sedation, memory problems). (D) For hypnotics with ultra-short half-lives (1–3 hours), receptor occupancies above the sleep threshold may not last long enough, causing loss of sleep maintenance.

The reason these concepts are important to the prescriber is not so much the precision of the estimates of thresholds, as these may vary from patient to patient. Instead, these concepts inform the prescriber about what to do to get the Goldilocks solution for individual patients. If the patient is not falling asleep quickly enough, theoretically the patient does not reach threshold fast enough, so either give the drug earlier in the evening, or don't take with food (food can delay the absorption of some agents), or raise the dose, or change the mechanism. If the patient is not sleeping long enough (Figure 10-41D), theoretically threshold levels are lost too early, so either raise the dose or switch to a drug with a longer duration of action above the threshold (generally, this would be drugs with a longer pharmacokinetic half-life; see Figures 10-41A and 10-41C). If the patient

is groggy in the morning, theoretically drug levels are continuing near or above threshold levels when it is time to arise, so lower the dose, give the drug earlier in the evening, or switch to an agent with a shorter duration of action (generally, this would be drugs with a shorter pharmacokinetic half-life; see Figures 10-41A and 10-41D).

One last word on how all this applies to the DORAs. Recall that inhibition of the $GABA_A$ receptor, serotonin receptor, noradrenergic receptor, and histamine receptor are not effectively competitive. There is no known endogenous ligand linked to the sleep/wake cycle that acts at the GABA PAM site that could compete cyclically with Z-drug hypnotics and benzodiazepines. Endogenous levels of the neurotransmitters serotonin, norepinephrine, and histamine are not likely to be in the range to reverse antagonist binding by hypnotic drugs. However, the affinity of orexin A for orexin 1 and 2 receptors is in the same range as the affinity of the DORAs suvorexant and lemborexant for these very same receptors. What this means is that during the middle of the night, when orexin levels are low, a given concentration of DORA will have a greater blockade of orexin receptors than later in the night and morning, when orexin levels rise and compete with DORAs for orexin receptors and reverse their blockade just as DORA levels are falling. How this applies in practice could depend upon whether orexin levels are abnormally high in certain cases of insomnia or comorbid conditions, in which case a higher dose of a DORA would be necessary. Also, a higher dose of a DORA would possibly be what is needed if the patient experiences early morning awakenings. On the other hand, a lower dose of a DORA may be needed if the patient experiences carryover effects the next morning, something that has been noted sometimes in clinical practice. With the variables of both drug levels and orexin levels determining net receptor blockade and thus duration of time above the threshold for sleep, the pharmacokinetic half-lives of DORAs are not particularly clinically relevant. There are no head-to-head studies to definitively demonstrate potential advantages of lemborexant versus suvorexant. However, the binding characteristics (affinities for orexin 1 and 2 receptors, association/dissociation kinetics, plasma drug levels and thus orexin receptor blockade for the first 8 hours after ingestion, and especially during the critical early morning hours) are sufficiently different between lemborexant and suvorexant to suggest that if a given patient does not respond optimally to one of these agents, the other might be better. Neither agent is associated with tolerance, withdrawal, dependence, or rebound.

Behavioral Treatments of Insomnia

Good sleep hygiene (Figure 10-42) may allow a patient with insomnia to avoid medication treatment altogether. Other treatments for insomnia that avoid medication use include relaxation training, stimulus control therapy, sleep restriction therapy, intensive sleep retraining, and cognitive behavioral therapy (Figure 10-43). These various interventions have been shown to have beneficial effects on several sleep parameters, including sleep efficiency and sleep quality, and can be very effective, and thus should often be considered before the use of hypnotic agents. In addition, behavioral approaches can be useful adjunctive treatments with hypnotic agents for patients who do not respond adequately to drugs alone.

EXCESSIVE DAYTIME SLEEPINESS

What Is Sleepiness?

The most common cause of sleepiness (Figure 10-44) is sleep deprivation and the treatment is sleep. However, there are also many other causes of sleepiness that require evaluation and specific treatment. These other causes of excessive daytime sleepiness are hypersomnias including narcolepsy (Figures 10-45 through 10-48), various medical disorders including obstructive sleep apnea (Figures 10-45 and 10-49), circadian rhythm disorders (Figures 10-45 and 10-50 through 10-55), and others (Figure 10-45). Although society often devalues sleep and can often imply that only wimps complain of sleepiness, it is clear that excessive daytime sleepiness is not benign, and in fact can even be lethal. That is, loss of sleep causes performance decrements equivalent to that of legal levels of intoxication with alcohol, and not surprisingly therefore, traffic accidents and fatalities. Thus, sleepiness is important to assess even though patients often do not complain about it when they have it. Comprehensive assessment of patients with sleepiness requires that additional information is obtained from the patient's partner, particularly the bed partner. Most conditions can be evaluated by patient and partner interviews, but sometimes augmented with subjective ratings of sleepiness such as the Epworth Sleepiness Scale, as well as objective evaluations of sleepiness such as overnight

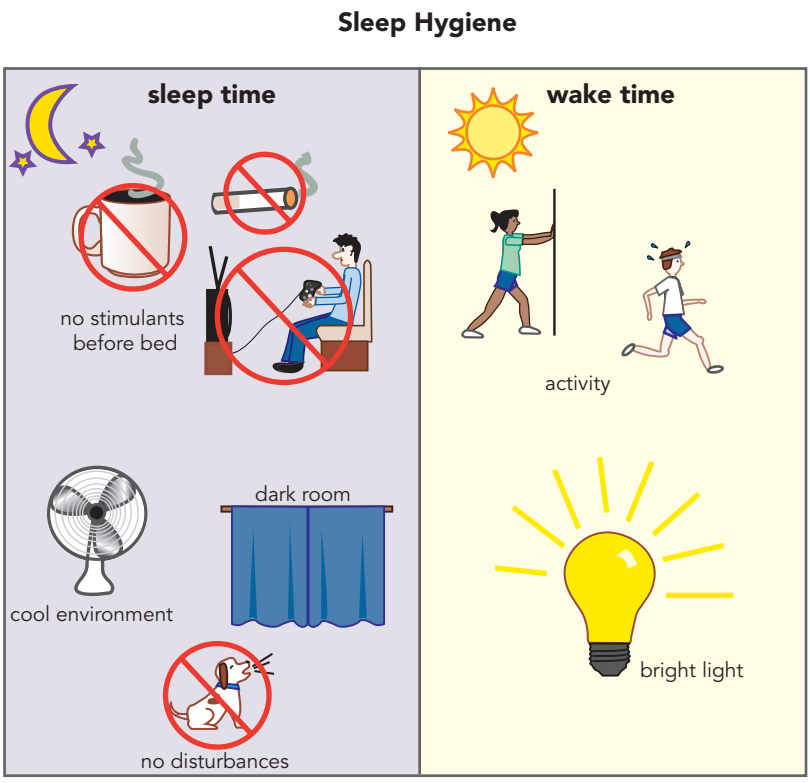


Figure 10-42 **Sleep hygiene.** Good sleep hygiene involves using the bed exclusively for sleep as opposed to activities such as reading or watching television; avoiding stimulants such as alcohol, caffeine, and nicotine as well as strenuous exercise before bed; limiting time spent awake in bed (if not asleep within 20 minutes, one should get up and return to bed when sleepy); not watching the clock; adopting regular sleep habits; and avoiding light at night.

Non-pharmacological Treatments for Insomnia

RELAXATION TRAINING Aimed to reduce somatic tension and intrusive thoughts that interfere with sleep
STIMULUS CONTROL THERAPY Get out of bed if not sleepy; use bed only for sleeping; no napping
SLEEP RESTRICTION THERAPY Limit time spent in bed to produce mild sleep deprivation; results in more consolidated sleep
INTENSIVE SLEEP RETRAINING 25-hour sleep deprivation period in which the patient is given 50 sleep onset trials but awoken following 3 minutes of sleep
COGNITIVE BEHAVIORAL THERAPY Reduce negative attitudes and misconceptions about sleep

Figure 10-43 **Non-pharmacological treatments for insomnia.** Non-pharmacological treatment options for patients with insomnia include relaxation training, stimulus control therapy, sleep restriction therapy, intensive sleep retraining, and cognitive behavioral therapy.

polysomnograms, plus next-day multiple sleep-latency testing and/or maintenance of wakefulness testing.

Causes of Hypersomnia

Hypersomnia is present in as much as 6% of the population. As many as 25% of individuals with hypersomnia may have a mood disorder. In treating various causes of hypersomnia, it is important to first eliminate and treat secondary causes of hypersomnia (Figure 10-45), such as obstructive sleep apnea (OSA) (Figure 10-49), psychiatric illnesses, and medication side effects. This can be accomplished by first conducting a full clinical interview and collecting data from a sleep/wake diary. If necessary, this information can be supplemented with 1–2 weeks' worth of actigraphy, a polysomnogram (sleep EEG), and administering the Multiple Sleep Latency Test (MSLT). One of the most common secondary causes of hypersomnia is OSA (Figure 10-49). Approximately one out of 15 adults suffer with moderate OSA, and as many as 75% of individuals with insomnia have a sleep-related breathing disorder.

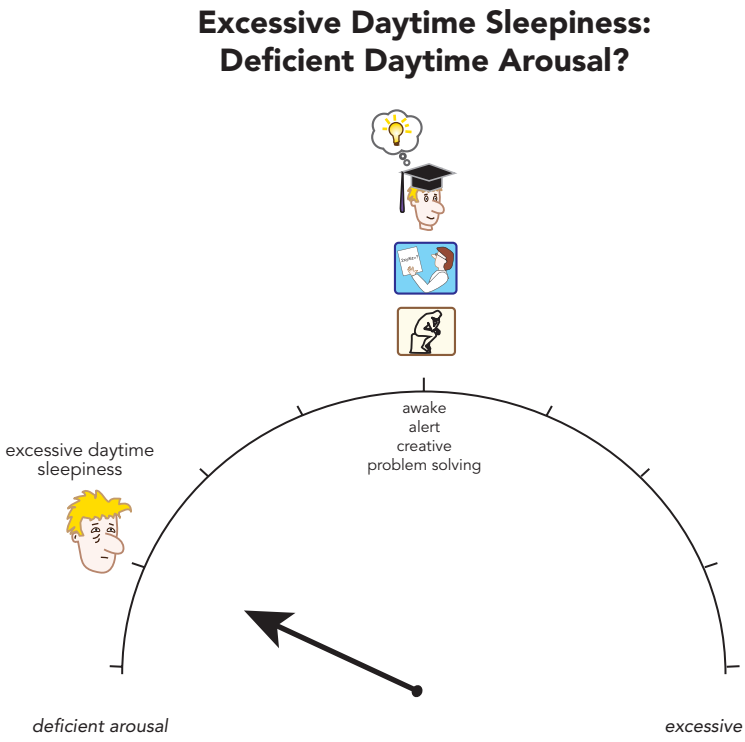


Figure 10-44 **Excessive daytime sleepiness: deficient daytime arousal?** Excessive daytime sleepiness is conceptualized as being related to hypoarousal during the day and is a symptom not only of sleep deprivation but also of narcolepsy, obstructive sleep apnea, and circadian rhythm disorders.

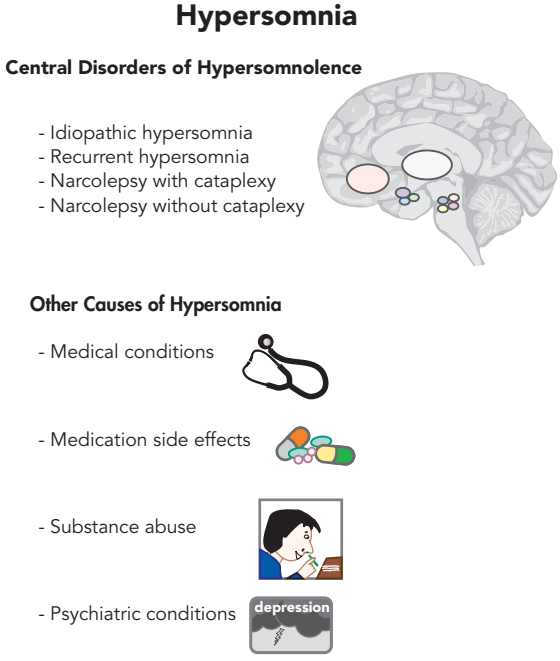


Figure 10-45 **Conditions associated with hypersomnia.** Central disorders of hypersomnia include idiopathic hypersomnia, recurrent hypersomnia, and narcolepsy with or without cataplexy. Other causes of hypersomnia can include medical conditions, medication side effects, substance abuse, and psychiatric conditions.

So, OSA can cause insomnia at night and hypersomnia in the day. Having OSA can nearly double general medical expenses, mainly due to the association of OSA with cardiovascular disease. Features of OSA include episodes of complete (apnea) or partial (hypopnea) upper airway obstruction that result in decreased blood oxygen saturation; these episodes are terminated by arousal.

There are also several disorders of hypersomnia that are thought to arise as a primary consequence of neuropathology in the sleep/wake circuitry of the brain (Figures 10-45 through 10-47). Such disorders are known as "central disorders of hypersomnolence" and include idiopathic hypersomnia (Figure 10-46), recurrent hypersomnia, and narcolepsy (Figure 10-47). With the exception of narcolepsy with cataplexy due to a profound loss of orexin/hypocretin neurons in the lateral hypothalamus (Figure 10-48), the underlying neuropathology of the central disorders of hypersomnolence is largely unknown.

Idiopathic hypersomnia (Figure 10-46) is characterized by either long or normal sleep duration accompanied by constant excessive daytime sleepiness, short sleep-onset latency, and complaints of non-refreshing sleep. Patients with idiopathic hypersomnia may also report sleep drunkenness and somnolence following sleep, as well as memory and attention deficits,

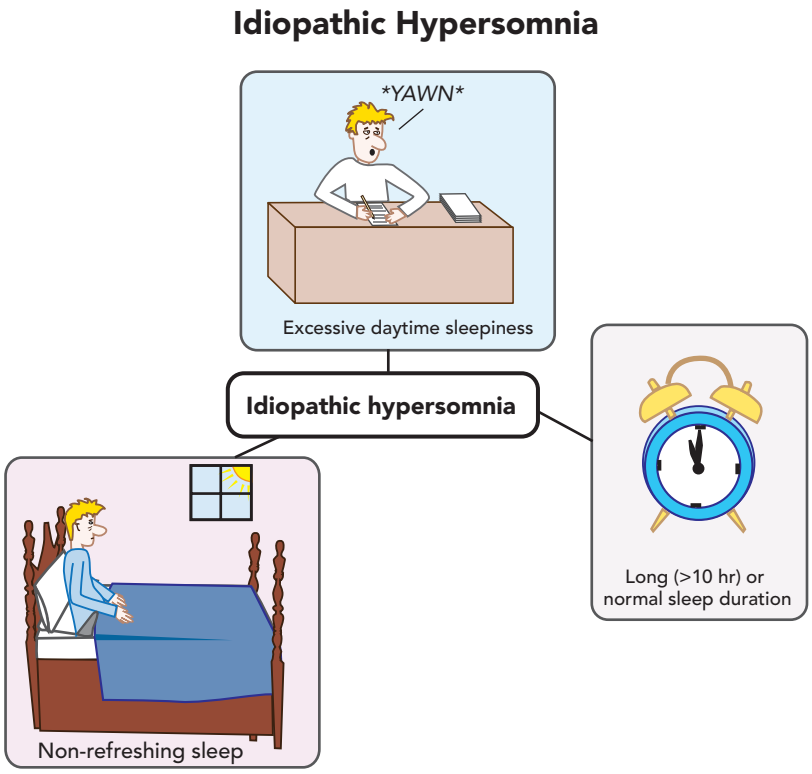


Figure 10-46 **Idiopathic hypersomnia.** Idiopathic hypersomnia is a central disorder of hypersomnolence – that is, it is thought to arise as a consequence of neuropathology in the sleep/wake circuitry of the brain. It is characterized by either long or normal sleep duration accompanied by excessive daytime sleepiness and complaints of non-refreshing sleep.

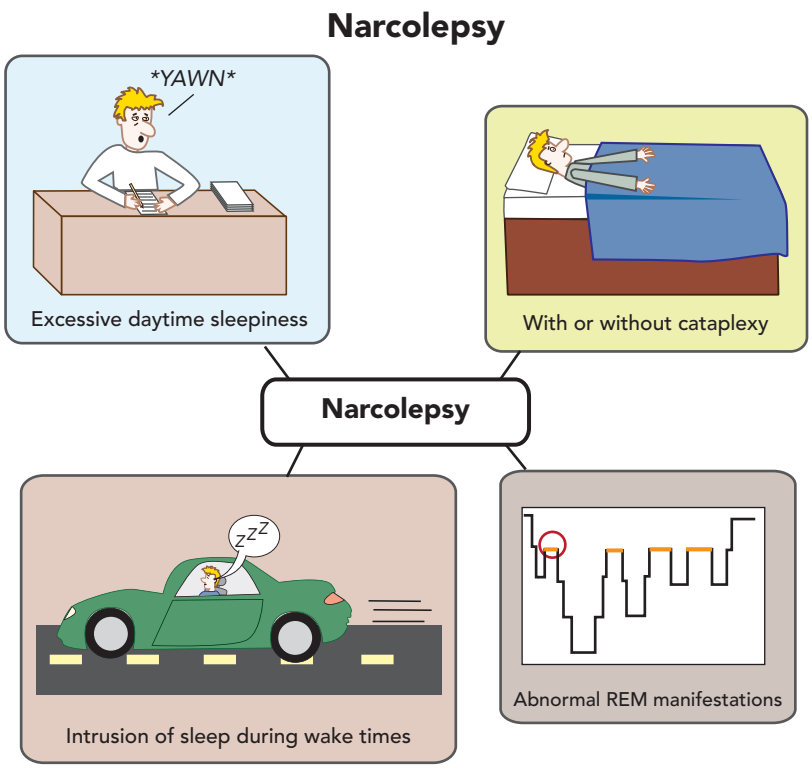


Figure 10-47 **Narcolepsy.** Narcolepsy is a central disorder of hypersomnolence – that is, it is thought to arise as a consequence of neuropathology in the sleep/wake circuitry of the brain. It is characterized by excessive daytime sleepiness, intrusion of sleep during wake times, and abnormal rapid eye movement (REM), including sleep-onset REM periods. Narcolepsy can occur with or without cataplexy (loss of muscle tone triggered by emotion).

Neurobiology of Narcolepsy with Cataplexy

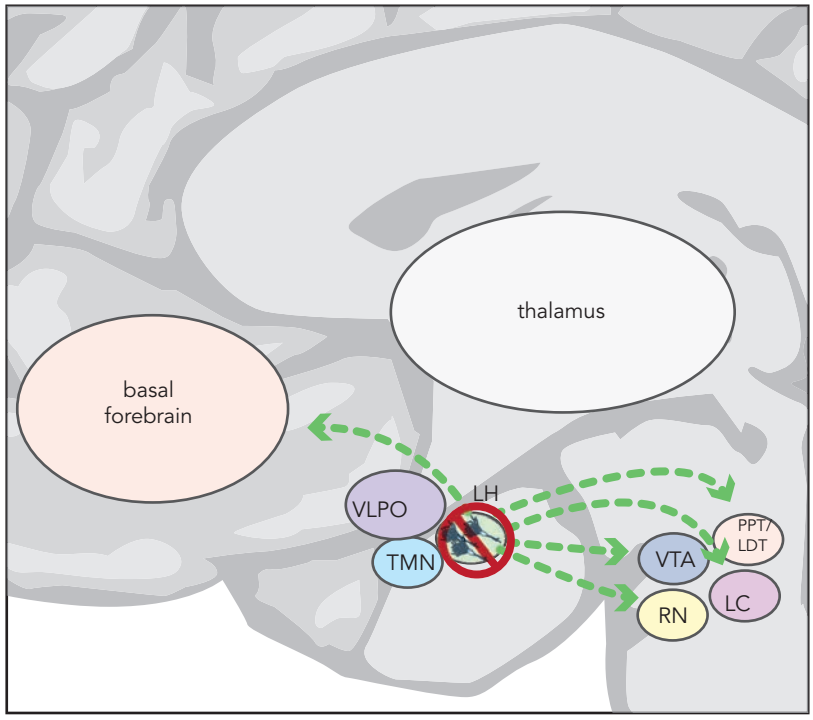


Figure 10-48 **Neurobiology of narcolepsy with cataplexy.** In addition to its role in wakefulness and motivated behaviors, orexin is also involved in stabilizing motor movements, allowing normal movement in the day (when orexin levels are high) and facilitating inhibition of motor movements at night (when orexin levels are low). When orexin levels are low due to the degeneration of orexin neurons, this allows intrusion of motor inhibition and loss of muscle tone during wakefulness, a condition known as cataplexy.

Obstructive Sleep Apnea



Clinical Features

- Loud snoring
- Obesity
- Hypertension
- Neck >17"
- Enlarged tonsils
- Loss of interest
- Excessive daytime sleepiness
- Fatigue
- Depression

Pathophysiology

- Partial/full collapse of upper airway
- Narrowing may occur at different levels
- Muscle tone, airway reflexes
- Metabolic abnormalities in frontal lobe white matter and hippocampus

Figure 10-49 **Obstructive sleep apnea.** Obstructive sleep apnea is a common cause of hypersomnia. It is characterized by episodes of complete (apnea) or partial (hypopnea) upper airway obstruction that results in decreased blood oxygen saturation.

digestive system problems, depression, and anxiety. The diagnosis of idiopathic hypersomnia includes excessive daytime sleepiness lasting at least 3 months; short sleep latency, and fewer than two periods of REM occurring at the onset of sleep (SOREMPs; sleep onset REM periods) on polysomnographic investigation. Cerebrospinal fluid (CSF) levels of histamine may be low; however, CSF orexin levels are not typically affected.

Narcolepsy (Figure 10-47) is characterized by excessive daytime sleepiness, the intrusion of sleep during periods of wakefulness, and abnormal REM sleep, including SOREMPs. Cataplexy, or loss of muscle tone triggered by emotions, may also be present (Figure 10-48). Hypnagogic hallucinations, which are present upon waking, are also often present. As mentioned, a clear neuropathological substrate has been identified for narcolepsy with cataplexy, namely profound loss of orexin neurons in the lateral hypothalamus. We have discussed extensively above how orexin neurons are involved in stabilizing wakefulness through stimulating release of wake-promoting neurotransmitters (serotonin, norepinephrine, dopamine, acetylcholine, and histamine). Thus, it is not surprising that when orexin neurons are lost in narcolepsy, wakefulness is no longer stabilized and patients have intrusion of sleep during periods of wakefulness.

Orexin also stabilizes motor movements, allowing normal movement in the day when orexin levels are high and facilitating inhibition of motor movements at night, especially during REM sleep, when orexin levels are low. When orexin levels are low in the daytime due to loss of orexin neurons (Figure 10-48), this destabilizes motor movements during the daytime, allowing intrusions of motor inhibition and loss of muscle tone, known as cataplexy, during periods of wakefulness.

For those suspected of having narcolepsy or narcolepsy with cataplexy, a CSF orexin level of <110 pg/mL is diagnostic for narcolepsy; however, orexin levels are often within the normal range in narcolepsy, especially without cataplexy, as well as in idiopathic and recurrent hypersomnia. Even in the absence of low orexin levels, patients with narcolepsy with or without cataplexy demonstrate ≥2 SOREMPs on the MSLT or 1 SOREMP on polysomnographic investigation as well as a short sleep latency (≤8 minutes) on the MSLT; thus, these measures are also considered diagnostic for narcolepsy. Additionally, the majority (90%) of patients with narcolepsy, particularly those with cataplexy, are positive for the *HLA DQB1-0602* polymorphism compared to only 20% of the general population.

Circadian Rhythm Disorders

Circadian rhythm disorders (Figure 10-50) arise when there is dyssynchrony between your internal circadian clock and external cues that signal "daytime" and "nighttime." This dyssynchrony leads to difficulty maintaining a sleep/wake cycle within the typical 24-hour period. There are several circadian rhythm disorders, including shift work disorder (Figure 10-51), advanced sleep phase disorder (Figure 10-52), delayed sleep phase disorder (Figure 10-53), and non-24-hour sleep–wake disorder (Figure 10-54).

Shift work is defined as work occurring between 6 pm and 7 am (outside the standard daytime working hours). Shift workers include those who work night shifts, evening shifts, or rotating shifts, and they make up approximately 15–25% of the workforce in the United States. Shift workers' sleep/wake schedules are often out of sync with their endogenous circadian rhythms, and many (but not all) individuals who work non-standard or rotating schedules develop shift work disorder (SWD). In fact, it is estimated that as many as 10–32% of shift workers develop SWD and as many as 9.1% of shift workers develop a severe form of the disorder. Younger age and a natural biological clock aligned more to "eveningness" may provide some protection from the development of SWD. However, for those who do develop SWD, there may be physical and psychiatric consequences that extend far beyond sleep/wake disturbances, such as excessive sleepiness during the work shift and insomnia during periods of sleep. Individuals with SWD have a dramatically increased risk of cardiometabolic issues, cancer, gastrointestinal diseases, and mood disorders.

Advanced sleep phase disorder (ASPD) (Figure 10-52) patients go to bed earlier and awaken earlier than desired, often by 6 hours outside of the typical sleep/wake cycle even though they have adequate total sleep time and quality of sleep. Polymorphisms in the *PER2* gene (an essential component of the molecular clock) have been associated with ASPD; in fact, there is an autosomal-dominant form of the disorder called familial advanced sleep phase syndrome (FASPS) in which a *PER2* mutation is present. In addition to ruling out other sleep/wake disorders, such as insomnia, diagnosing ASPD may include the use of a sleep diary and/or actigraphy for at least a week and the administration of the Morningness–Eveningness Questionnaire (MEQ). Normal elderly people often have a mild or moderate form of ASPD.

In delayed sleep phase disorder (DSPD) (Figure 10-53), individuals are unable to fall asleep until early

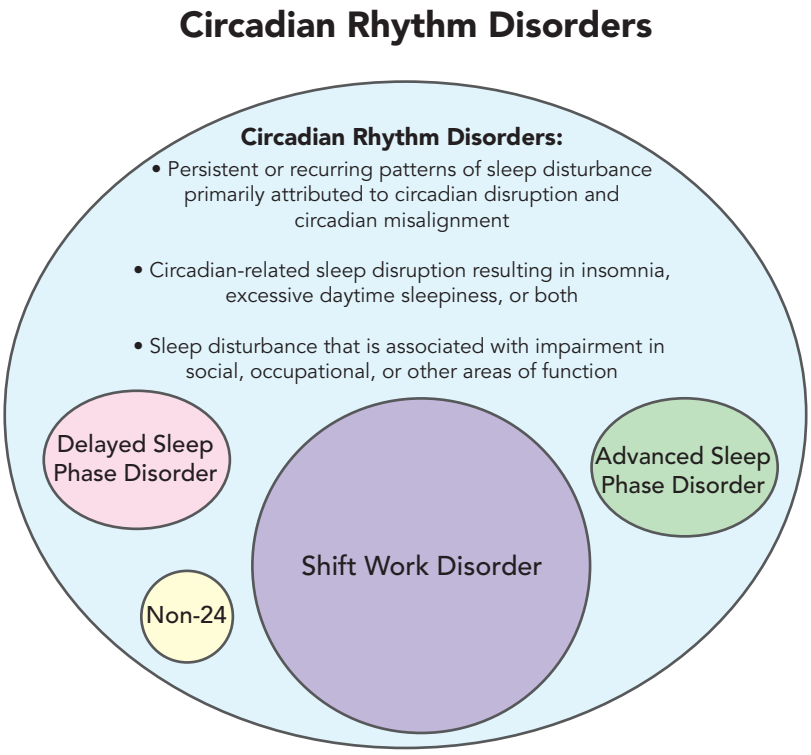


Figure 10-50 Circadian rhythm disorders. Circadian rhythm disorders occur when the internal circadian clock is out of sync with external cues that signal daytime and nighttime. Shift work disorder, advanced sleep phase disorder, delayed sleep phase disorder, and non-24-hour sleep–wake disorder are all circadian rhythm disorders.

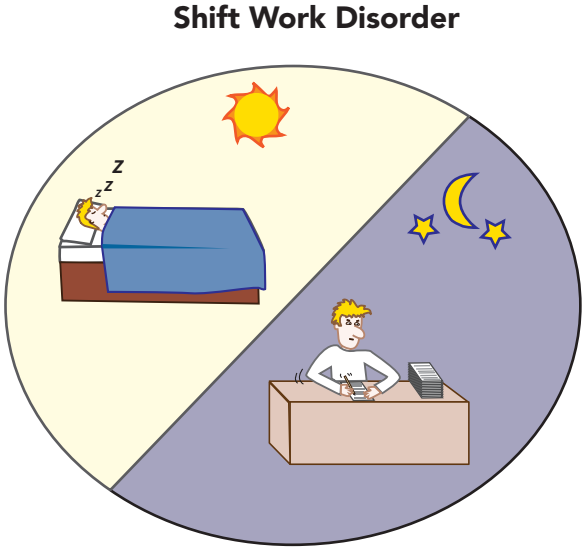


Figure 10-51 Shift work disorder. Shift work is defined as work occurring between the hours of 6pm and 7am. Shift workers' sleep/wake schedules are often out of sync with their endogenous circadian rhythms. Some shift workers therefore develop shift work disorder, in which insomnia or excessive sleepiness is temporarily associated with their recurring work schedule that overlaps with the usual time for sleep.

- Insomnia or excessive sleepiness temporarily associated with a recurring work schedule that overlaps with the usual time for sleep
- Symptoms associated with shift work schedule are present for at least 1 month
- Sleep log or actigraphy monitoring (with sleep diaries) for at least 7 days demonstrates disturbed sleep (insomnia) and circadian and sleep-time misalignment
- Sleep disturbance is not due to another current sleep disorder, medical disorder, mental disorder, substance use disorder, or medication use

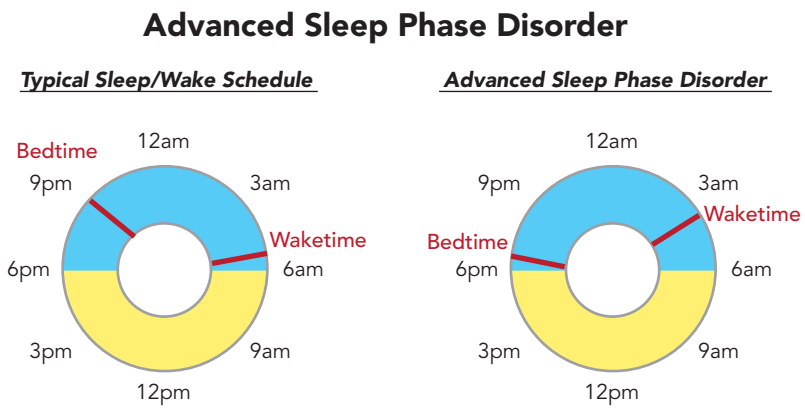


Figure 10-52 **Advanced sleep phase disorder.** Patients with advanced sleep phase disorder become sleepy and thus go to bed earlier than desired and also wake up earlier than desired. These individuals have adequate total sleep time and quality of sleep.

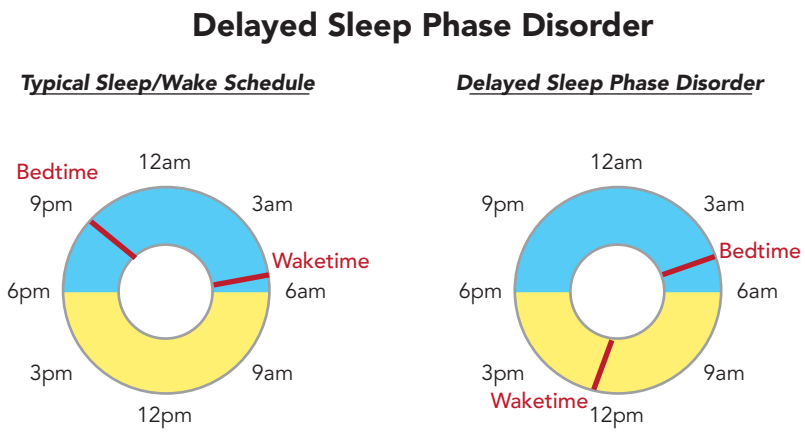


Figure 10-53 **Delayed sleep phase disorder.** Patients with delayed sleep phase disorder are unable to fall asleep until the early morning hours and have difficulty waking until late morning/early afternoon. These individuals have adequate total sleep time and quality of sleep; however, the shifted sleep schedule can often interfere with activities of daily functioning.

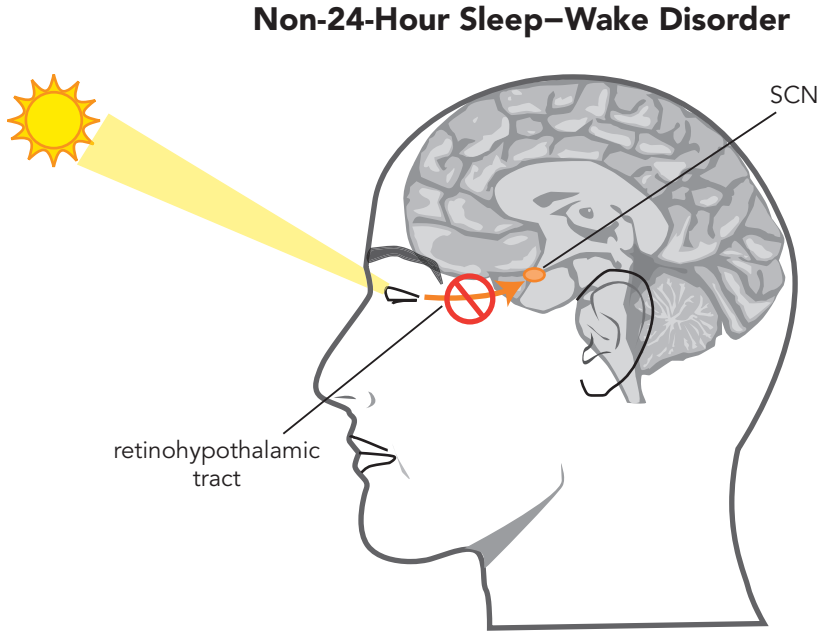


Figure 10-54 **Non-24-hour sleep-wake disorder.** Individuals who are visually impaired are unable to entrain the internal circadian clock with light acting on the suprachiasmatic nucleus (SCN) via the retinohypothalamic tract. This free-running internal clock can cause non-24-hour sleep-wake disorder, characterized by irregular sleep/wake patterns and potentially both insomnia and excessive daytime sleepiness.

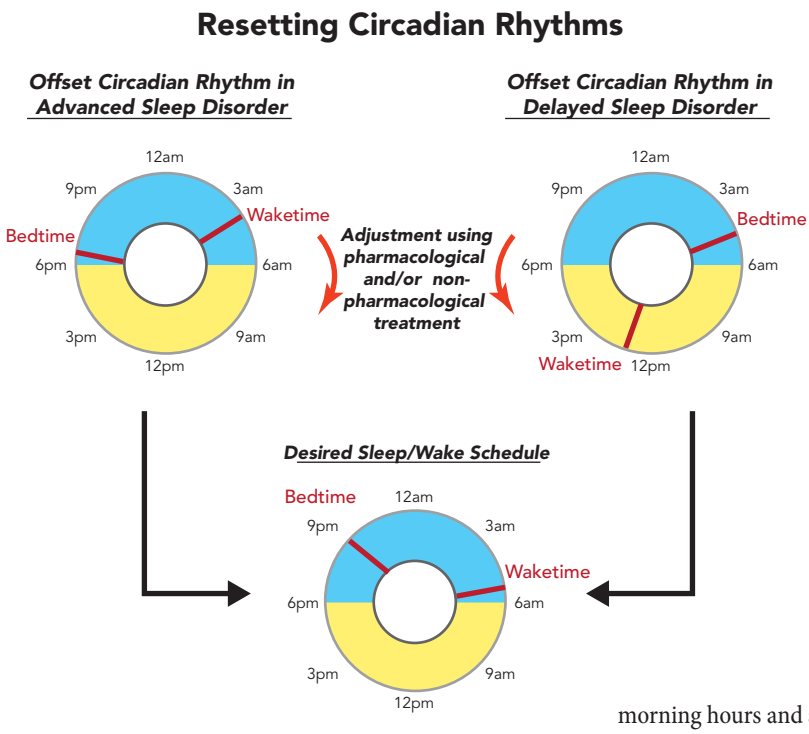


Figure 10-55 Resetting circadian rhythms. Circadian treatments, such as bright light and melatonergic agents, can be used to reset circadian rhythms in both advanced and delayed sleep phase disorders. For advanced sleep phase disorder, early evening bright light and early morning melatonin can be useful. For delayed sleep phase disorder, morning bright light and evening melatonin can be useful.

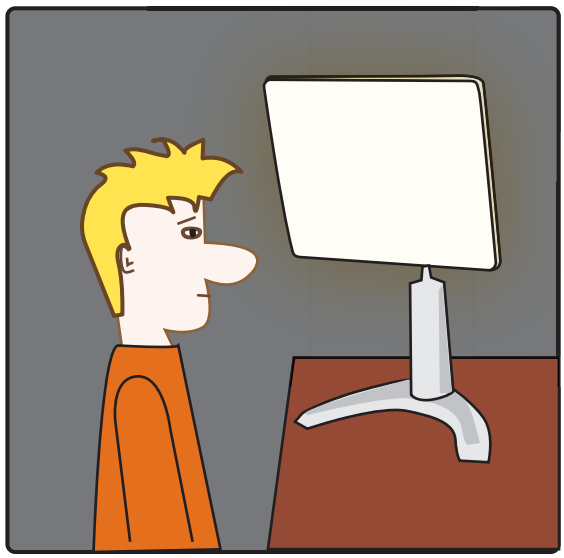


Figure 10-56 Bright light therapy. Bright light therapy is a circadian treatment. Morning bright light can be used for patients with delayed sleep phase disorders and may also be beneficial for patients with shift work sleep disorder. Bright light therapy is also used as a treatment for depression.

morning hours and awaken in the late morning/early afternoon. DSPD is the most common of the circadian rhythm disorders and has been associated with polymorphisms in the *CLOCK* gene (another essential element of the molecular clock). Similarly to advanced sleep phase disorder (ASPD), sleep duration and quality of sleep are normal; however, the shift in the sleep/wake schedule interferes with daily functioning. Many normal teens have a mild to moderate form of ASPD, as do many patients with depression.

Non-24-hour sleep–wake disorder (Figure 10-54) is a circadian rhythm disorder that primarily affects individuals who are blind. Those who are visually impaired lack the ability to entrain the internal circadian clock with light acting on the suprachiasmatic nucleus via the retinohypothalamic tract. This free-running internal clock leads to irregular sleep/wake patterns that may cause both insomnia and excessive daytime sleepiness.

Circadian Treatments

Circadian treatments can be helpful in resetting the offset circadian rhythms of both advanced sleep phase disorder and delayed sleep phase disorder (Figure 10-55). This includes both bright light (Figure 10-56) and melatonergic agents (Figure 10-57). These same circadian treatments can be used adjunctively to drugs for depression in the

treatment of mood disorders or adjunctively to modafinil/armodafinil for shift work disorder.

Morning light and evening melatonin can help depression, delayed sleep phase disorder, and shift work disorder. On the other hand, early evening light and early morning melatonin can help advanced sleep phase disorder. Non-24-hour sleep–wake disorder benefits from synchronization of circadian rhythms by the powerful melatonergic agent tasimelteon (Figure 10-57). These various circadian treatments can also be beneficial in resetting the biological clock in normal elderly people (morning melatonin and evening light) and normal teens (morning light and evening melatonin). Parents have long recognized the benefits of letting in early morning sunlight by opening the shades to get hibernating teens up and going in time for school.

Melatonergic Hypnotics

Melatonin is the neurotransmitter secreted by the pineal gland, and acts especially in the suprachiasmatic nucleus to regulate circadian rhythms (discussed in Chapter 6 and illustrated in Figures 6-34 to 6-36). Melatonin shifts circadian rhythms, especially in those with phase delay when taken at the desired appropriate bedtime, not only for depressed patients, those who have delayed phase sleep disorder, and many normal teenagers, but also for many experiencing jet lag from travel-induced shifts in circadian rhythms. In all cases, melatonin can facilitate sleep onset.

Melatonin acts at three different sites, not only melatonin 1 (MT_1) and melatonin 2 (MT_2) receptors, but also at a third site, sometimes called the melatonin 3 site, which is now known to be the enzyme NRH–quinone oxidoreductase 2, and which is probably not involved in sleep physiology (Figure 10-57). MT_1-mediated inhibition of neurons in the suprachiasmatic nucleus (SCN) could help to promote sleep by decreasing the wake-promoting actions of the circadian "clock" or "pacemaker" that functions there, perhaps by attenuating the SCN's alerting signals, allowing sleep signals to predominate, and thus inducing sleep. Phase shifting and circadian rhythm effects of the normal sleep/wake cycle are thought to be primarily mediated by MT_2 receptors, which entrain these signals in the SCN.

Ramelteon is a MT_1/MT_2 agonist marketed for insomnia, and tasimelteon, another MT_1/MT_2 agonist, is marketed for non-24-hour sleep–wake disorder (Figure 10-57). These agents improve sleep onset, sometimes better when used for several days in a row.

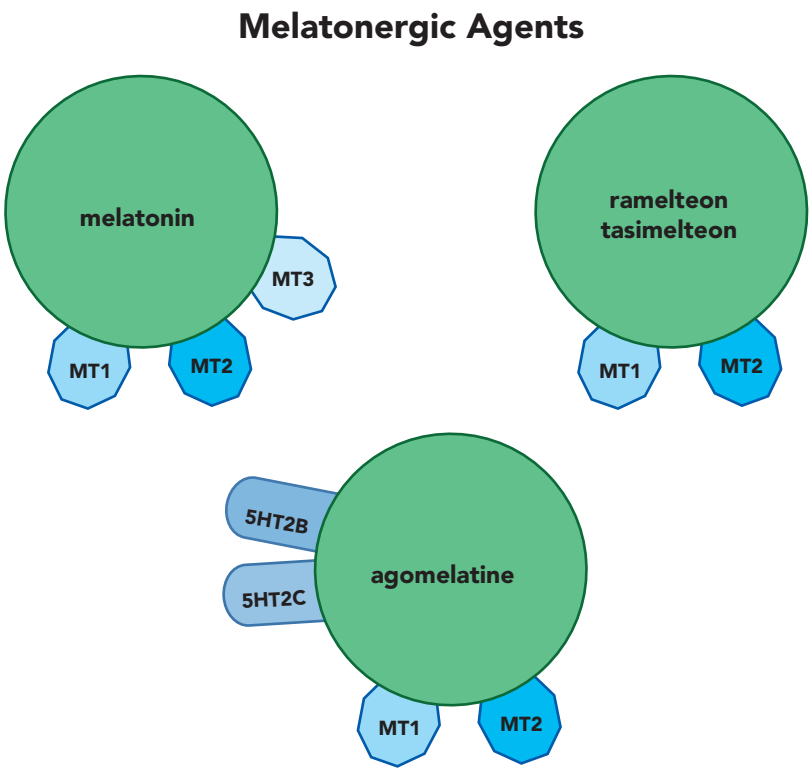


Figure 10-57 Melatonergic agents. Endogenous melatonin is secreted by the pineal gland and mainly acts in the suprachiasmatic nucleus to regulate circadian rhythms. There are three types of receptors for melatonin: MT_1 and MT_2, which are both involved in sleep, and MT_3, which is actually the enzyme NRH–quinine oxidoreductase 2 and not thought to be involved in sleep physiology. There are several different agents that act at melatonin receptors. Melatonin itself, available over the counter, acts at MT_1 and MT_2 receptors as well as at the MT_3 site. Both ramelteon and tasimelteon are MT1 and MT_2 receptor agonists and seem to provide sleep onset though not necessarily sleep maintenance. Agomelatine is not only a MT_1 and MT_2 receptor agonist, but is also a serotonin $5HT_{2C}$ and $5HT_{2B}$ receptor antagonist and is available as an antidepressant outside the US.

They are not known to help sleep maintenance, but will induce natural sleep in those subjects who suffer mostly from initial insomnia. The actions of tasimelteon at MT_2 receptors are thought to underlie its effectiveness at retraining the circadian clock.

WAKE-PROMOTING AGENTS AND TREATMENT OF EXCESSIVE DAYTIME SLEEPINESS

Why treat sleepiness? If the most common cause of sleepiness is sleep deprivation can't we treat sleepiness with sleep and not with drugs? The short answer is unfortunately not. Here we will discuss the treatment of excessive daytime sleepiness with various wake-promoting agents such as caffeine, stimulants, modafinil/armodafinil, and others, as well as some newer agents, including an NDRI (norepinephrine–dopamine reuptake inhibitor) and an H_3 antagonist. Non-pharmacological treatments are also presented.

If disorders characterized by excessive daytime sleepiness can be conceptualized as deficient daytime arousal (Figure 10-44), then wake-promoting treatments can be seen as agents that increase brain activation and arousal (Figure 10-58). There are a number of ways to do this, but most involve enhancing the release of wake-promoting neurotransmitters, especially dopamine and histamine.

Caffeine

Caffeine is the world's most widely consumed psychoactive drug. How does it work? The answer is that it is an antagonist of the neurotransmitter adenosine (Figure 10-59). Adenosine was first mentioned in this chapter as the chemical known to be linked to the homeostatic sleep drive (illustrated in Figure 10-18). Since adenosine accumulates as you get tired, it essentially is taking account of your homeostatic drive and some say that adenosine acts as the "accountant" or "bean counter" of fatigue, documenting and quantitating the homeostatic drive for sleep. Interestingly, one way to make a deposit into this homeostatic account to reduce this drive and diminish fatigue is with a coffee bean! That is, caffeine, from coffee or other sources, is wake-promoting, reduces fatigue, and diminishes the homeostatic sleep drive. How does it do this? Caffeine is an antagonist of adenosine and thus can block some of the effects of adenosine buildup, both molecularly and behaviorally (Figure 10-59).

Native dopamine 2 (D_2) receptors bind dopamine with high affinity (Figure 10-59A) but in the presence of adenosine, D_2 receptors can couple (i.e., heterodimerize) with adenosine receptors, reducing the affinity of the D_2 receptor for dopamine (Figure 10-59B). However, caffeine blocks adenosine binding to the adenosine receptor and restores the affinity of the D_2 receptor for dopamine even

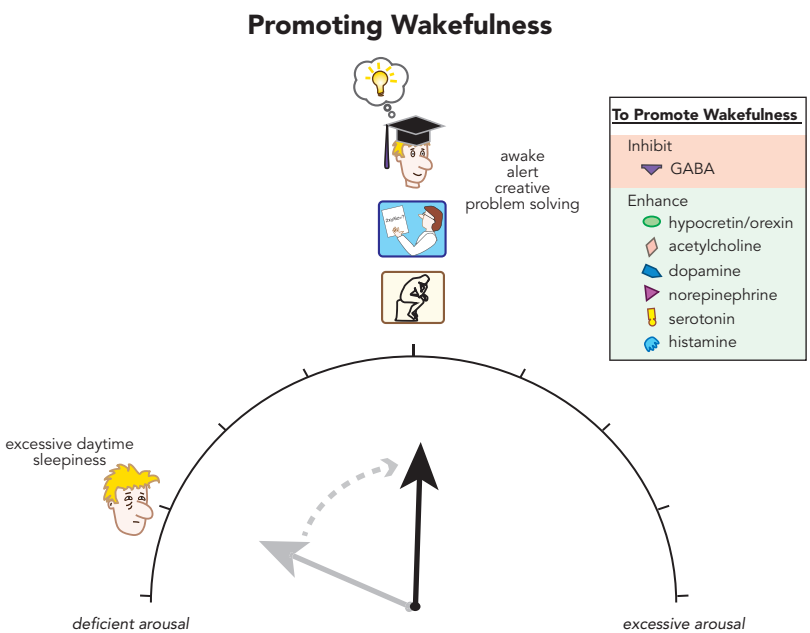


Figure 10-58 Promoting wakefulness. To treat excessive daytime sleepiness, one can administer medications that promote arousal by enhancing neurotransmission involved in wakefulness; most notably, by enhancing dopamine and histamine neurotransmission.

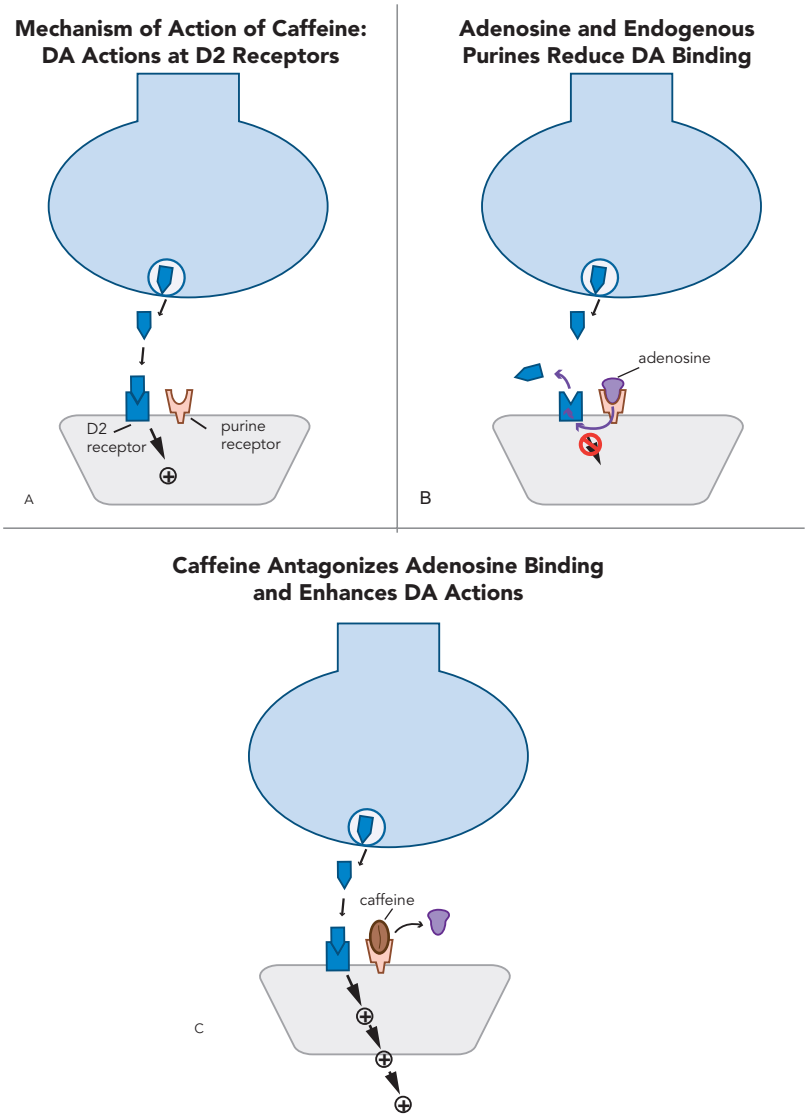


Figure 10-59 Caffeine. Caffeine is an antagonist at purine receptors, and in particular adenosine receptors. (A) These receptors are functionally coupled with certain postsynaptic dopamine (DA) receptors, such as dopamine D_2 receptors, at which dopamine binds and has a stimulatory effect. (B) When adenosine binds to its receptors, this causes reduced sensitivity of D_2 receptors. (C) Antagonism of adenosine receptors by caffeine prevents adenosine from binding there, and thus can enhance dopaminergic actions.

in the presence of adenosine (Figure 10-59C). When caffeine does this, dopamine action is enhanced and this is wake-promoting and reduces fatigue (Figure 10-59C).

Amphetamine and Methylphenidate

Wake promotion from enhancing the wake-promoting neurotransmitters dopamine and norepinephrine is classically done with amphetamines and methylphenidate (Figure 10-60). Because this is activating, wake-promoting, and fatigue-reducing, the effects of amphetamines and methylphenidate are stimulating, and these drugs have classically been called stimulants. Here we will refer to these agents by their properties as norepinephrine–dopamine reuptake inhibitors and, in the case of the amphetamines, as dopamine releasers and competitive VMAT2 inhibitors as well. VMAT2 inhibition was discussed in Chapter 5 and illustrated in Figures 5-10A and 5-10B. Norepinephrine–dopamine reuptake inhibition as an antidepressant mechanism was discussed in Chapter 7 and illustrated in Figures 7-34 through 7-36. D-amphetamine, DL-amphetamine, and methylphenidate are all approved for use specifically as wake-promoting agents in the treatment of narcolepsy, but not in obstructive sleep apnea or shift work disorder, although often used "off-label" for these indications. Many formulations of both amphetamine and methylphenidate

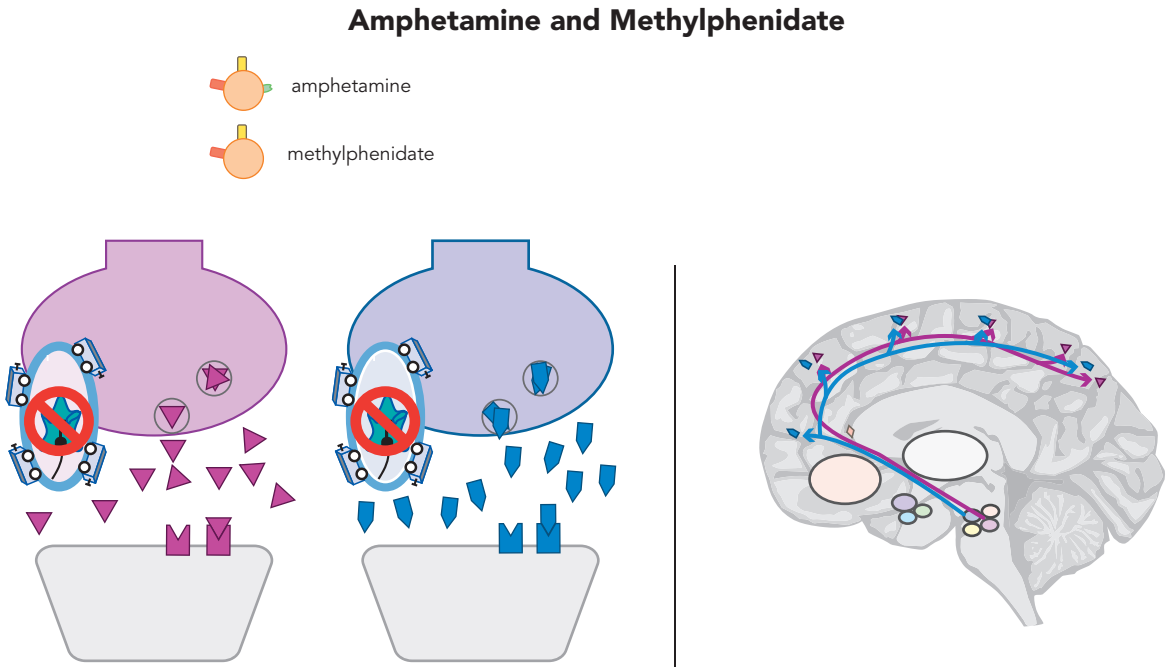


Figure 10-60 Amphetamine and methylphenidate. Amphetamine and methylphenidate are both norepinephrine (left) and dopamine (right) reuptake inhibitors; amphetamine has the additional property of inhibition of the vesicular monoamine transporter 2 (VMAT2), which can lead to dopamine release. Enhancing these neurotransmitters in sleep/wake circuitry (far right) can be wake-promoting and fatigue-reducing; thus, they are both approved for excessive daytime sleepiness in narcolepsy and used off-label in other conditions associated with hypersomnia.

are now available for the treatment of ADHD and are reviewed in detail in Chapter 11 (see Figures 11-9, 11-10, 11-33, 11-35, and 11-36) and in Chapter 13 on substance abuse (see Figure 13-8).

Amphetamine and methylphenidate can be dosed to treat sleepiness in narcolepsy in order to enhance the synaptic availability of the wake-promoting and arousal neurotransmitters dopamine and norepinephrine and thereby improve wakefulness in narcolepsy without causing significant reinforcement (Figure 10-60). Nevertheless, amphetamine and methylphenidate are controlled substances because of high abuse and diversion potential, as well as the possibility of inducing psychosis, mania, high blood pressure, and other side effects, especially at doses higher than those used to treat sleepiness or ADHD (discussed in Chapters 11 and 13). However, they are highly effective agents to promote wakefulness in narcolepsy.

Modafinil/Armodafinil

Mechanism of Action

Racemic modafinil and its R enantiomer armodafinil (Figure 10-61) are wake-promoting agents not only approved for the treatment of narcolepsy, but also as adjunctive treatments for obstructive sleep apnea and for shift work disorder. These agents are thought to act predominantly as inhibitors of the dopamine transporter (DAT) or dopamine (DA) reuptake pump (Figure 10-62). Although modafinil is a weak DAT inhibitor, the concentrations of the drug achieved after oral dosing are quite high, and sufficient to have substantial actions on DATs. In fact, the pharmacokinetics of modafinil suggest that this drug acts via a slow rise in plasma levels, sustained plasma levels for 6–8 hours, and incomplete occupancy of DAT, all properties that could be ideal for enhancing tonic dopamine activity to promote wakefulness (Figure 10-63) rather than phasic dopamine activity to promote reinforcement and abuse (see Chapter 11 on ADHD and Figures 11-9, 11-10, 11-33, 11-35, and 11-36 as well as Chapter 13 on substance abuse and Figure 13-8). Once dopamine release is activated by modafinil, and the cortex is aroused, this can apparently lead to downstream release of histamine from the tuberomammillary nucleus (TMN) and then further activation of the lateral hypothalamus with orexin release to stabilize wakefulness (Figure 10-63).

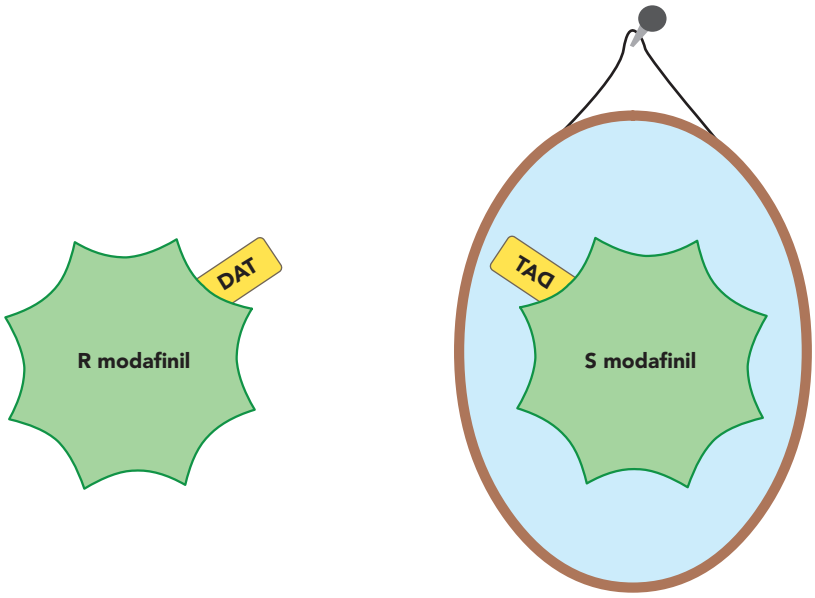


Figure 10-61 Modafinil and armodafinil. Modafinil consists of two enantiomers, R and S; the R enantiomer has been developed and marketed as armodafinil. Both modafinil and armodafinil are thought to act predominantly as inhibitors of the dopamine transporter (DAT).

However, the activation of the lateral hypothalamus and release of orexin do not appear to be necessary for the action of modafinil, since modafinil still promotes wakefulness in patients who have loss of hypothalamic orexin neurons in narcolepsy. The activation of TMN and lateral hypothalamic neurons may be secondary and downstream actions resulting from modafinil's effects on dopamine neurons.

A related wake-promoting agent is the R enantiomer of modafinil, called armodafinil (Figure 10-61). Armodafinil has a later time to peak levels, a longer half-life, and higher plasma drug levels 6–14 hours after oral administration than racemic modafinil. The pharmacokinetic properties of armodafinil could theoretically improve the clinical profile of modafinil, with greater activation of phasic dopamine firing, possibly eliminating the need for a second daily dose, as is often required with racemic modafinil.

Narcolepsy

Modafinil/armodafinil are effective treatments of sleepiness in narcolepsy, although possibly not as powerful as amphetamine and methylphenidate. However, head-to-head trials have not been conducted. Furthermore, the abuse potential of modafinil/armodafinil is much reduced compared to amphetamine and methylphenidate, and the side effects are not as severe. In addition, both modafinil and armodafinil are approved for treatment of two additional disorders for which amphetamine and methylphenidate are not approved, namely, for shift work disorder and as adjunctive treatment for obstructive sleep apnea (OSA).

Obstructive Sleep Apnea

First-line treatment for OSA (Figure 10-49) is continuous positive airway pressure (CPAP) (Figure 10-64). Although CPAP treatment is quite effective and has been shown to reduce hospitalization rates and healthcare costs, adherence rates are poor (54%). For patients who find CPAP intolerable, there are other treatment options that may be considered, including bilevel positive airway pressure (BPAP), auto-titrating positive airway pressure (APAP), oral appliances designed to stabilize the jaw and/or tongue during sleep, and various surgeries aimed at correcting physical attributes that may contribute to OSA. Additionally, several behavioral interventions may be useful for ameliorating OSA; these include weight loss (to a BMI <25), exercise, the avoidance of alcohol and sedatives at bedtime, and positional therapy (i.e., the use of a backpack or other object that prevents the patient from sleeping on their back). Modafinil and armodafinil are approved specifically as adjuncts to standard treatment of underlying airway obstruction, which is frequently inadequate to treat the hypersomnia associated with OSA. Given the low adherence rates to CPAP, modafinil/armodafinil are sometimes used "off-label" for OSA as monotherapies for patients who do not tolerate CPAP.

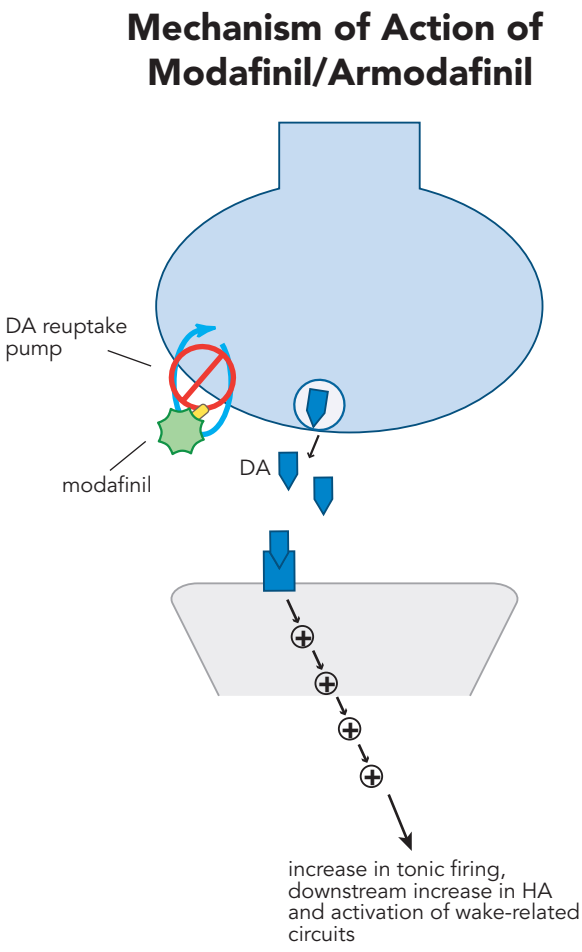


Figure 10-62 Mechanism of action of modafinil/armodafinil. Modafinil and armodafinil bind with weak affinity for the dopamine transporter (DAT); however, their plasma levels are high and this compensates for the low binding. Increased synaptic dopamine (DA) following blockade of DAT leads to increased tonic firing and downstream effects on neurotransmitters involved in wakefulness, including histamine (HA) and orexin/hypocretin.

Shift Work Disorder

Shift work disorder (Figure 10-51) can be tricky to treat, especially if the patient has an ever-evolving and unstable shift work schedule. Suffice it to say, shift workers are frequently sleepy, but still must work, drive, and function. Modafinil/armodafinil can make a big difference in an individual's ability to function with alertness when suffering from shift work disorder. Supplementing modafinil/armodafinil with circadian rhythm adjunctive therapy is often helpful (Figure 10-55). This includes trying to reset the biological clock with morning light (Figure 10-56), especially when needing to function during the daytime when sleepy. Exposure to light alters circadian rhythms and suppresses melatonin release. Treatment with 10,000 lux, bright, blue light for 30 minutes a day may be used to reset circadian rhythms (Figure 10-56). Importantly, the administration of bright light therapy must be appropriately timed in accordance with the patient's circadian phase of melatonin secretion, with light administration occurring approximately 8 hours after evening melatonin secretion (possibly amplified by oral dosing with a melatonin agent, Figure 10-57) or in accordance with a predetermined bright light phase response curve. One form of bright light therapy, dawn simulation therapy, applies a slow, incremental light signal at the end of the sleep cycle. Data show that performance, alertness, and mood during the night shift can be improved in shift workers using bright light re-entrainment of circadian rhythms.

Solriamfetol, a Wake-Promoting NDRI

Solriamfetol is a recently approved agent for daytime sleepiness, both in patients with narcolepsy and as an adjunct to mechanical treatments for airway obstruction in patients with OSA. It works by norepinephrine and dopamine reuptake inhibition (see Chapter 7 and Figures 7-34 through 7-36), and seems to be more potent than bupropion in this aspect, and less potent but more tolerable and less abusable than amphetamines or methylphenidate. Its short half-life is consistent with morning dosing wearing off in time for sleep.

Pitolisant, H_3 Presynaptic Antagonist

Pitolisant (Figure 10-65) is a drug with a novel mechanism for improving wakefulness in narcolepsy by blocking the normal action of presynaptic H_3 autoreceptors (Figure 10-66A,B) to inhibit histamine release. Inhibiting the presynaptic H_3 receptor causes the disinhibition (that is, the release) of presynaptic histamine (Figure 10-66C), and this is wake-promoting. Pitolisant, a presynaptic H_3 autoreceptor antagonist (Figures 10-65 and 10-66C), is approved for the treatment of narcolepsy, and there are anecdotal observations that it may be effective in cataplexy as well. Pitolisant is not a controlled substance and has no known abuse potential and is in testing for improving excessive daytime sleepiness in OSA. Pitolisant can be overly activating, causing anxiety or insomnia. Studies suggest it may be about as effective as modafinil but perhaps not as effective as amphetamine/methylphenidate for improving excessive daytime sleepiness.

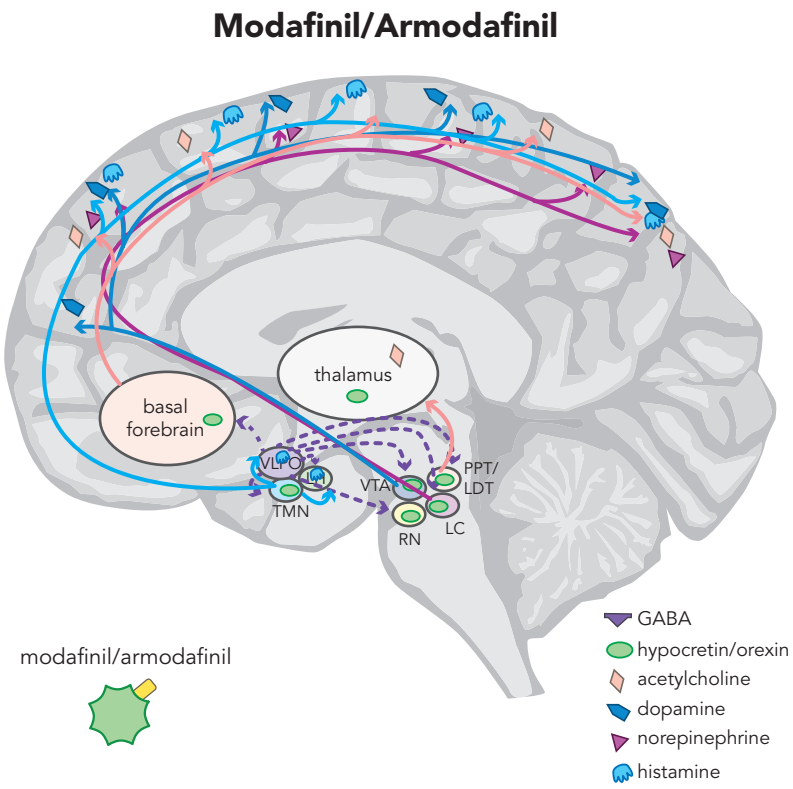


Figure 10-63 **Modafinil/armodafinil in wake circuits.** Blockade of the dopamine transporter (DAT) by modafinil/armodafinil leads to increased tonic dopaminergic firing and downstream effects on wake-promoting neurotransmitters. Specifically, cortical release of wake-promoting neurotransmitters is increased, which leads to downstream release of histamine from the tuberomammillary nucleus (TMN) and further activation of the lateral hypothalamus (LH), with corresponding orexin release that stabilizes wakefulness.

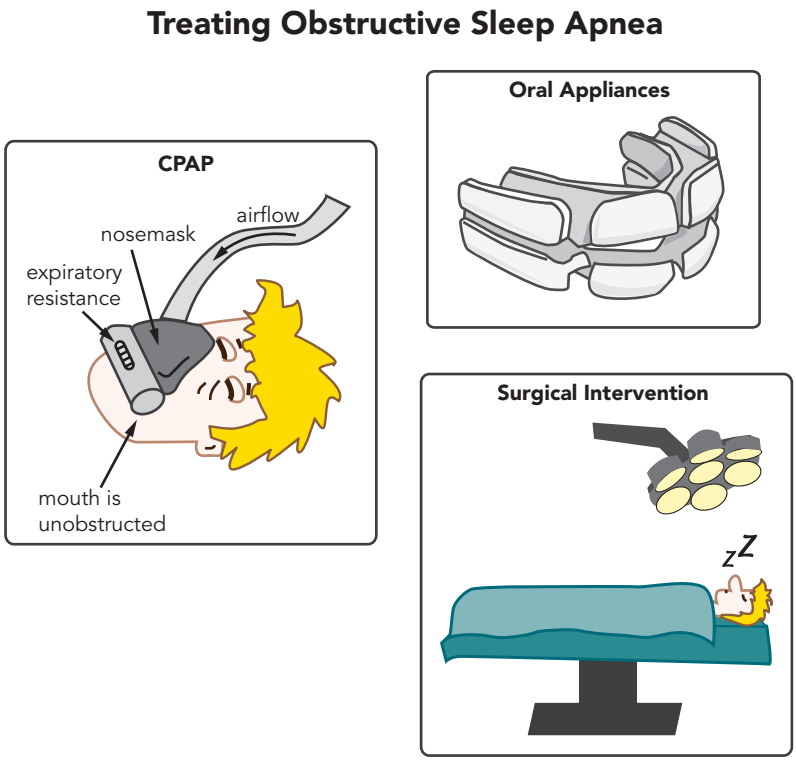


Figure 10-64 **Treating obstructive sleep apnea.** First-line treatment for obstructive sleep apnea (OSA) is continuous positive airway pressure (CPAP). Other treatment options are also available, including oral appliances and surgical interventions. Medications can be used as adjuncts to treat excessive daytime sleepiness associated with OSA.

Sodium Oxybate and Narcolepsy/Cataplexy

Sodium oxybate (Figure 10-67) is also known as γ-hydroxybutyrate (GHB), and acts as a full agonist at GHB receptors and a partial agonist at $GABA_B$ receptors (Figure 10-68). As a $GABA_B$ partial agonist, sodium oxybate acts as an antagonist when GABA levels are elevated and as an agonist when GABA levels are low. GHB is actually a natural product present in the brain with its own GHB receptors upon which it acts (Figure 10-68). GHB is formed from the neurotransmitter GABA. It is hypothesized that sodium oxybate increases slow-wave sleep and improves cataplexy via these actions at $GABA_B$ receptors.

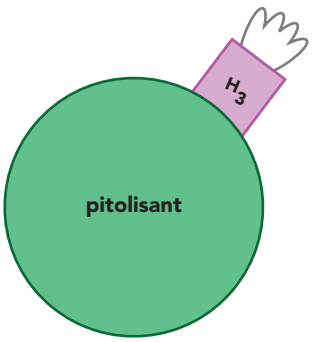


Figure 10-65 Pitolisant. Pitolisant is an antagonist at presynaptic histamine 3 (H_3) autoreceptors. It is approved for the treatment of excessive daytime sleepiness in patients with narcolepsy.

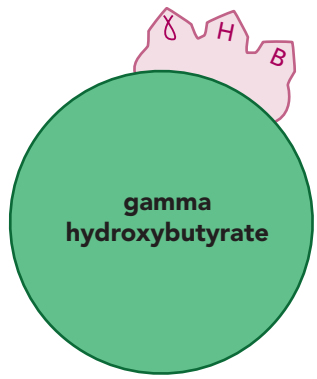


Figure 10-67 Sodium oxybate. Sodium oxybate, also known as γ-hydroxybutyrate (GHB), acts as a full agonist at GHB receptors and as a partial agonist at $GABA_B$ receptors. It is approved for use both in cataplexy and for excessive sleepiness, and appears to enhance slow-wave sleep.

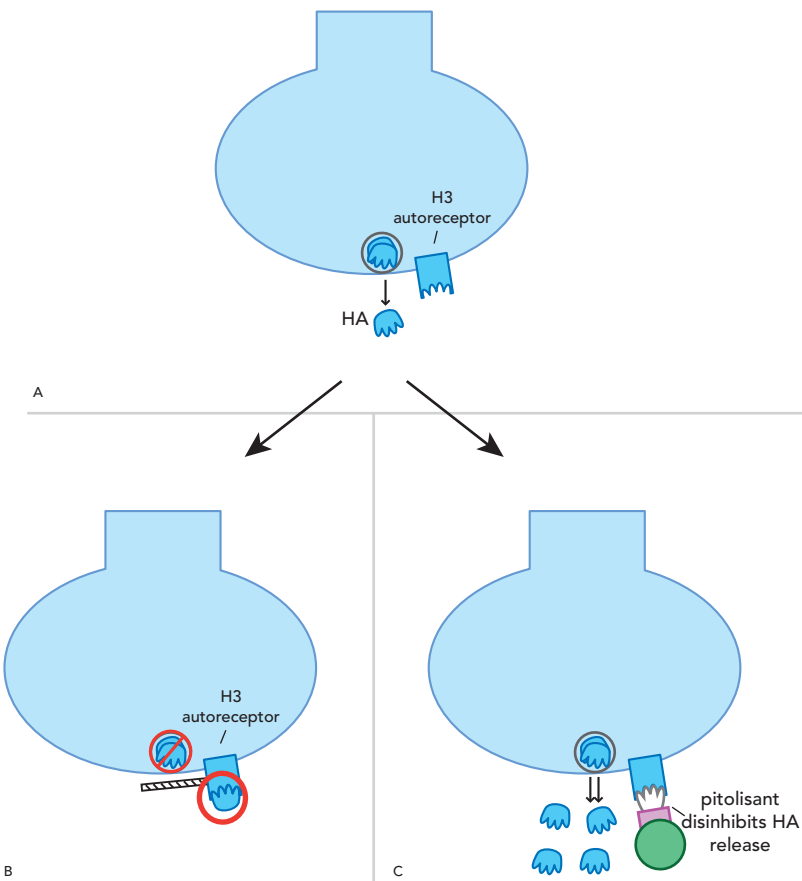


Figure 10-66 Mechanism of action of pitolisant. Histamine 3 (H_3) receptors are presynaptic autoreceptors and function as gatekeepers for histamine (HA). (A) When H_3 receptors are not bound by histamine, the molecular gate is open and allows histamine release. (B) When histamine binds to the H_3 receptor, the molecular gate closes and prevents histamine from being released. (C) When pitolisant blocks the H_3 receptor, this disinhibits, or turns on, the release of histamine.

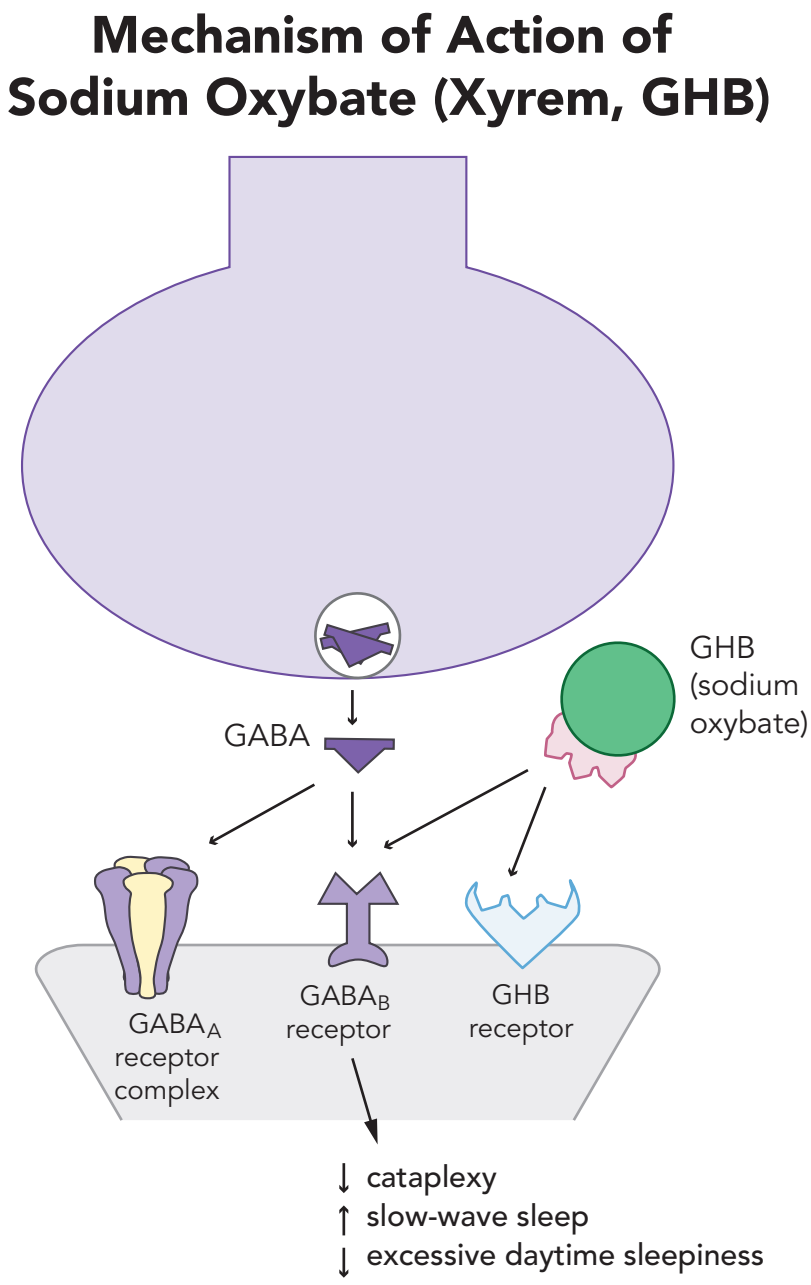


Figure 10-68 Mechanism of action of sodium oxybate. Sodium oxybate binds as a full agonist to γ-hydroxybutyrate (GHB) receptors and as a partial agonist at $GABA_B$ receptors. Its actions at $GABA_B$ receptors are presumed to be responsible for its clinical effects of improving slow-wave sleep and reducing cataplexy. As a partial agonist, sodium oxybate causes less stimulation of $GABA_B$ receptors than GABA itself, but more than in the absence of GABA. Thus, it can reduce $GABA_B$ stimulation when GABA levels are high, and increase it when GABA levels are low.

Sodium oxybate is approved for use in both cataplexy and excessive sleepiness, and it appears to enhance slow-wave sleep and reduce hypnagogic hallucinations and sleep paralysis. Thus, rather than improving wake-promoting neurotransmitters as every other treatment for excessive daytime sleepiness does, sodium oxybate supposedly makes you sleep so well at night with slow-wave sleep restoration that you are not sleepy in the daytime.

Because of its abuse potential and colorful history, it is scheduled as a controlled substance and its supplies are tightly regulated through a central pharmacy in the US. It has been labeled a "date rape" drug by the press as it can be used with alcohol for this purpose, "knocking someone out" and causing amnesia for the time while involuntarily intoxicated. Because it profoundly increases slow-wave sleep and the growth hormone

surge that accompanies slow-wave sleep, it was also used (abused) by athletes as a performance-enhancing drug, especially in the 1980s when it was sold over the counter in health food stores. GHB is used in some European countries as a treatment for alcoholism. Due to the observed enhancement of slow-wave sleep, GHB has been successfully tested in fibromyalgia (see Chapter 9 for discussion of pain syndromes such as fibromyalgia) and is occasionally used "off-label" to treat refractory cases.

SUMMARY

The neurobiology of wakefulness is linked to an arousal system that utilizes the five neurotransmitters histamine, dopamine, norepinephrine, acetylcholine, and serotonin and the wake-stabilizing neurotransmitters orexins as components of the ascending reticular activating system. Sleep and wakefulness are also regulated by a hypothalamic sleep/wake switch, with wake-promoter neurons in the tuberomamillary nucleus that utilize histamine as neurotransmitter, and sleep-promoter neurons in the ventolateral preoptic nucleus that utilize GABA as neurotransmitter. The synthesis, metabolism, receptors, and pathways for the neurotransmitter histamine and orexin are reviewed in this chapter. Insomnia and its treatments are reviewed, as are the mechanisms of action of several classic hypnotic agents including the benzodiazepines and the popular "Z drugs," which act as positive allosteric modulators (PAMs) for $GABA_A$ receptors. Other hypnotics reviewed include trazodone, melatonergic hypnotics, and antihistamines, as well as the novel dual orexin receptor antagonists (DORAs). Excessive daytime sleepiness is also described as are the mechanisms of action of the wake-promoting drugs modafinil, caffeine, and stimulants. The actions of γ-hydroxybutyrate (GHB) plus a number of novel sleep- and wake-promoting drugs are also reviewed.

11 Attention Deficit Hyperactivity Disorder and Its Treatment

Symptoms and Circuits: ADHD as a Disorder of the Prefrontal Cortex 449
ADHD as a Disorder of Inefficient "Tuning" of the Prefrontal Cortex by Dopamine and Norepinephrine 454
Neurodevelopment and ADHD 463
Treatments for ADHD 466
Which Symptoms Should Be Treated First? 466
Stimulant Treatment of ADHD 467
Noradrenergic Treatment of ADHD 480
Future Treatments for ADHD 484
Summary 485

Attention deficit hyperactivity disorder (ADHD) is not just a disorder of "attention," nor does it have to include "hyperactivity." Paradigm shifts are altering the landscape for treatment options across the full range of ADHD symptoms, from inattention to impulsivity to hyperactivity, as well as across all the waking hours and across the whole lifespan, from young children through adulthood. This chapter will provide an overview of the psychopharmacology of ADHD, including only short discussions of the symptoms of ADHD. The mechanism of action of treatments classically called stimulants and nonstimulants for ADHD will be emphasized. Information on the full clinical descriptions and formal criteria for how to diagnose and rate ADHD and its symptoms should be obtained by consulting standard reference sources. The discussion here will emphasize the links between various brain circuits and their neurotransmitters with the various symptoms and comorbidities of ADHD and how these are linked to effective psychopharmacological treatments. The goal of this chapter is to acquaint the reader with ideas about the clinical and biological aspects of attention, impulsivity, and hyperactivity. For details of doses, side effects, drug interactions, and other issues relevant to the prescribing of drugs for ADHD in clinical practice, the reader should consult standard drug handbooks (such as *Stahl's Essential Psychopharmacology: the Prescriber's Guide*).

SYMPTOMS AND CIRCUITS: ADHD AS A DISORDER OF THE PREFRONTAL CORTEX

ADHD is noted for a trio of symptoms: inattention, hyperactivity, and impulsivity (Figure 11-1). It is currently hypothesized that all these symptoms arise from inefficient information processing in various circuits involving the prefrontal cortex (Figures 11-2 through 11-8). Specifically, the prominent symptom of "inattention" in ADHD can also be described more precisely as "executive dysfunction" and the inability to *sustain* attention long enough to solve problems. Executive dysfunction is hypothetically linked to inefficient information processing in the dorsolateral prefrontal cortex (DLPFC) (Figures 11-2, 11-3, and 11-7). The DLPFC is activated by a cognitive task known as the *n*-back test which can be monitored in living patients doing it while in a functional brain scanner (shown in Figure 11-3). Having difficulty in efficiently activating this part of the brain cuts across many psychiatric disorders that share the symptom of executive dysfunction, not just ADHD but also schizophrenia (discussed in Chapter 4), major depression (discussed in Chapter 6), mania (discussed in Chapter 6), anxiety (discussed in Chapter 8), pain (Chapter 9), and disorders of sleep and wakefulness (discussed in Chapter 10). One can see how inefficient information processing in this particular DLPFC circuit, especially when put under a cognitive "load," can be associated with the same symptom of executive dysfunction and difficulty in sustaining attention and solving problems in many different psychiatric disorders. This is why diagnosis in psychiatry is now progressively moving from describing *categorical* syndromes that mix together many symptoms to make a diagnosis (as in the DSM and ICD), towards characterizing single *symptom dimensions* or *domains* such as executive dysfunction that cut across many psychiatric disorders. The emphasis on symptoms rather than diagnosis is the trend in much of neurobiological research, with the goal of finding better correlates with neuroimaging, biomarkers, and genetics.

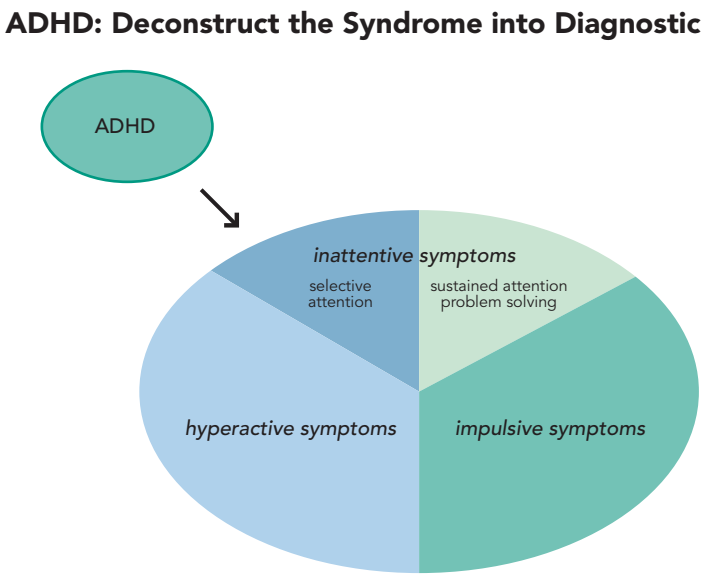


Figure 11-1 **Symptoms of ADHD.** There are three major categories of symptoms associated with attention deficit hyperactivity disorder (ADHD): inattention, hyperactivity, and impulsivity. Inattention itself can be divided into difficulty with selective attention and difficulty with sustained attention and problem solving.

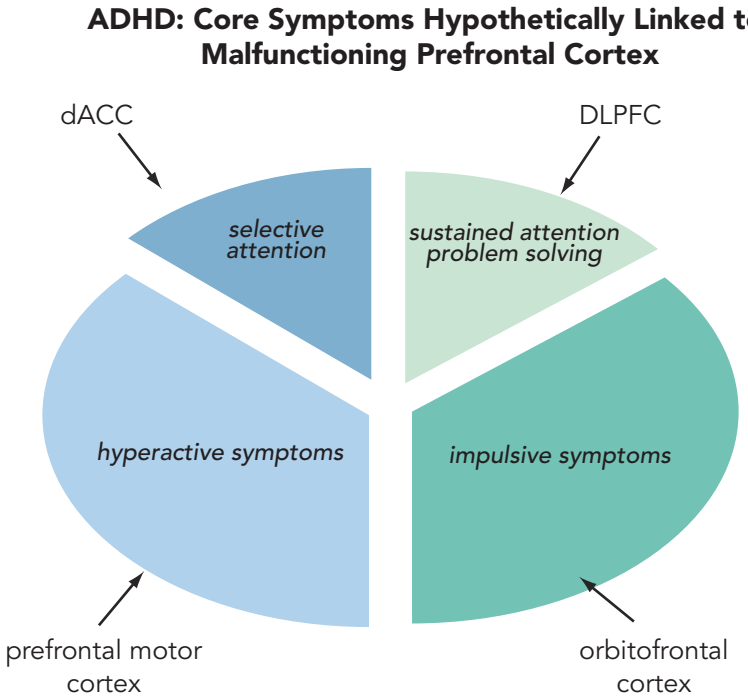


Figure 11-2 **Matching ADHD symptoms to circuits.** Problems with selective attention are believed to be linked to inefficient information processing in the dorsal anterior cingulate cortex (dACC), while problems with sustained attention are linked to inefficient information processing in the dorsolateral prefrontal cortex (DLPFC). Hyperactivity may be modulated by the prefrontal motor cortex and impulsivity by the orbital frontal cortex.

Another dimension of executive dysfunction in ADHD is *selective* inattention, or not being able to *focus*, and thus differs from problems with *sustaining* attention described above. The symptom of problems focusing/selective inattention is hypothetically linked to inefficient information processing in a different brain area, namely the dorsal anterior cingulate cortex (dACC) (Figures 11-2, 11-4, and 11-7). The dACC can be activated by tests of selective attention, such as the Stroop test (explained in Figure 11-4). ADHD patients may either fail to activate the dACC when they should be focusing their attention, or they may activate this part of the brain very inefficiently and only with great effort and easy fatiguability.

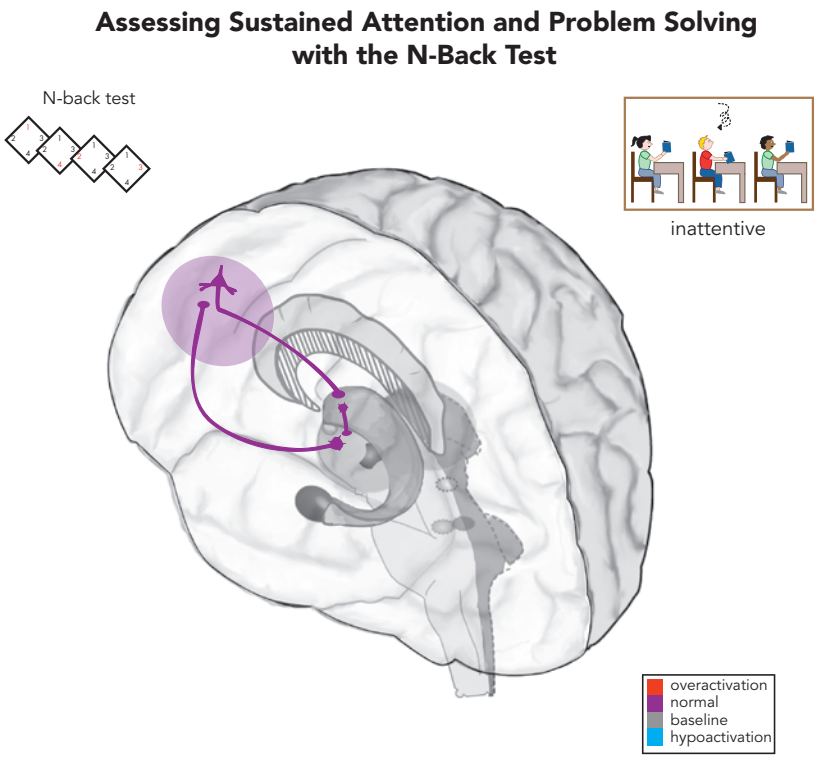


Figure 11-3 Sustained attention and problem solving: the *n*-back test. Sustained attention is hypothetically modulated by a cortico-striato-thalamo-cortical loop that involves the dorsolateral prefrontal cortex (DLPFC) projecting to the striatal complex. Inefficient activation of the DLPFC can lead to difficulty following through or finishing tasks, disorganization, and trouble sustaining mental effort. Tasks such as the *n*-back test are used to measure sustained attention and problem-solving abilities. In the 0-back variant of the *n*-back test, a participant looks at a number on the screen, and presses a button to indicate which number it is. In the 1-back variant, a participant only looks at the first number; when the second number appears the participant is supposed to press a button corresponding to the first number. Higher "*n*" values are correlated with increased difficulty in the test.

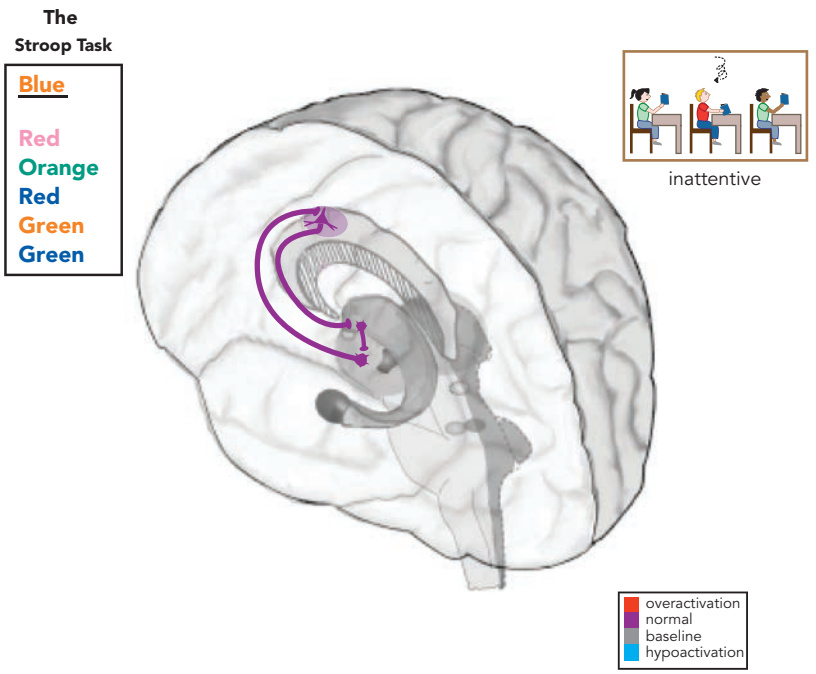
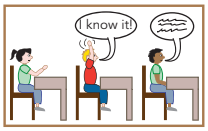
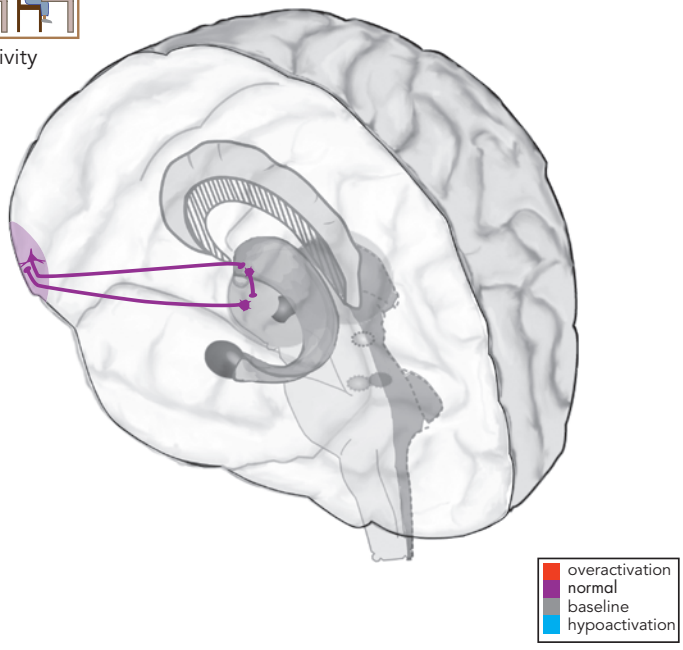


Figure 11-4 Selective attention: the Stroop task. Selective attention is hypothetically modulated by a cortico-striato-thalamo-cortical loop arising from the dorsal anterior cingulate cortex (dACC) and projecting to the striatal complex, then the thalamus, and back to the dACC. Inefficient activation of dACC can result in symptoms such as paying little attention to detail, making careless mistakes, not listening, losing things, being distracted, and forgetting things. An example of a test that involves selective attention, and thus should activate the dACC, is the Stroop task. The Stroop task requires the participants to name the color in which a word is written, instead of saying the word itself. For example, if the word "blue" is written in orange, then the correct answer is "orange," while "blue" is the incorrect choice.

Impulsivity Is Modulated by the Orbitofrontal Cortex



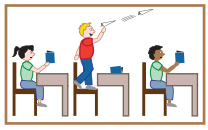
impulsivity



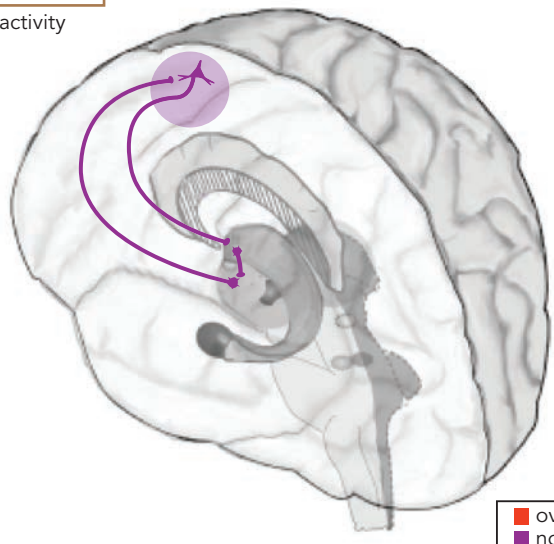
overactivation
normal
baseline
hypoactivation

Figure 11-5 Impulsivity. Impulsivity is associated with a cortico-striato-thalamo-cortical loop that involves the orbital frontal cortex (OFC), the striatal complex, and the thalamus. Examples of impulsive symptoms in ADHD include talking excessively, blurting things out, not waiting one's turn, and interrupting.

Motor Hyperactivity Is Modulated by the Prefrontal Cortex



hyperactivity



overactivation
normal
baseline
hypoactivation

Figure 11-6 Hyperactivity. Motor activity, such as hyperactivity and psychomotor agitation or retardation, can be modulated by a cortico-striato-thalamo-cortical loop from the prefrontal motor cortex to the putamen (lateral striatum) to the thalamus and back to the prefrontal motor cortex. Common symptoms of hyperactivity in children with ADHD include fidgeting, leaving one's seat, running/climbing, being constantly on the go, and having trouble playing quietly.

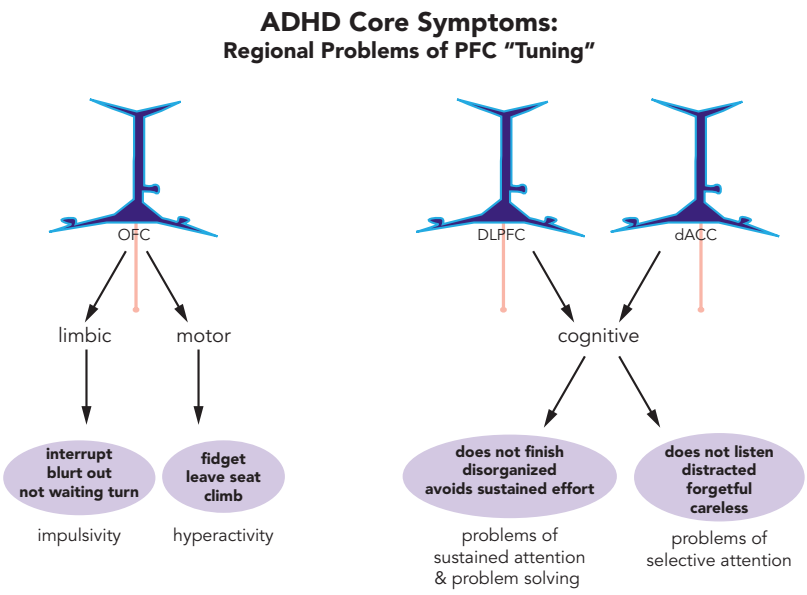


Figure 11-7 **ADHD core symptoms: regional problems of PFC tuning.** The symptoms of ADHD may occur because patients do not activate prefrontal cortical areas appropriately in response to cognitive tasks. Alterations within the orbital frontal cortex (OFC) are hypothesized to lead to problems with impulsivity or hyperactivity. Inadequate tuning of the dorsolateral prefrontal cortex (DLPFC) or the dorsal anterior cingulate cortex (dACC) can respectively lead to sustained or selective attention symptoms.

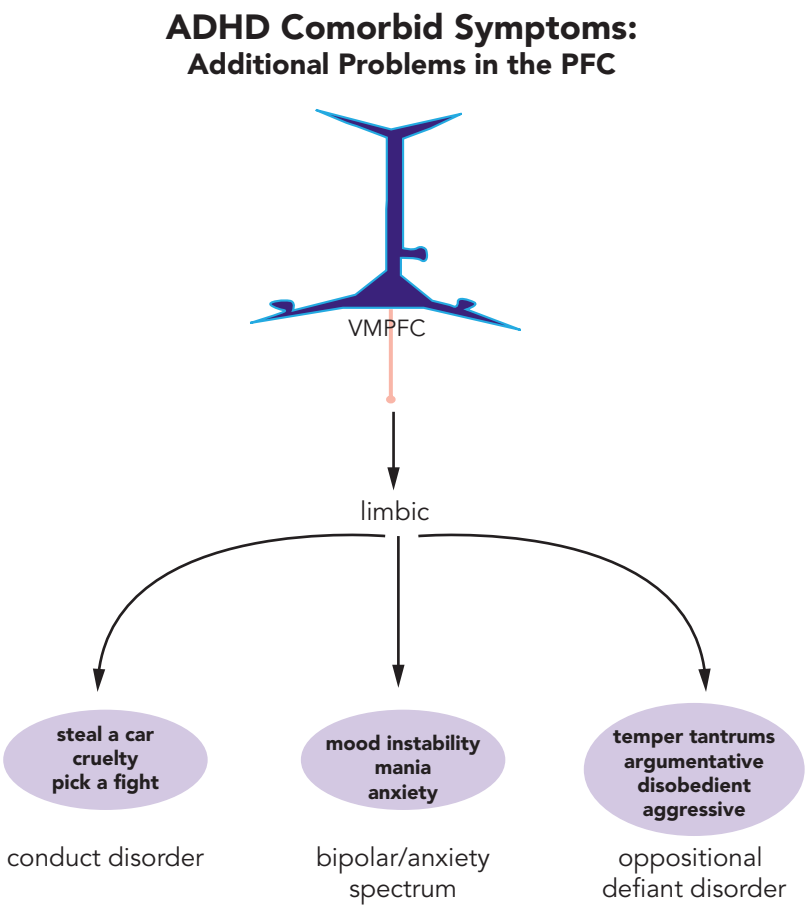


Figure 11-8 **ADHD and comorbid symptoms.** Inadequate tuning of the ventromedial prefrontal cortex (VMPFC) may be associated with comorbid symptoms often seen in patients with ADHD, such as symptoms of conduct disorder or oppositional defiant disorder, as well as mood instability and anxiety.

Other areas of prefrontal cortex that are hypothetically functioning inefficiently in ADHD are the orbital frontal cortex (OFC), linked to symptoms of impulsivity (Figures 11-2, 11-5, and 11–7), and the supplementary motor area, linked to symptoms of motor hyperactivity (Figures 11-2, 11-6, and 11–7). The OFC is hypothetically linked to a wide variety of symptoms that cut across several psychiatric conditions, including impulsivity in ADHD (Figures 11-2, 11-5, and 11-7), impulsivity and violence in schizophrenia (discussed in Chapter 4), suicidality in depression (discussed in Chapter 6), impulsivity in mania (discussed in Chapter 6), and impulsivity/compulsivity in substance abuse and related disorders (discussed in Chapter 13). Impulsive symptoms in other psychiatric conditions commonly comorbid with ADHD are also hypothetically related to the OFC such as conduct disorder, oppositional defiant disorder, and bipolar disorder (Figure 11-8). See Chapter 13 for further discussion of impulsivity and compulsivity in a variety of psychiatric disorders including substance abuse, eating disorders, obsessive–compulsive disorder (OCD), and others.

ADHD AS A DISORDER OF INEFFICIENT "TUNING" OF THE PREFRONTAL CORTEX BY DOPAMINE AND NOREPINEPHRINE

Hypothetically, ADHD patients do not activate prefrontal cortex areas appropriately in response to cognitive tasks of attention and problem solving (executive functioning) (Figures 11-7 through 11-21). This could be due to the observed neurodevelopmental delays in prefrontal cortical synaptic connections in ADHD (see Figures 11-22 and 11-23), causing inefficient "tuning" of information processing in prefrontal circuits regulated by norepinephrine (NE) and dopamine (DA)

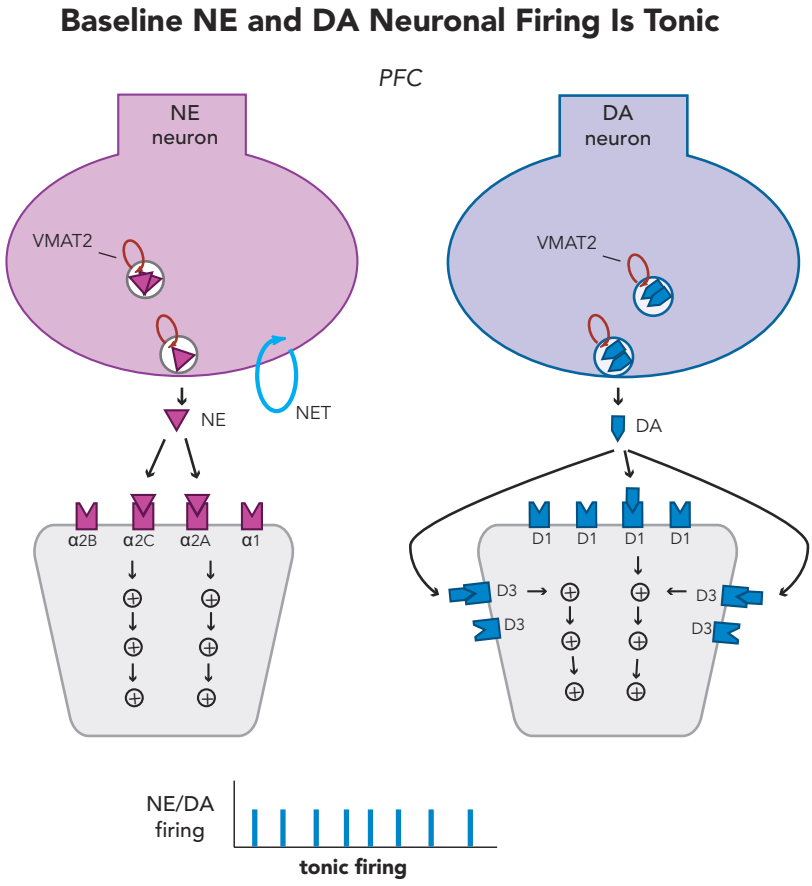


Figure 11-9 Baseline norepinephrine and dopamine tonic firing. Modulation of prefrontal cortical function, and therefore regulation of attention and behavior, rely on the optimum release of norepinephrine (NE) and dopamine (DA). Under normal conditions, NE and DA in the prefrontal cortex (PFC) stimulate a few receptors on postsynaptic neurons, allowing for optimal signal transmission and neuronal firing. At modest levels, NE can improve prefrontal cortical functioning by stimulating postsynaptic α_{2A} receptors. Similarly, modest levels of DA will stimulate dopamine 1 and 3 (D_1 and D_3) receptors and be beneficial to prefrontal cortical functioning. In the case of both the NE and DA systems, moderation is certainly key.

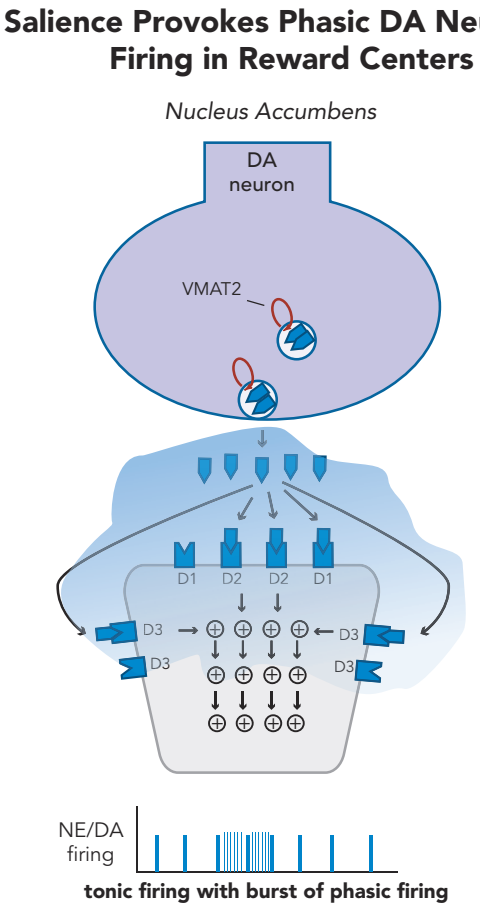


Figure 11-10 Salience-provoked phasic dopamine firing. While tonic firing, as seen in the prefrontal cortex, is often preferred in neuronal systems, a little bit of phasic firing of dopamine (DA) neurons in the nucleus accumbens can be a good thing. Phasic firing will lead to bursts of DA release and when this happens in a controlled manner it can reinforce learning and reward conditioning, which can provide the motivation to pursue naturally rewarding experiences (e.g., education, career development, etc.). When this system is out of bounds, however, it can induce uncontrolled DA firing that reinforces the reward of taking drugs of abuse, for example, in which case the reward circuitry can be hijacked, and impulses are followed by the development of uncontrolled compulsions to seek drugs.

neurotransmission (Figure 11-9 and Figure 11-10). This is the same arousal network that was discussed in Chapter 10 on sleep and illustrated in Figures 10-1 and 10-44.

If the firing of NE neurons innervating the prefrontal cortex is too low in ADHD (Figures 11-11 and 11-12), there would be inadequate "tonic" NE stimulation setting the baseline "tone" of noradrenergic neurotransmission too low. Low NE tone hypothetically contributes to the cognitive dysfunction in ADHD (Figure 11-11) and preferentially stimulates the most sensitive noradrenergic receptors on postsynaptic neurons (Figure 11-12). Increasing NE levels modestly would hypothetically improve prefrontal cortical function by stimulating the more sensitive postsynaptic α_{2A} receptors (Figure 11-12) but increasing NE too high – as may occur in stressful situations or in various comorbid conditions such as anxiety, substance abuse, and mania – could lead to impaired working memory when the less sensitive α_1 and β_1 receptors are also recruited (Figures 11-13 to 11-15). Thus, NE neurotransmission must occur within a "sweet spot" of neither too high nor too low (Figure 11-15) in order to optimize cognitive functioning.

Similarly, if the firing of DA neurons innervating the prefrontal cortex is also too low in ADHD, there would hypothetically be inadequate "tonic" DA stimulation, setting the baseline "tone" of the DA synapse too low at rest (Figures 11-11 and 11-12). Low release of DA preferentially stimulates the most sensitive DA receptors on postsynaptic neurons (i.e., D_3 receptors; Figure 11-9; see also Chapter 4 and Figure 4-9) but inadequately stimulates the less sensitive D_1 receptors (Figures 11-11, 11-12, 11-15, and 11-16), and this would cause inadequate downstream neuronal signaling and cognitive dysfunction. Increasing DA levels modestly would hypothetically improve prefrontal cortical function in part by first boosting tonic signaling at D_3 receptors, then at moderately sensitive D_2 receptors, and finally at the least sensitive D_1 receptors (Figures 11-9, 11-11 through 11-13, 11-15, and 11–16; see also Chapter 4 and Figure 4-9).

Dopamine neurons also exhibit bursts of firing called *phasic* DA stimulation (Figure 11-10), with a flurry of dopamine release that recruits all three DA receptor subtypes. Phasic DA release is thought to reinforce learning and reward conditioning, providing the motivation to pursue naturally rewarding experiences. The DA system is adaptively programmed to fire in a *phasic* manner when there are pertinent and notable sensory inputs such as those associated with education, recognition, career development, enriching social and family connections, etc. Enhancing phasic DA signaling modestly so that cognitive tasks can be performed efficiently is hypothetically the therapeutic goal in treatment of ADHD. However, when the phasic DA system is overly activated by stress or comorbid

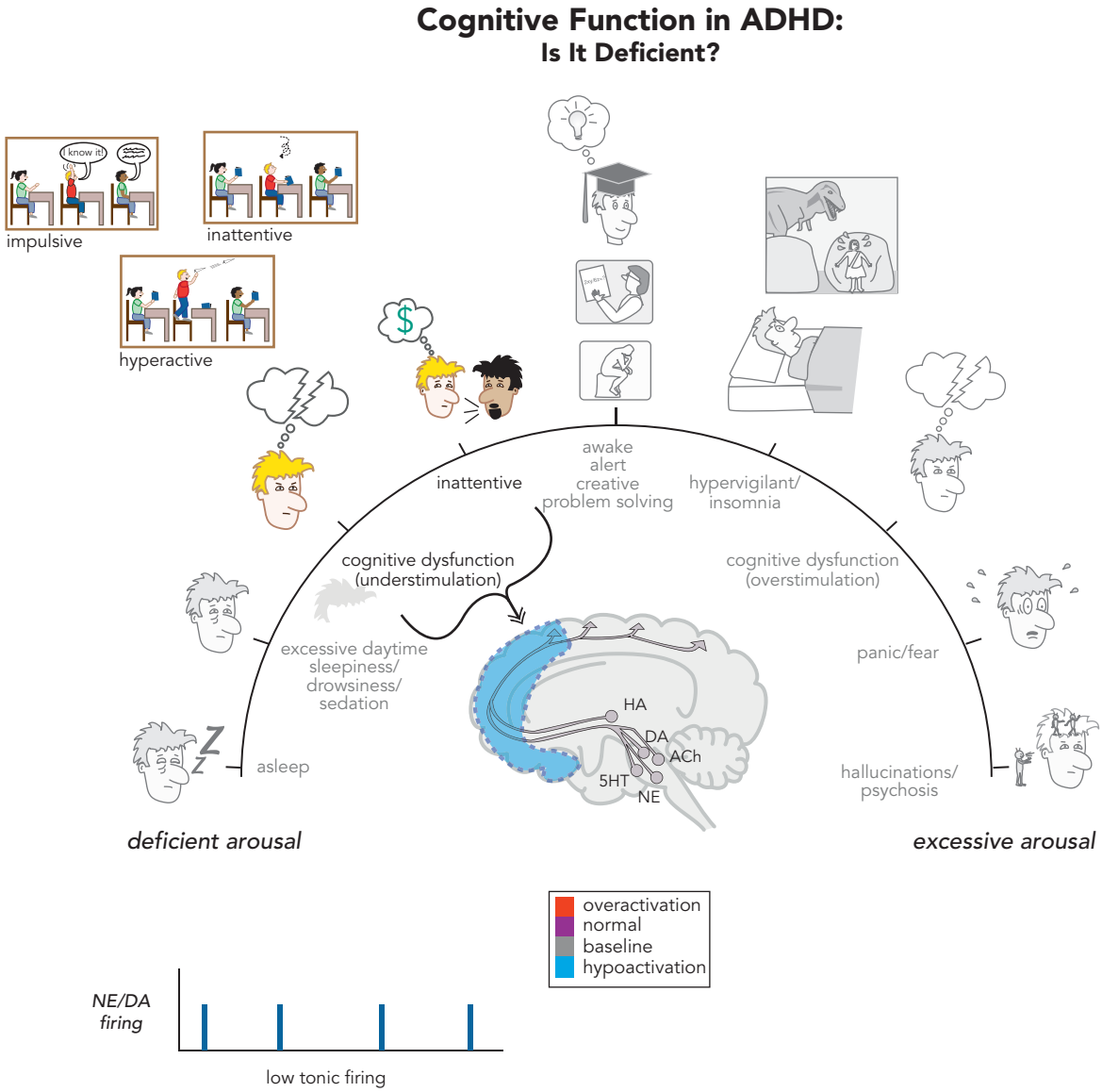


Figure 11-11 Cognitive function in ADHD: is it deficient? Arousal exists as if on a dimmer switch, with many phases along the spectrum. Where on the spectrum one lies is influenced by several key wake-promoting neurotransmitters, including histamine (HA), dopamine (DA), norepinephrine (NE), serotonin (5HT), and acetylcholine (ACh). When neurotransmission is balanced, one is awake, alert, and able to function well. Alterations in the functioning of these key neurotransmitters, whether too much or too little, can cause cognitive dysfunction. Cognitive dysfunction in ADHD may be a result of low tonic noradrenergic and dopaminergic firing.

conditions such as anxiety, substance abuse, or mania, it worsens cognitive functioning with too much arousal (Figures 11-13 through 11-16). The phasic DA system can even be hijacked by drugs, and induce uncontrolled DA firing, reinforcing the reward of drugs, leading to compulsive drug abuse (discussed extensively in Chapter 13). Therefore, moderate, but not high or low, levels of D_1 receptor stimulation is what is thought to be beneficial to set the optimal tone and to optimize prefrontal cortical functioning (Figures 11-15 and 11-16). Postsynaptic D_1 receptors predominate in the prefrontal cortex and the best functional outcome is when they are "tuned" and neither understimulated nor overstimulated (Figures 11-15 and 11-16).

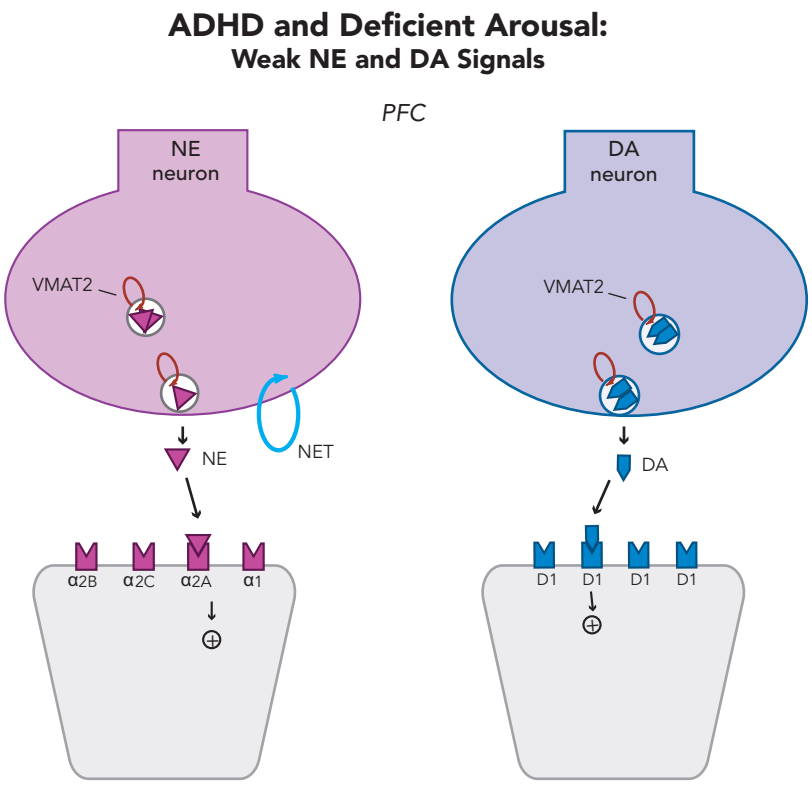


Figure 11-12 **ADHD and deficient arousal.** Besides being a key player in the arousal pathways, the prefrontal cortex (PFC) is also the main brain area where imbalances in norepinephrine (NE) and dopamine (DA) systems hypothetically occur in ADHD. Deficient signaling in prefrontal cortical NE and DA pathways is reflected by reduced stimulation of postsynaptic receptors. Specifically, D_1 receptors, which are relevant to cognitive functioning, are not very sensitive to dopamine; thus, they are not stimulated when DA levels are low. Increasing levels of NE and DA would hypothetically improve prefrontal cortical functioning through increased stimulation of postsynaptic α_{2A} receptors and increased stimulation of D_1 receptors.

In the prefrontal cortex, α_{2A} and D_1 receptors are often located on the spines of cortical pyramidal neurons, and can thus gate incoming signals (Figures 11-17 through 11-21). Alpha-2A receptors are linked to the molecule cyclic adenosine monophosphate (cAMP) via the inhibitory G protein (Gi) (Figure 11-17). D_1 receptors, on the other hand, are linked to the cAMP signaling system via the stimulatory G protein (Gs) (Figure 11-17). In either case, the cAMP molecule links the receptors to the hyperpolarization-activated cyclic nucleotide-gated (HCN) cation channels. An open channel will lead to a low membrane resistance, thus shunting inputs out of the spine. In the presence of an open channel, the signal leaks out and is therefore lost. However, when these channels are closed, the incoming signal survives and can be directed down the neuron to strengthen the network connectivity of similar neurons and lead to the appropriate signal and response.

When NE, or a noradrenergic agonist, binds to an α_{2A} receptor, the activated Gi-linked system inhibits cAMP, thereby closing the HCN channel (Figure 11-18). Closure of the channel allows the signal to go through the spine and down the neuron, thereby strengthening network connectivity with similar neurons (Figure 11-18). So, in general, in the prefrontal cortex, stimulation of α_{2A} receptors strengthens an incoming signal.

By contrast, stimulation of D_1 receptors leads to weakening of the signal (Figure 11-19). That is, when DA, or a DA agonist, binds to a D_1 receptor, the activated Gs-linked system will lead to increased stimulation – or opening – of HCN channels. The opening of the HCN channels, especially if excessive, will lead to leakage of the signal, thereby shunting any input out of the spine. So, excessive stimulation of D_1 receptors will, in contrast to stimulation of α_{2A} receptors, result in the dissipation and/or weakening of a signal. The mechanism of action of α_{2A} (Figure 11-18) and D_1 receptors (Figure 11-19) explains in general why moderate stimulation of both types of receptors (Figure 11-17) is preferred in order to strengthen the signal-to-noise ratio in prefrontal cortical neurons (see Figure 11-20).

What happens following concurrent stimulation of α_{2A} and D_1 receptors by NE and DA, respectively (Figure 11-20)? While the exact localization and density of α_{2A} and D_1 receptors within various cortical areas are still

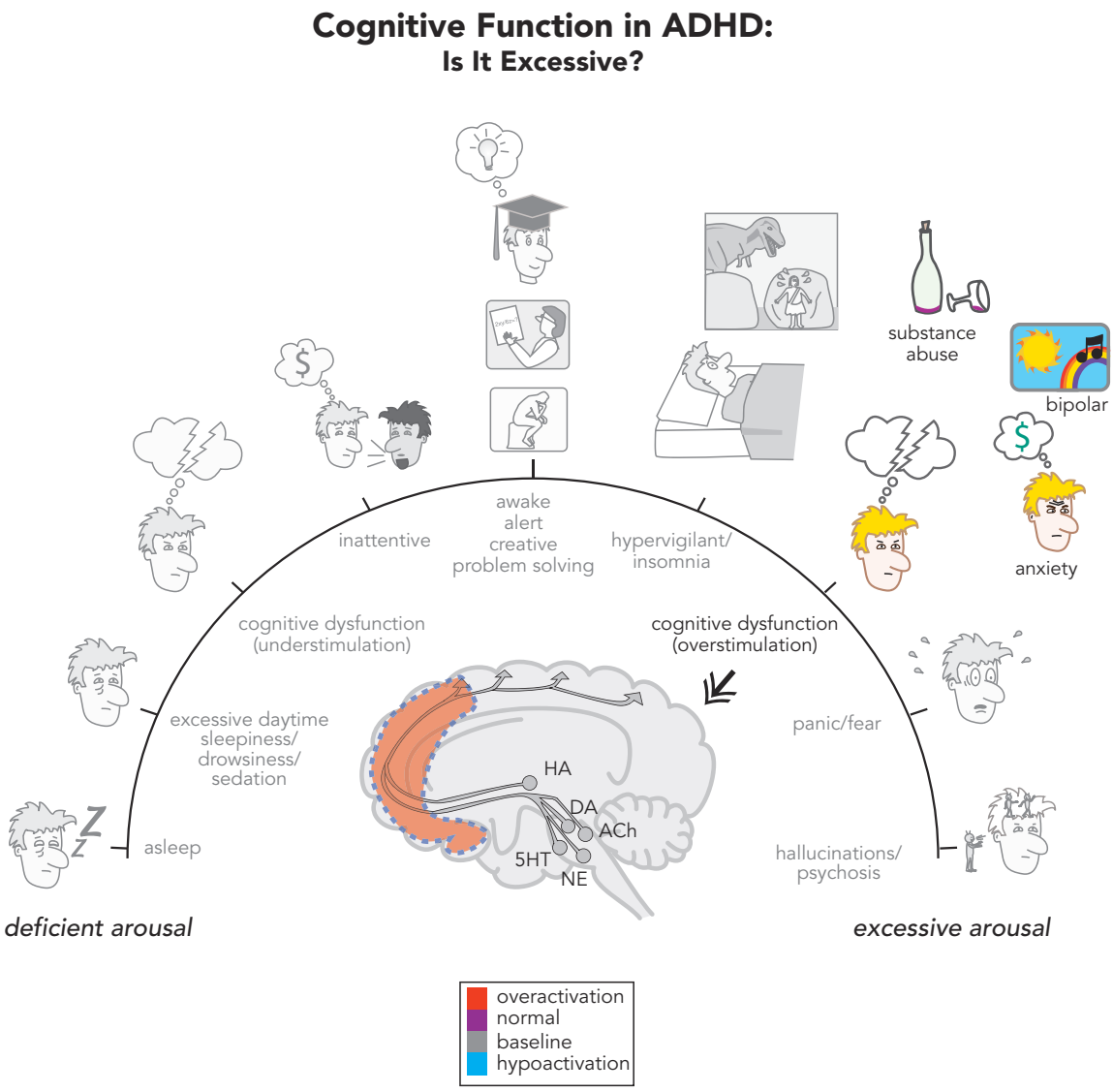


Figure 11-13 Cognitive function in ADHD: is it excessive? Arousal exists as if on a dimmer switch, with many phases along the spectrum. Where on the spectrum one lies is influenced by several key wake-promoting neurotransmitters, including histamine (HA), dopamine (DA), norepinephrine (NE), serotonin (5HT), and acetylcholine (ACh). When neurotransmission is balanced, one is awake, alert, and able to function well. Alterations in the functioning of these key neurotransmitters, whether too much or too little, can cause cognitive dysfunction. Increasing norepinephrine or dopamine too high could lead to excessive stimulation of postsynaptic receptors and cause cognitive dysfunction.

under intense investigation, it is possible to imagine the same pyramidal neuron receiving NE input from the locus coeruleus (LC) on one spine and DA input from the ventral tegmental area (VTA) on another spine. If the systems are properly "tuned," D_1 receptor stimulation can reduce the noise and α_{2A} receptor stimulation can increase the signal to result in proper prefrontal cortex functioning (Figure 11-20). Theoretically, this will result in adequate guided attention (Figures 11-15, 11-16), focus on a specific task, and adequate control of emotions and impulses.

What happens, however, when there is low release of both DA and NE and thus low stimulation of both D_1 and α_{2A} receptors on the spines of these pyramidal neurons (Figure 11-21)? Deficient DA and NE input will theoretically lead to increased noise and decreased

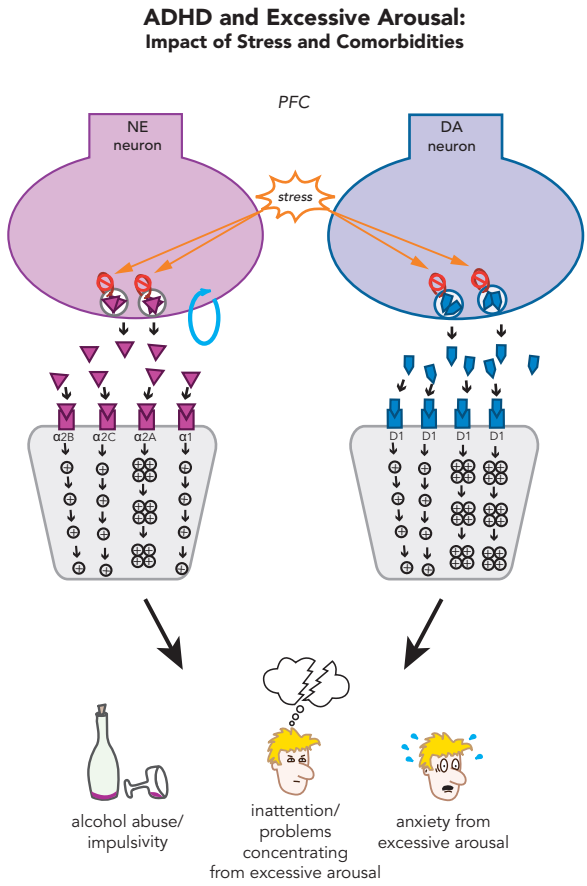


Figure 11-14 **ADHD and excessive arousal.** When norepinephrine (NE) and dopamine (DA) neurotransmission in the prefrontal cortex (PFC) are optimally tuned, modest stimulation of postsynaptic α_{2A} receptors and D_1 receptors allows for efficient cognitive functioning. If NE or DA neurotransmission is excessive, as in situations of stress or comorbid conditions such as anxiety or substance abuse, this can lead to overstimulation of postsynaptic receptors and consequently to cognitive dysfunction as well as other symptoms. Specifically, excessive noradrenergic neurotransmission can lead to impaired working memory due to stimulation of α_1 (and β_1) receptors. Excessive dopaminergic neurotransmission can lead to overstimulation of D_1 receptors in the prefrontal cortex.

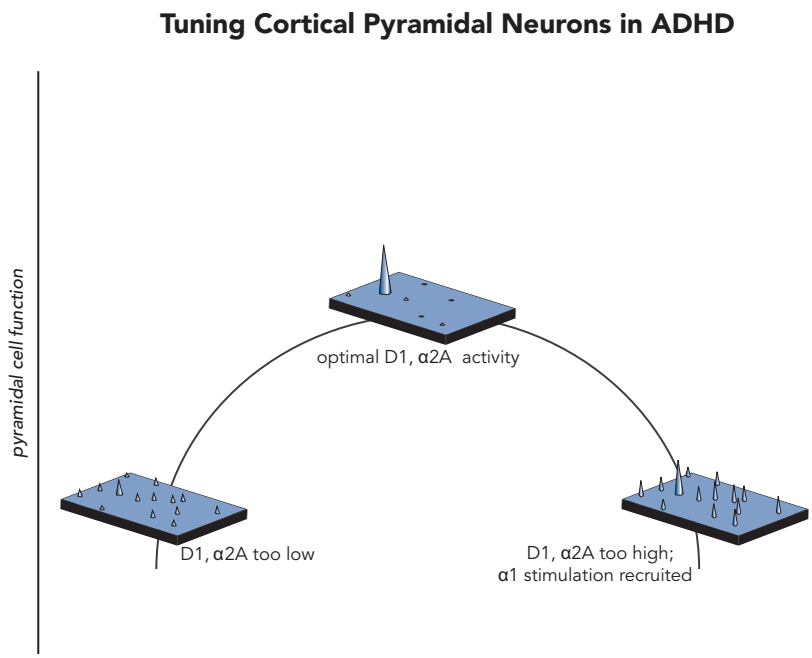


Figure 11-15 **ADHD and maladaptive signal-to-noise ratios.** In order for the prefrontal cortex to work properly, moderate stimulation of α_{2A} receptors by norepinephrine (NE) and of D_1 receptors by dopamine (DA) is required. In theory, the role of NE is to increase the incoming signal by allowing for increased connectivity of the prefrontal networks, while the role of DA is to decrease the noise by preventing inappropriate connections from taking place. At the top of the inverted U-shaped curve depicted here, stimulation of both α_{2A} and D_1 receptors is moderate and pyramidal cell function is optimal. If stimulation at α_{2A} and D_1 receptors is too low (left side), all incoming signals are the same, making it difficult for a person to focus on one single task (unguided attention). If stimulation is too high (right side), incoming signals get jumbled as additional receptors are recruited, resulting in the misdirection of attention.

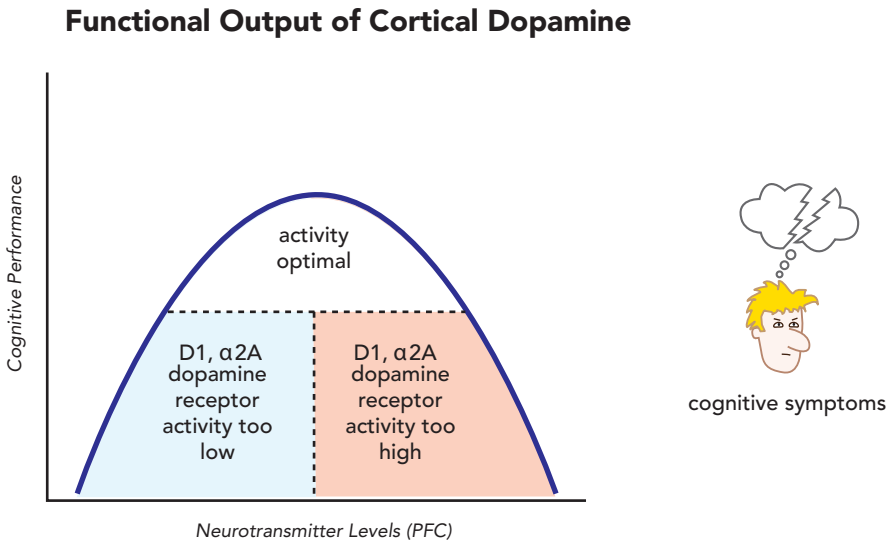


Figure 11-16 Functional output of cortical dopamine. In order for the prefrontal cortex (PFC) to work properly and for cognitive performance to be optimized, moderate stimulation of α_{2A} receptors by norepinephrine (NE) and D_1 receptors by dopamine (DA) is required. If stimulation at α_{2A} and D_1 receptors is either too low or too high, cognitive dysfunction can occur.

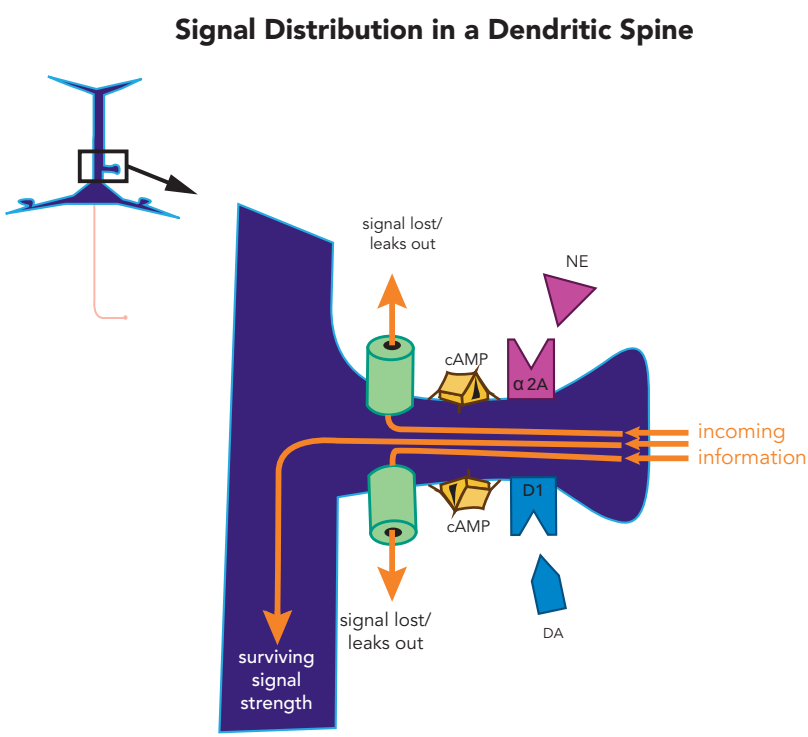


Figure 11-17 Signal distribution in a dendritic spine. The location of α_{2A} and D_1 receptors on dendritic spines of cortical pyramidal neurons in the prefrontal cortex allows them to gate incoming signals. Both α_{2A} and D_1 receptors are linked to the molecule cyclic adenosine monophosphate (cAMP). The effects on cAMP from norepinephrine (NE) and dopamine (DA) binding at their respective receptors are opposite (inhibitory in the case of NE and excitatory in the case of DA). In either case, the cAMP molecule links the receptors to the hyperpolarization-activated cyclic nucleotide-gated (HCN) cation channels. When HCN channels are open, incoming signals leak out before they can be passed along. However, when these channels are closed, the incoming signal survives and can be directed down the neuron.

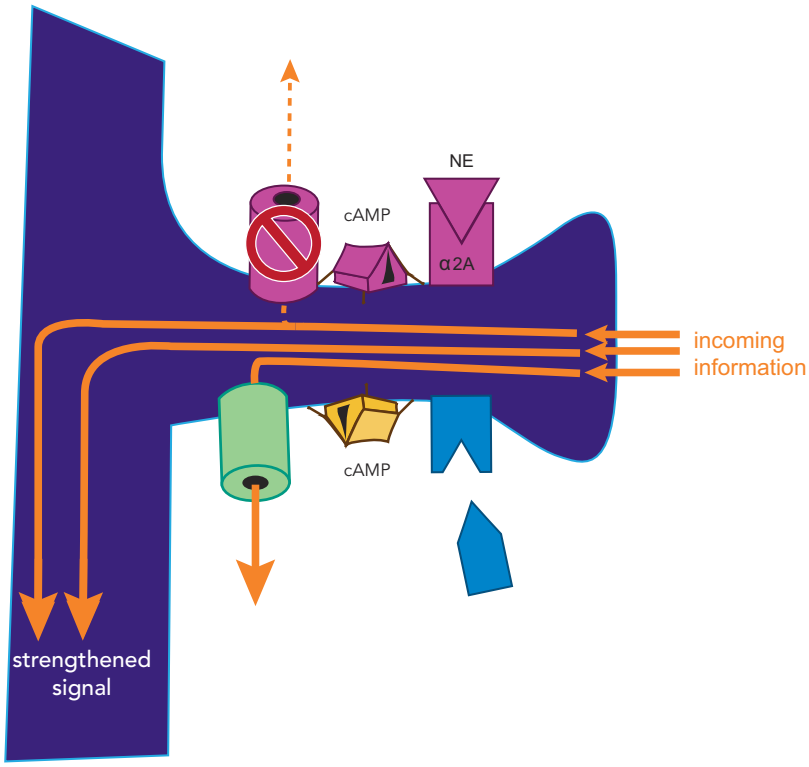


Figure 11-18 Norepinephrine actions at α_{2A} receptors strengthen the incoming signal. Alpha-2A receptors are linked to cyclic adenosine monophosphate (cAMP) via an inhibitor G protein (Gi). When NE occupies these α_{2A} receptors, the activated Gi-linked system inhibits cAMP and the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel is closed, preventing loss of the incoming signal.

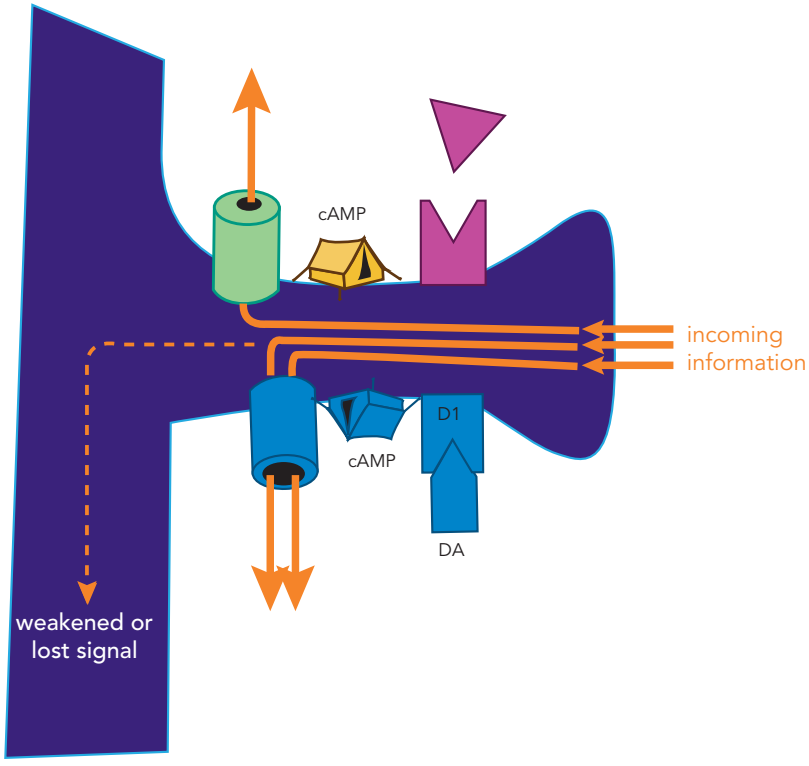


Figure 11-19 Dopamine actions at D_1 receptors weaken the incoming signal. D_1 receptors are linked to cyclic adenosine monophosphate (cAMP) via a stimulatory G protein (Gs). When dopamine (DA) occupies these D_1 receptors, the activated Gs-linked system activates cAMP leading to opening of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. The opening of HCN channels, especially if excessive, will lead to loss of the incoming signal before it can be passed along.

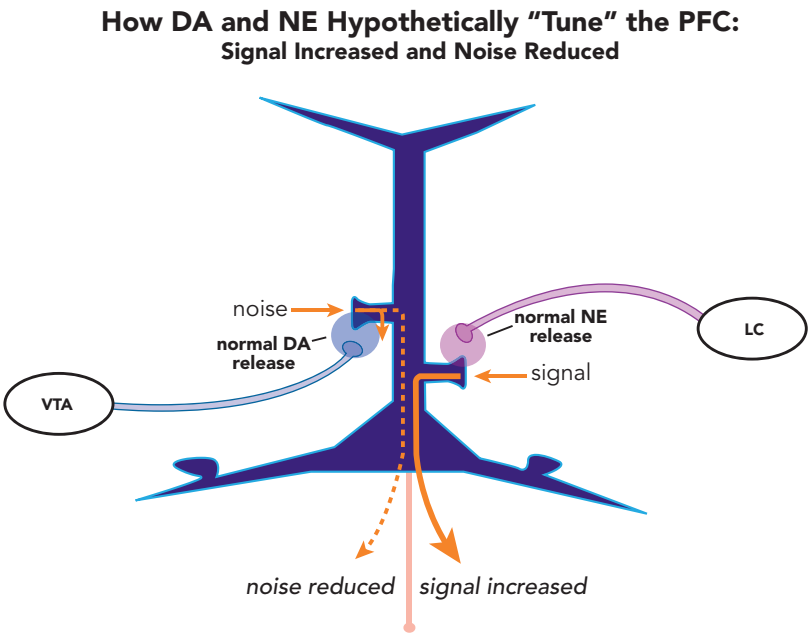


Figure 11-20 Dopamine and norepinephrine "tune" the prefrontal cortex (PFC). The same pyramidal neuron may receive norepinephrine (NE) input from the locus coeruleus (LC) on one spine and dopamine (DA) input from the ventral tegmental area (VTA) on another spine. When properly "tuned," D_1 receptor stimulation will reduce the noise while α_{2A} receptor stimulation will increase the signal, resulting in appropriate prefrontal cortical functioning, guided attention, focus on a specific task, and control of emotions and impulses.

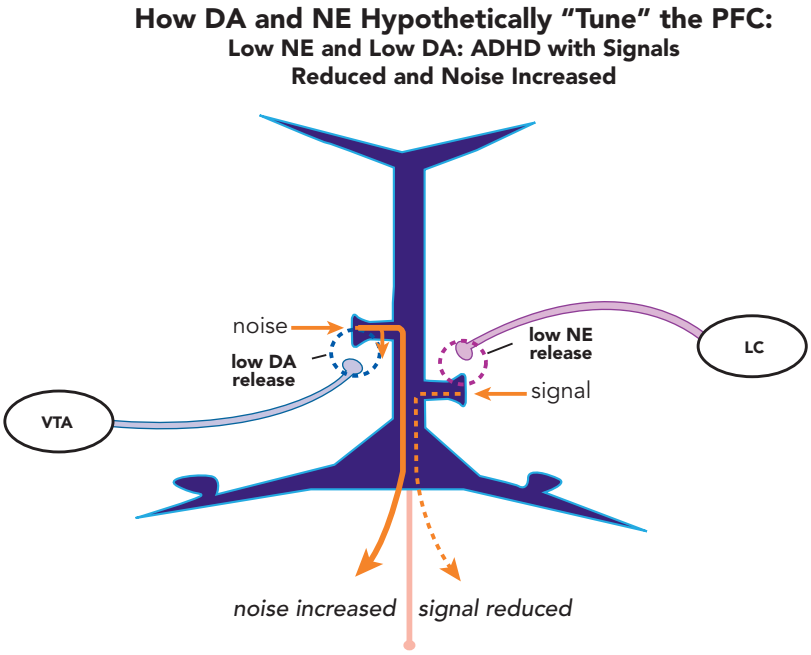


Figure 11-21 Dopamine and norepinephrine improperly "tune" the prefrontal cortex (PFC) in ADHD. The same pyramidal neuron may receive norepinephrine (NE) input from the locus coeruleus (LC) on one spine and dopamine (DA) input from the ventral tegmental area (VTA) on another spine. Deficient DA input will theoretically lead to increased noise, while deficient NE input will cause a decrease in the incoming signal. Hypothetically, this improper tuning of the PFC by DA and NE can lead to hyperactivity, or inattention, or both.

signal, respectively, thus preventing a coherent signal from being sent (Figure 11-21). Hypothetically, this could cause hyperactivity, inattention, impulsivity, or some combination of symptoms, depending upon the localization of the mis-tuned pyramidal neuron in the prefrontal cortex (see Figures 11-3 through 11-8). Furthermore, if one neurotransmitter is low while the other is high, then a person could be exhibiting a whole different set of symptoms. By knowing both the levels of DA and NE neurotransmission and the specific area of the possible disturbances, it may one day be possible to predict the degree and type of symptoms from which a patient is ailing. With this in mind, Figures 11-7 and 11-8 show how pyramidal neurons in different brain areas may be responsible for the different symptom presentations in ADHD.

NEURODEVELOPMENT AND ADHD

ADHD is traditionally considered a childhood disorder, but the concept of ADHD has evolved to be considered childhood in onset but often persisting into adulthood. In fact, most psychiatric disorders have onset in childhood and young adult years and then persist into adulthood (Figures 11-22 and 11-23). The reason for this may be that childhood and young-adult development is when the brain is undergoing critical maturation (Figure 11-22A and 11-23).

Brain development is directed by both genetic and environmental influences (discussed for psychotic disorders in Chapter 4 and illustrated in Figures 4-61 and 4-62). ADHD has one of the strongest genetic components in psychiatry at about 75%. Multiple genes are implicated in ADHD and the genetic causation is complex and multifactorial, as it is in any mental disorder. A unifying formulation of ADHD is that it is caused by delayed maturation of prefrontal cortex circuitry that manifests in ADHD symptoms at least by age 12. Synapses rapidly increase in the prefrontal cortex by age 6, and then up to half of them are rapidly eliminated by adolescence (Figure 11-22A; see also Chapter 4 and Figures 4-63 and 4-64). The timing of onset of ADHD suggests that the formation of synapses and, perhaps more importantly, the selection of synapses for removal in the prefrontal cortex during childhood may contribute to the onset and lifelong pathophysiology of this condition (Figures 11-22 and 11-23). Those who are able to compensate for these prefrontal cortical abnormalities by new synapse formation after age 12 and into early adulthood may be the ones who "grow out of their ADHD" and why the prevalence of ADHD in adults is only half that in children and adolescents.

What causes these problems in the circuits of the prefrontal cortex in ADHD? Currently, leading hypotheses propose that neurodevelopmental abnormalities occur in the circuits of the prefrontal cortex in ADHD (Figures 11-2 through 11-8). Many of the ideas about the neurodevelopmental basis of schizophrenia, such as abnormal synapse formation and abnormal synaptic neurotransmission, serve as a conceptual framework and neurobiological model for ADHD as well, and are discussed in Chapter 4. The impact of neurodevelopment on the specific symptom patterns of ADHD is shown in Figure 11-24. Inattentive symptoms can exist but are not easily identified in preschool children with ADHD, perhaps because they do not have a sufficiently mature prefrontal cortex to manifest this symptom in a manner that is abnormal compared to normal development. Preschool ADHD and its treatment are a current controversial concept in the field because most studies of stimulants involve children over the age of 6. Once inattention becomes a prominent symptom of ADHD, it remains so over the life cycle (Figure 11-24). However, impulsivity and hyperactivity decline notably by adolescence and early adulthood, while recognized comorbidities skyrocket in frequency as ADHD patients enter adulthood (Figure 11-24).

The diagnostic criteria most recently changed from requiring onset prior to age 7 in the past diagnostic schemes of DSM-IV, now to onset prior to age 12 in DSM-5. There is even debate as to whether or not there is such a thing as adult-onset ADHD (or at least recognized first as an adult with unclear onset). The prevalence of ADHD in adults may be only about half of that in children, but it is not recognized nearly as often as it is in children, possibly because it is much harder to diagnose and its symptoms are very often not treated. Whereas half of all children or adolescents with ADHD are thought to be diagnosed and treated, less than one in five adults with ADHD is thought to be diagnosed and treated. The reasons for this are multiple, starting with the diagnostic requirement that ADHD symptoms must begin by age 12. Adults often have difficulty making accurate retrospective diagnoses, especially if the condition was not identified

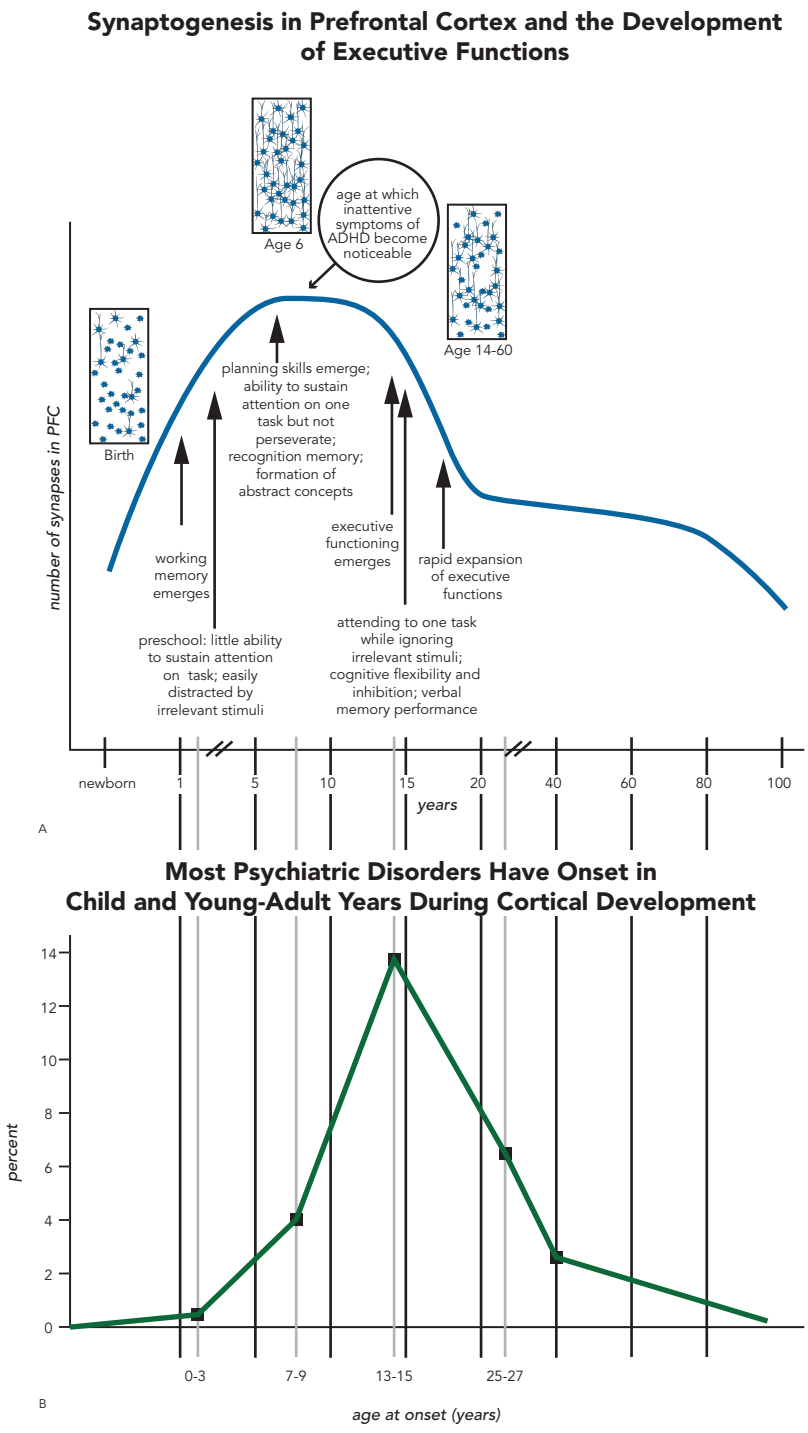


Figure 11-22 Cortical development and ADHD. Synaptogenesis in the prefrontal cortex (PFC) might be responsible for altered connections that could prime the brain for ADHD. Specifically, executive function develops throughout adolescence. (A) At 1 year of age, working memory emerges. Around 3–4 years of age, children do not yet have the capability to sustain attention for long periods of time, and can be easily distracted. By age 6–7, this changes; attention can be sustained and planning can take place. This age is also characterized by "synaptic pruning," a process during which overproduced or "weak" synapses are "weeded out," thus allowing for the child's cognitive intelligence to mature. Errors in this process could hypothetically affect the further development of executive function and be one of the causes of ADHD. This timeline also represents when symptoms of ADHD often become noticeable, which is around the age of 6. (B) Most psychiatric disorders have onset in childhood and young-adult years and then persist into adulthood, coinciding with critical cortical development.

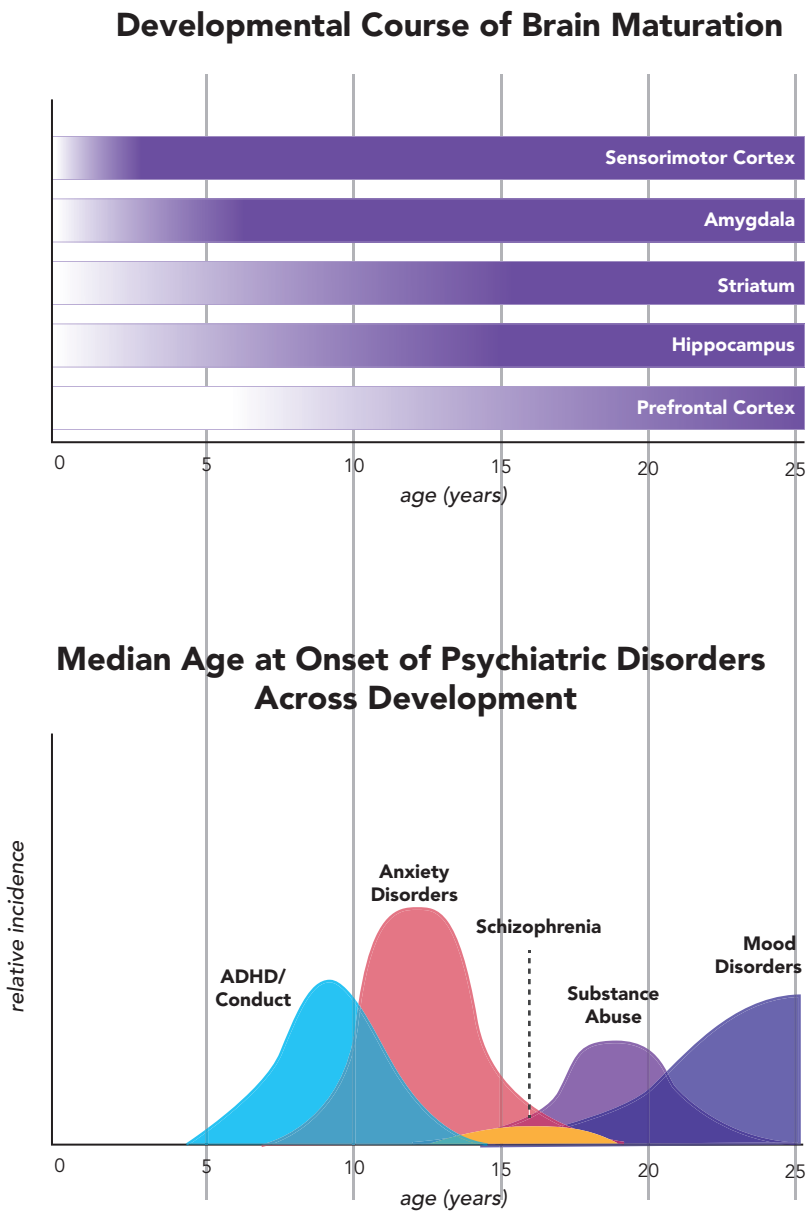


Figure 11-23 Developmental course of brain maturation and onset of psychiatric disorders. The developmental course of brain development is such that the sensorimotor cortex and limbic brain regions develop first, and the prefrontal cortex develops later. In ADHD, this same pattern is observed; however, cortical development is delayed. This may account for the childhood onset of ADHD and why, although ADHD may continue into adulthood, its onset does not occur in adulthood. In contrast, other disorders can also begin in childhood but are typically diagnosed later than ADHD, with onset continuing into adulthood.

and treated as a child. Furthermore, many experts now question whether it is appropriate to exclude from the diagnosis of ADHD those adults whose ADHD symptoms started after age 12, so-called late-onset ADHD. Some cases may even have onset up to the age of 45. Do these patients have ADHD? Or is their executive dysfunction a symptom of a comorbid disorder such as depression, anxiety, or sleep disorder? The point is to screen for cognitive symptoms and to treat them, whether part of an ADHD disorder or a comorbidity.

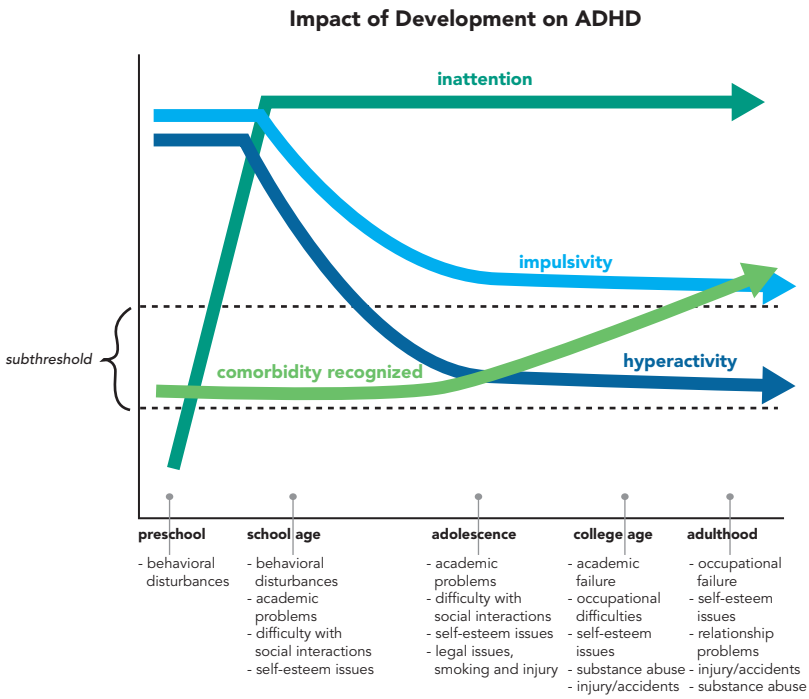


Figure 11-24 Impact of development on ADHD. Consistent with our understanding of neurodevelopment, the evolution of symptoms in ADHD shows that inattention is generally not identified in preschool but becomes prevalent as the patient ages and continues into adulthood. Hyperactivity and impulsivity are key symptoms in childhood but are less likely to manifest overtly in adulthood, although they may simply be expressed differently. The rates of comorbidities increase over time; this could be due to the fact that the comorbidities were overlooked in children with ADHD or that they truly develop later, consistent with data showing later onset of other psychiatric disorders compared to ADHD.

TREATMENTS FOR ADHD

Which Symptoms Should Be Treated First?

It can be helpful in managing ADHD to prioritize which symptoms to target first with psychopharmacological treatments, even at the expense of delaying treatment for a while for some conditions, or even making some of these comorbid conditions transiently worse if other symptoms are targeted for improvement first (Figure 11-25). Although there are no definitive studies on this approach, clinical experience from many experts suggests that, in complex cases, it can be very difficult to make any therapeutic progress if the patient continues to abuse alcohol or stimulants; thus, substance abuse problems must often be managed top line (Figure 11-25). Treating ADHD may also have to await improvement from mood and anxiety disorder treatments, with ADHD cognitive symptoms seen as more of a fine-tune adjustment to a patient's overall symptom portfolio (Figure 11-25).

There are problems, however, with this approach of setting priorities of which symptoms and disorders to treat first. For example, many children are treated for their ADHD first, and without adequately evaluating possible comorbidities until patients fail to respond robustly to stimulant treatment. In adults, it can be so difficult to treat substance abuse, mood disorders, and anxiety disorders that the focus of therapeutic attention never gets to ADHD, and certainly not to nicotine dependence. That is, ADHD can be considered a mere afterthought in adults to be addressed if cognitive symptoms do not remit once the primary focus of therapeutic intervention, namely the mood or anxiety disorder, is treated. It is interesting that ADHD is not often the focus of treatment in adults unless it presents with no comorbid conditions. Since lack of comorbidity in adults with ADHD is rare, this may explain why the majority of adults with ADHD are not treated.

The modern, sophisticated psychopharmacologist keeps a high index of suspicion for the presence of ADHD in mood, anxiety, and substance abuse disorders especially in adults, always aiming for complete symptomatic remission in patients under treatment. In practice, this means exploring the use of ADHD treatments as augmenting agents to first-line treatments of mood, anxiety, and substance abuse disorders, rather than the other way around. It also means that long-term management of ADHD is eventually to address the treatment of nicotine dependence in ADHD once cognitive symptoms are under control (Figure 11-25). Adults and adolescents with ADHD smoke as frequently

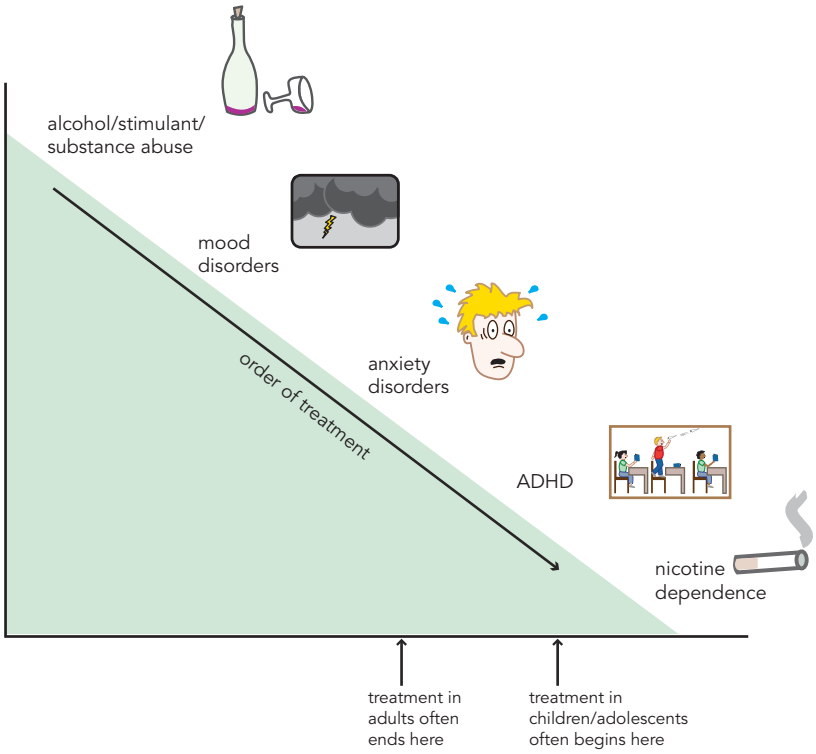


Figure 11-25 ADHD and comorbidities: what should be treated first? In a patient with ADHD and comorbid disorders, it is imperative to treat all disorders appropriately, and in terms of highest degree of impairment. This might mean that in one patient it is necessary to first stabilize the alcohol abuse, while in another patient the symptoms of ADHD might be more impairing than the underlying anxiety disorder. Additionally, some medications used to treat these disorders could exacerbate the comorbid ailment. Thus, care needs to be taken when choosing the appropriate treatment. An individualized treatment plan should be established for each patient based on his/her symptomatic portfolio.

as adults and adolescents with schizophrenia, about twice the rate of the normal population in the US. This may be due to the fact that nicotine subjectively improves ADHD symptoms, especially in patients who are not treated for their ADHD. Nicotine enhances dopamine release and enhances arousal, so it is not surprising that it may be subjectively effective for ADHD symptoms. Nicotine dependence and psychopharmacological treatments for smoking cessation are discussed in more detail in Chapter 13 on impulsivity, compulsivity, and addiction.

Stimulant Treatment of ADHD

General Principles

As discussed above and as illustrated in Figures 11-11 and 11-12, when both DA and NE are too low, the strength of signal output in the prefrontal cortex is also too low, thus leading to reduced signal and increased noise (Figure 11-26A; see also Figures 11-15, 11-16, and 11-21). Behaviorally, this could translate into a person not being able to sit in his/her seat and focus, and to fidget and shift attention, respectively (Figure 11-26A). In order to treat these symptoms, it is necessary to increase signal strength output by dialing up the release of both DA and NE until they reach the optimal levels (Figure 11-26B). This can be done both by norepinephrine and dopamine reuptake blocking stimulants and by some noradrenergic agents as discussed below. Strengthening prefrontal cortical output is hypothesized to be beneficial in restoring a patient's ability to tease out important signals from unimportant ones, and to manage to sit still and focus.

What if NE and DA signals are excessive? Excessive as well as deficient activation of NE and DA in the prefrontal cortex can lead to ADHD, as discussed above, namely by increasing the noise and decreasing the signal (see Figures 11-13 through 11-16). The theory is that at first, and in some patients, the added stress of suffering from ADHD plus other stressors from the environment can even further dial up the noise and reduce the signal, resulting at first in high NE and DA release, causing reduced signals and inefficient information processing (Figure 11-27A). As stress becomes chronic, however, NE and DA levels eventually plummet due to depletion over time, but with no relief in terms of poor signal output (Figure 11-27B). Ultimately the appropriate treatment is to increase NE and DA concentrations to allow for normalization of behavior (Figure 11-27C, noise is reduced and signal is increased).

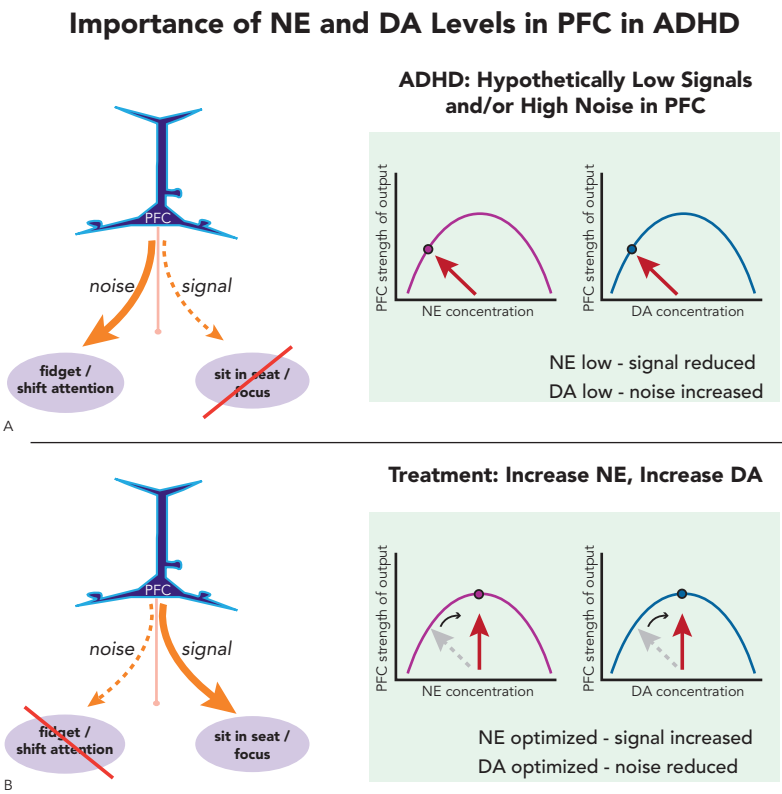


Figure 11-26 **The importance of norepinephrine and dopamine levels in the prefrontal cortex in ADHD.** (A) When both norepinephrine (NE) and dopamine (DA) are too low (on the left side of the inverted U-shaped curve), the strength of output in the prefrontal cortex (PFC) is too low, leading to reduced signal and increased noise. The inability to sit still and focus, together with fidgeting and shifting attention, are often clinical manifestations of this imbalanced signal-to-noise ratio. (B) In order to treat these symptoms, it is necessary to increase strength output by dialing up the concentrations of both NE and DA until they reach the optimal dose (top of the inverted U-shaped curve).

Experienced clinicians are well aware that such patients with too much DA and NE (represented in Figure 11-27A), too little DA and NE (represented in Figure 11-27B), or a combination of these in different pathways, can be very difficult to treat. For example, in children, the combination of tics generally representing hypothetically *excessive* DA activation in the motor striatum, and requiring DA blockade for treatment, can be very difficult to manage simultaneously in patients with ADHD who have hypothetically *deficient* DA activation in the cortex, requiring DA-enhancing stimulants. Stimulants may help the ADHD symptoms but worsen the tics. Children and adolescents who have conduct disorder, oppositional disorders, intermittent explosive disorder, disruptive behavioral disorder, psychotic disorders and/or bipolar mania, or mixed conditions (theoretically associated with excessive DA activation in some prefrontal circuits) (Figure 11-8), who are unlucky enough to have comorbid ADHD (theoretically associated with deficient DA activation in different prefrontal circuits) (Figure 11-7), are among the most challenging patients for clinicians.

Thus, conditions associated with hypothetically excessive DA activation suggest treatment with dopamine blocking agents (see Chapter 5), yet comorbid ADHD suggests treatment with a stimulant. Can dopamine blockers and stimulants be combined? In fact, in heroic cases, stimulants can be combined with serotonin–dopamine antagonists. The rationale for this combination exploits the fact that serotonin–dopamine blockers hypothetically release DA in the prefrontal cortex, to stimulate postsynaptic D_1 receptors there (see Figure 5-17C), while simultaneously blocking D_2 receptors in limbic areas, to reduce DA activity at D_2 receptors there. Such an approach is controversial and best left to experts for difficult patients who fail to improve adequately on monotherapies. This mechanism of action of dopamine–serotonin blockers and their actions in different areas of the brain are discussed in detail in Chapter 5.

For patients with ADHD and anxiety, it can be difficult or even self-defeating to try to improve the ADHD with stimulant treatment, only to cause the anxiety to worsen. For patients with ADHD and substance abuse, it makes little sense to give stimulants to drug abusers in

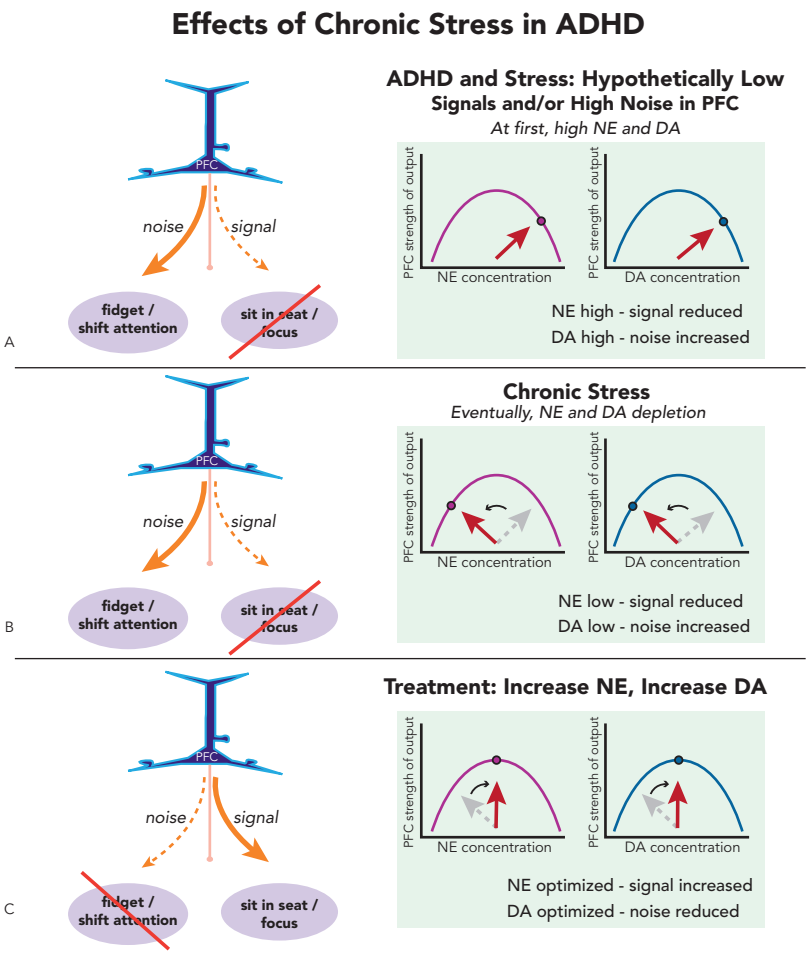


Figure 11-27 **Chronic stress in ADHD.** Excessive activation of norepinephrine (NE) and dopamine (DA) in the prefrontal cortex (PFC) can lead to ADHD by increasing the noise and decreasing the signal. (A) At first, the added stress of suffering from the disorder can further dial up the noise and reduce the signal (high NE and DA concentration leading to decreased output). (B) As chronic stress sets in, NE and DA levels plummet (low NE and DA concentration also leading to decreased output), but with no relief in terms of signal output. (C) Treatments that increase NE and DA concentrations may reduce symptoms by increasing strength output (noise is reduced and signal is increased).

order to treat their ADHD. In these cases, augmenting antidepressant or anxiolytic therapies with a tonic activator of DA and/or NE systems, such as a long-lasting norepinephrine transport (NET) inhibitor or an α_{2A}-adrenergic agonist, rather than a stimulant, can be an effective long-term approach for comorbid anxiety, depression, or substance abuse with ADHD. Some studies of NET inhibitors report improvement in both ADHD and anxiety symptoms, and other studies report improvement in both ADHD and heavy drinking.

Methylphenidate

The mechanism of action of the so-called stimulants – perhaps better designated as norepinephrine and dopamine reuptake blockers – is shown in Figures 11-28 through Figure 11-37. Oral administration of clinically approved doses of the stimulant methylphenidate blocks the transporters both for NE and DA (NETs and DATs, respectively) (Figures 11-28 and 11-29A–C). Normally, DA is released (arrow 1 in Figure 11-29A), and then taken back up into the dopaminergic neuron by DATs (arrows 2 in Figure 11-29A), and finally stored in the synaptic vesicle by VMATs (arrows 3 in Figure 11-29A). Methylphenidate blocks DATs and NETs allosterically, stopping the reuptake of DA via DATs (Figure 11-29B) and NE via NETs (Figure 11-29C), with no actions on VMAT2 (Figures 11-29B and 11-29C). Methylphenidate blocks NETs and DATs in much the same way as reuptake blockers used to treat depression (see discussion in Chapter 7 and Figure 7-36), namely by binding to NETs and DATs at sites distinct from where monoamines bind NETs and DATs, i.e., allosterically. Thus, methylphenidate stops the reuptake pumps so that no methylphenidate is

transported into the presynaptic neuron (Figure 11-29B and 11-29C).

Methylphenidate has a D- and an L-isomer (Figure 11-28), with the D-isomer being much more potent than the L-isomer on both NET and DAT binding.

Methylphenidate is also available as the single enantiomer D-methylphenidate, in both immediate-release and controlled-release preparations. A listing of the wide range of D,L-methylphenidate preparations is shown in Table 11-1, and those for D-methylphenidate shown in Table 11-2.

Table 11-1 D,L-Methylphenidate formulations

Formulation	Brand names	Duration	Dosing	Approval
Immediate-release tablet	Ritalin	Early peak, 3–4-hr duration	Second dose at lunch	Ages 6 to 12 and adults
Immediate-release oral solution	Methylin	Early peak, 3–4-hr duration	Second dose at lunch	Ages 6 to 12
Extended-release tablet	Ritalin SR Methylin ER Metadate ER	Early peak, 3–8-hr duration	Lunch dosing may be needed	Ages 6 and older
Extended-release tablet	Concerta	Small early peak, 12-hr duration	Once daily in the morning	Ages 6 and older
Extended-release chewable tablet	QuilliChew ER	Peak at 5 hr, 8-hr duration	Once daily in the morning	Ages 6 and older
Extended-release capsule	Metadate CD	Strong early peak, 8-hr duration	Once daily in the morning	Ages 6 to 17
Extended-release capsule	Ritalin LA	Two strong peaks (early and at 4 hrs), 6–8-hr duration	Once daily in the morning	Age 6 to 12
Extended-release capsule	Aptensio XR	Up to 12-hr duration	Once daily in the morning	Ages 6 and older
Extended-release oral suspension	Quillivant XR	Peak at 5 hr, 12-hr duration	Once daily in the morning	Ages 6 and older
Extended-release transdermal patch	Daytrana	One peak at 7–10 hrs, 12-hr duration	Once daily in the morning	Ages 6 to 17
Orally disintegrating tablet	Cotempla XR-ODT	12-hr duration	Once daily in the morning	Ages 6 to 17
Extended-release capsule	Jornay PM	Initial absorption delayed by 10 hrs, single peak at 14 hrs	Once daily in the evening	Ages 6 and older
Extended-release capsule	Adhansia XR	Two peaks (at 1.5 and 12 hrs)	Once daily in the morning	Ages 6 and older

Table 11-2 D-Methylphenidate formulations

Formulation	Brand Names	Duration	Dosing	Approval
Immediate-release tablet	Focalin	Early peak, 4–6-hr duration	Second dose at lunch	Ages 6 to 17
Extended-release capsule	Focalin XR	Two peaks (after 1.5 and 6.5 hrs), 8–10-hr duration	Once daily in the morning	Ages 6 to 17 and adults

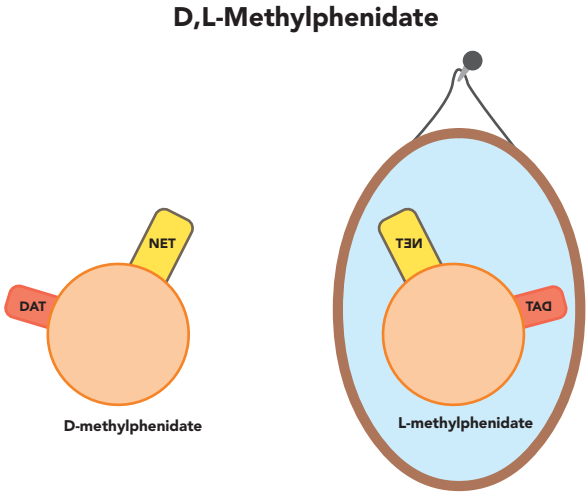
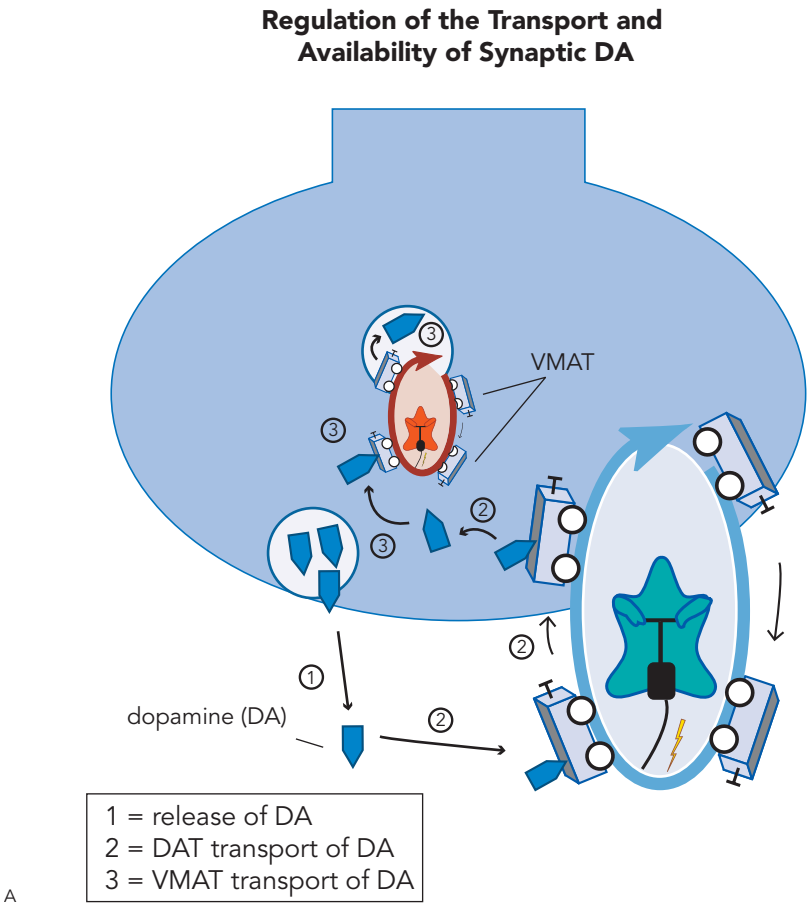


Figure 11-28 **D,L-methylphenidate.** Methylphenidate consists of two enantiomers, D and L; both racemic D,L-methylphenidate and D-methylphenidate are available as therapeutic options. D,L-methylphenidate and D-methylphenidate both block the norepinephrine transporter (NET) and the dopamine transporter (DAT). D-methylphenidate has greater potency for both transporters than does the L enantiomer.



A

Figure 11-29A **Regulation of transport and availability of synaptic dopamine.** The regulation of synaptic dopamine (DA) is dependent upon proper functioning of two transporters, namely the dopamine transporter (DAT) and the vesicular monoamine transporter (VMAT). After DA is released (1) it can act at postsynaptic receptors or it can be transported back into the terminal via DATs (2). Once inside the terminal, DA is "encapsulated" into vesicles via VMAT (3). These DA-filled vesicles can then merge with the membrane and lead to more DA release. This finely tuned machinery ensures that DA levels never reach toxic levels in the synapse or in the DA terminal. By "engulfing" DA into vesicles it is possible for the DA neuron to ensure the viability of DA.

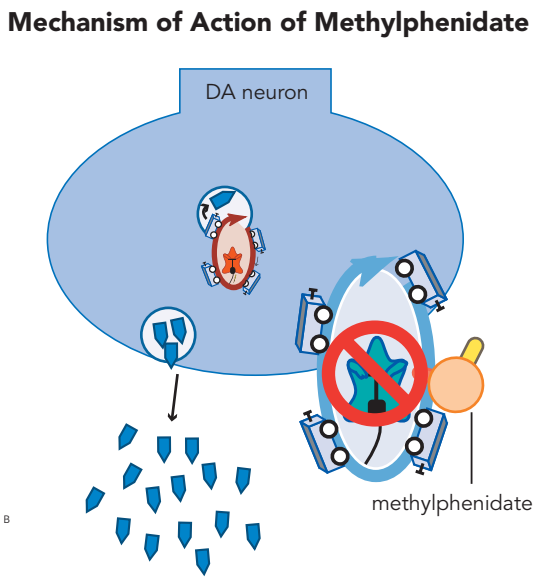


Figure 11-29B Mechanism of action of methylphenidate at dopamine neurons. Methylphenidate blocks the reuptake of dopamine (DA) into the terminal by binding at an allosteric site (i.e., different than the DA binding site). Methylphenidate basically stops the transporter, preventing DA reuptake and thus leading to increased synaptic availability of DA.

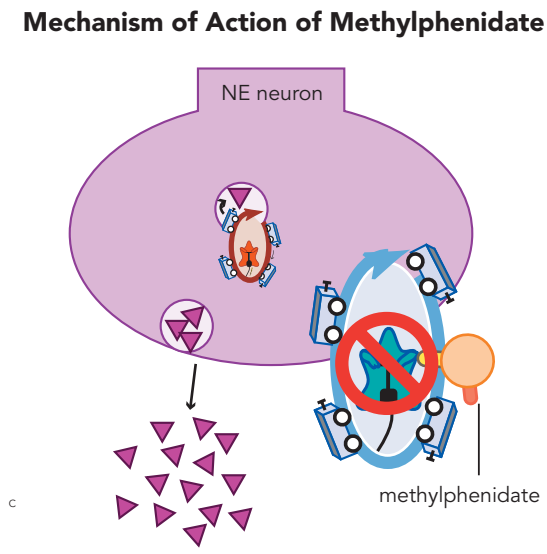


Figure 11-29C Mechanism of action of methylphenidate at norepinephrine neurons. Methylphenidate blocks the reuptake of norepinephrine (NE) into the terminal by binding at an allosteric site (i.e., different than the NE binding site). Methylphenidate basically stops the transporter, preventing NE reuptake and thus leading to increased synaptic availability of NE.

Amphetamine

Oral administration of clinically approved doses of the stimulant amphetamine, like methylphenidate, also blocks the transporters both for NE and DA (NETs and DATs), but in a different manner (Figures 11-30 through 11-32). Unlike methylphenidate and reuptake blocking drugs used for depression, amphetamine is a *competitive* inhibitor and pseudosubstrate for NETs and DATs (Figure 11-32, top left), binding at the *same* site that the monoamines bind to the transporters, thus inhibiting NE and DA reuptake (Figure 11-32, top left). At the doses of amphetamine used for the treatment of ADHD, the clinical differences between the actions of amphetamine versus methylphenidate can be relatively small. However, at the high doses of amphetamine used by stimulant addicts, additional pharmacological actions of amphetamine are triggered. Following competitive inhibition of DATs (Figure 11-32, top left) amphetamine is actually transported as a hitch-hiker into the presynaptic DA terminal, an action not shared by methylphenidate or reuptake blocking drugs used for depression (Figure 11-32, top left). Once there in sufficient quantities, such as occurs at doses taken for abuse, amphetamine is also a competitive inhibitor of the vesicular transporter (VMAT2) for both DA and NE (Figure 11-32, top right). Once amphetamine hitch-hikes another ride into synaptic vesicles, it displaces DA there, causing a flood of DA release (Figure 11-32, bottom left). As DA accumulates in the cytoplasm of the presynaptic neuron, it causes the DATs to reverse directions, spilling intracellular DA into the synapse, and also opening presynaptic channels to further release DA in a flood into the synapse (Figure 11-32, bottom right). These pharmacological actions of high-dose amphetamine are not linked to therapeutic action in ADHD but to reinforcement, reward, and euphoria in amphetamine abuse. Actions of high-dose amphetamine, methamphetamine, and cocaine (another inhibitor of DATs), given orally in immediate-release formulations, or intranasally, intravenously, or smoked, are discussed further in Chapter 13 on drug abuse.

Amphetamine has a D- and an L-isomer (Figure 11-30). The D-isomer of amphetamine is more potent than the L-isomer for DAT binding, but D- and L-amphetamine isomers are more equally potent in their actions on NET binding. Thus, D-amphetamine preparations will have relatively more action on DATs

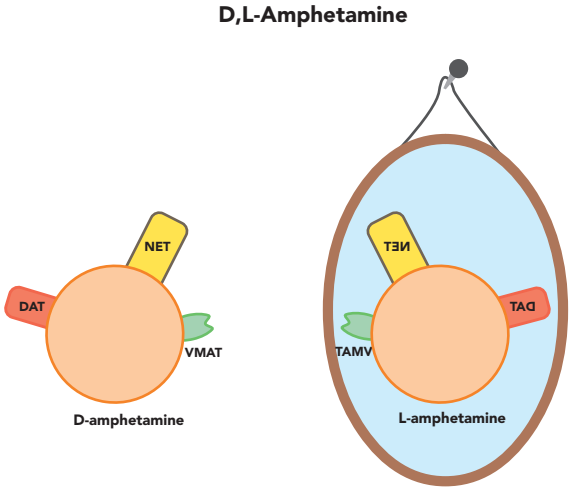


Figure 11-30 D,L-amphetamine. Amphetamine consists of two enantiomers, D and L; both racemic D,L-amphetamine and D-amphetamine are available as therapeutic options. D,L-amphetamine and D-amphetamine are both competitive inhibitors at norepinephrine transporters (NETs), dopamine transporters (DATs), and vesicular monoamine transporters (VMATs). D-amphetamine has greater potency for DAT binding than does the L enantiomer, while the D and L enantiomers are equipotent for NET binding.

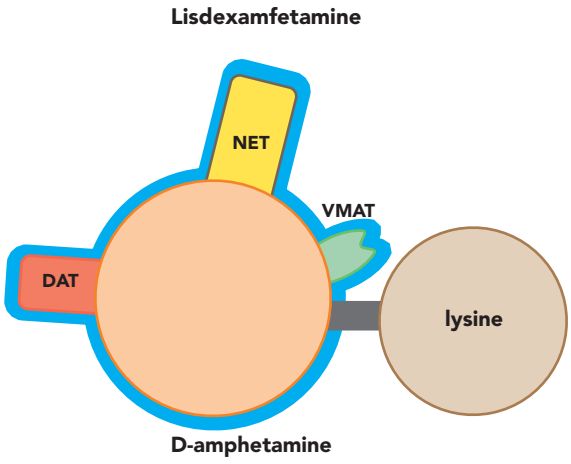


Figure 11-31 Lisdexamfetamine. Lisdexamfetamine is the prodrug of D-amphetamine, linked to the amino acid lysine. It is only centrally active as D-amphetamine once it has been cleaved in the stomach into the active compounds D-amphetamine plus free L-lysine.

than NETs; mixed salts of both D- and L-amphetamine will have relatively more action on NETs than D-amphetamine but overall still more action on DATs than NETs (Figure 11-33). These pharmacological mechanisms of action of the stimulants come into play particularly at lower therapeutic doses utilized for the treatment of ADHD. D-amphetamine also comes in a formulation linked to the amino acid lysine (lisdexamfetamine; Figure 11-31) which is not absorbed until slowly cleaved into active D-amphetamine in the stomach, and slowly, rather than rapidly, absorbed. A listing of the wide range of D,L amphetamine preparations is shown in Table 11-3, and those for D-amphetamine shown in Table 11-4.

The Mysterious DAT

Targeting the dopamine transporter (DAT) is not like targeting any other site in psychopharmacology. There are at least three parts to solving the mystery of why there are so many different outcomes from targeting the same DAT, simply depending upon how you zero in on it. Targeting DATs can result in immediate therapeutic actions (in ADHD and daytime sleepiness), delayed therapeutic actions (in depression), immediate abuse (euphoria, high), and delayed addiction, all depending upon how the DAT is engaged: how fast, how long, and how much. Understanding the neurobiology of DATs and dopamine will not only unravel this mystery and solve the riddle of the curious properties of this site, but empower the prescriber to best engage this target for best outcomes for whatever clinical application is intended.

First, we have discussed how engaging monoamine neurotransmitter transporters leads to delayed therapeutic actions in depression hypothetically linked to downstream molecular events such as neurotrophic factor production (discussed in Chapter 6 and illustrated in Figure 6-27 and in Chapter 7 and Figure 7-62). The immediate rise in dopamine levels (often accompanied by increasing norepinephrine levels from simultaneously blocking the NET) are not linked to antidepressant effects. Instead, DATs (and NETs) must be engaged at therapeutic levels more or less continuously, round the clock, so synaptic levels of neurotransmitter are sufficiently robust and sustained to trigger delayed downstream molecular events, usually taking a few weeks. Likely, these therapeutic actions may be linked to improvement of tonic dopamine neurotransmission that is theoretically deficient in depression.

Second, engaging this same DAT can produce immediate onset of therapeutic effects in ADHD and in daytime sleepiness by attaining occupancy levels above a critical threshold, with therapeutic action that is immediately terminated as soon as DAT occupancy falls below this threshold (Figure 11-34A). This notion of a threshold for immediate therapeutic action onset and

Mechanism of Action of Amphetamine:
The Yin and the Yang

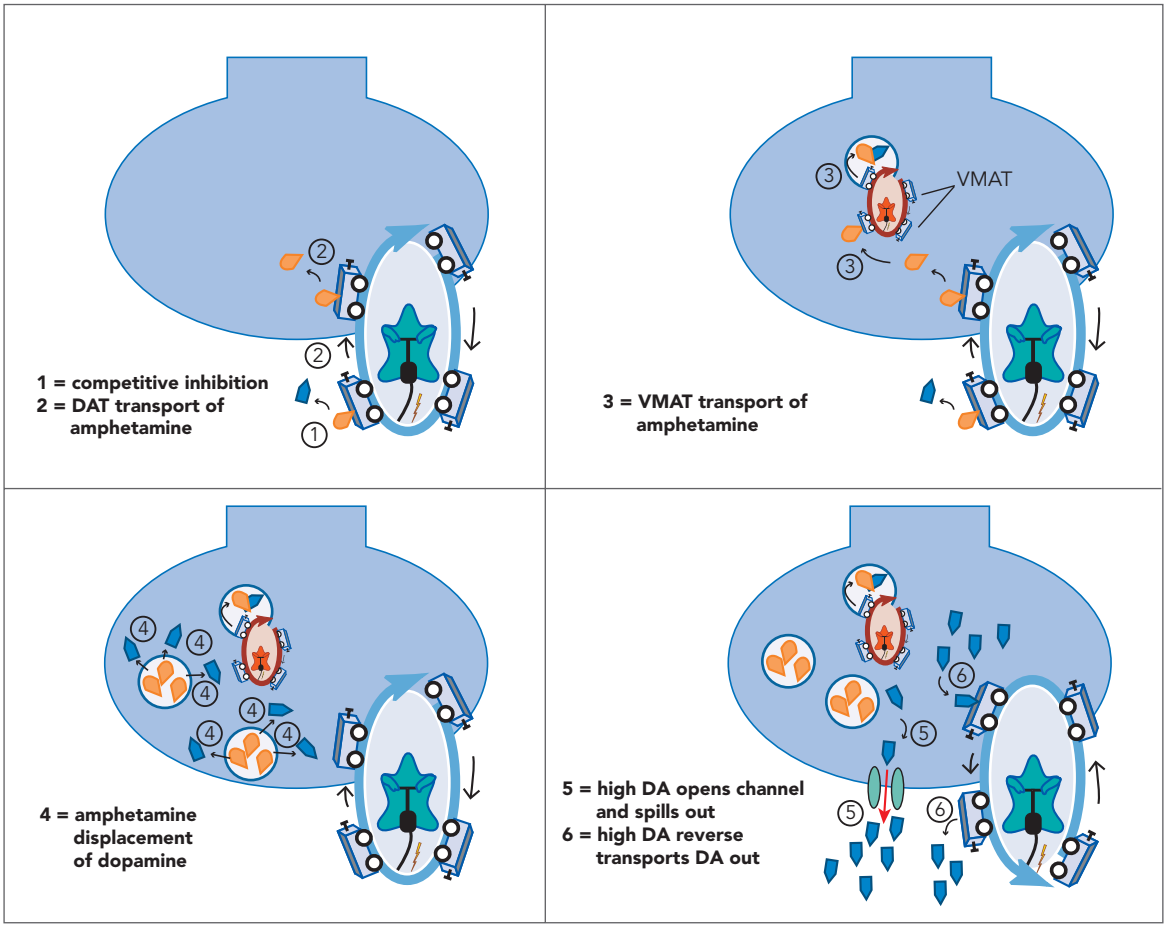


Figure 11-32 Mechanism of action of amphetamine at dopamine (DA) neurons. Amphetamine is a competitive inhibitor at the dopamine transporter (DAT), thus blocking DA from binding (1). This is unlike methylphenidate's actions at DATs and NETs, which are not competitive. Additionally, since amphetamine is also a competitive inhibitor of VMAT (a property that methylphenidate lacks) it is actually taken into the DA terminal via DATs (2), where it can then be packaged into vesicles (3). At high levels, amphetamine will lead to the displacement of DA from the vesicles into the terminal (4). Furthermore, once a critical threshold of DA has been reached, DA will be expelled from the terminal via two mechanisms: the opening of channels to allow for a massive dumping of DA into the synapse (5) and the reversal of DATs (6). This fast release of DA will lead to the euphoric effect experienced after amphetamine use. Amphetamine has these same actions at noradrenergic neurons.

offset is also seen in another area of psychopharmacology, namely, for treatments of insomnia discussed in Chapter 10 and illustrated in Figure 10-41A. A similar idea is illustrated here, with a minimum threshold for ADHD therapeutic action, probably around 50–60% DAT occupancy (Figure 11-34).

This property of DAT targeting for ADHD above a critical threshold is so prominent that it has spawned an entire industry of technologies in an attempt to capture the best way to attain, sustain, and drop below the threshold in just the exact manner desired. There are over two dozen versions of the two stimulant molecules methylphenidate and amphetamine now available for clinical use (Tables 11-1 through 11-4) and several more in development. Each version tries to capture the ideal drug delivery for the ideal DAT occupancy for a given patient type (e.g., Figure 11-34B). That usually takes the form of rapidly getting above threshold levels

Table 11-3 D,L-Amphetamine formulations

Formulation	Brand names	Duration	Dosing	Approval
Immediate-release tablet	Adderall	4–6 hrs	Second dose at lunch	Ages 3 and older
Immediate-release tablet	Evekeo	6 hrs	Second dose at lunch	Ages 3 and older
Extended-release orally disintegrating tablets	Adzenys XR-ODT	8–12 hrs, peak at 5 hrs	Once daily in the morning	Ages 6 and older
Extended-release oral suspension	Dyanavel XR	10–12 hrs, peak at 4 hrs	Once daily in the morning	Ages 6 to 17
Extended-release capsule	Adderall XR	8–12 hrs, peak at 6–8 hrs	Once daily in the morning	Ages 6 and older
Extended-release capsule	Mydayis	Up to 16 hrs	Once daily in the morning	Ages 13 and older
Extended-release oral suspension	Adzenys ER	Not published	Once daily in the morning	Ages 6 and older

Table 11-4 D-Amphetamine formulations

Formulation	Brand names	Duration	Dosing	Approval
Immediate-release tablet	Zenzedi	4–5 hrs	Second dose at lunch	Ages 3 to 16
Immediate-release oral solution	ProCentra (previously Liquadd)	4–6 hrs	Second dose at lunch	Ages 3 to 16
Extended-release capsule	Dexedrine	6–8 hrs	Once daily in the morning	Ages 6 to 16
Lisdexamfetamine dimesylate capsule	Vyvanse	Up to 12 hrs, peak at 3.5 hrs	Once daily in the morning	Ages 6 to 17 and adults

upon awakening in the morning, staying at this DAT occupancy level for as long as needed for a productive day, yet getting below threshold levels in time for bed. And to do this with once-daily dosing. Doing this too late means morning symptoms (Figure 11-34B); having it last too short a time means late afternoon and evening symptoms (Figure 11-34B); having this last too long a time means late afternoon and evening side effects and insomnia (Figure 11-34C). There is also a rebound phenomenon, in which evening serum levels drop too early and hyperactivity and insomnia ensue. Just as was discussed for hypnotic actions, the goal is not "too hot" (too long, too high, too fast), not "too cold" (too low, too short) but "just right" (Figure 11-34A), the ideal "Goldilocks" solution, more a goal than a perfectly executed reality.

There is no "one size fits all" profile of stimulant delivery that fits every patient every day and no single technology that is ideal for all patients. For that reason, it can be prudent to search among the many options available for the best fit for an individual patient (see Tables 11-1 through 11-4). Do you want the effect to last 6 hours or 16 hours? Do you want greater or lesser effect in the evening hours before bedtime? Morning can be difficult for many with ADHD, so do you want rapid morning onset or even waking up with drug above threshold? All of these are currently attainable from available formulations (Tables 11-1 through 11-4). Different patients have different responses, and the same patient may wish different responses on different days to fit a flexible lifestyle. And all this because of the mysterious DAT and its threshold for therapeutic efficacy

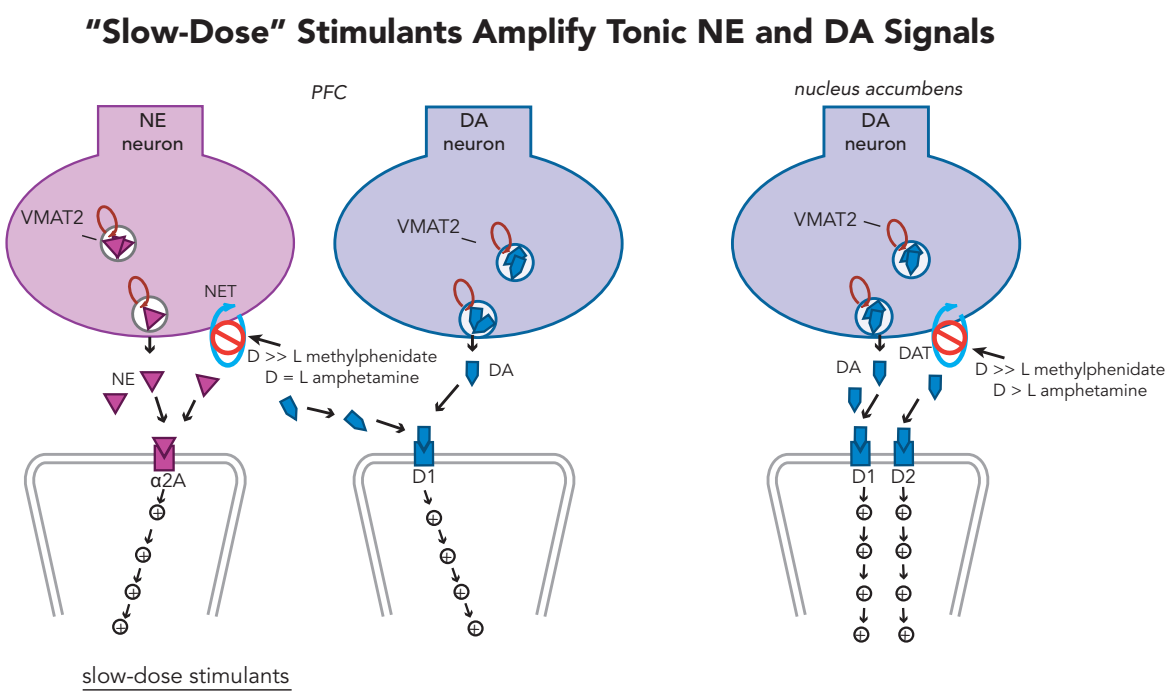


Figure 11-33 Slow-dose stimulants amplify tonic norepinephrine (NE) and dopamine (DA) signals. Hypothetically, whether a drug has abuse potential depends on how it affects the DA pathway. In other words, the pharmacodynamic and pharmacokinetic properties of stimulants affect their therapeutic as well as their potential abuse profiles. Extended-release formulations of oral stimulants, the transdermal methylphenidate patch, and the prodrug lisdexamfetamine are all considered "slow-dose" stimulants and may amplify tonic NE and DA signals, presumed to be low in ADHD. These agents block the norepinephrine transporters (NETs) in the prefrontal cortex and the DA transporters (DATs) in the nucleus accumbens. Hypothetically, the "slow-dose" stimulants occupy NETs in the prefrontal cortex (PFC) with slow enough onset, and for long enough duration, that they enhance tonic NE and DA signaling via α_{2A} and D_1 postsynaptic receptors, respectively, but they do not occupy DATs quickly or extensively enough in the nucleus accumbens to increase phasic signaling via D_2 receptors. The latter hypothetically suggests reduced abuse potential.

in ADHD (and excessive daytime sleepiness). Likely these therapeutic actions may be linked to judicious and controlled enhancement of phasic dopamine neurotransmission, along with a boost in tonic dopamine neurotransmission, both of which may be theoretically somewhat deficient in ADHD and sleepiness.

One last piece of the puzzle. How can the DAT target that is therapeutic immediately for ADHD and sleepiness and with a delay for depression lead to problematic drug abuse rather than therapeutic use? This only makes sense if you are aware that the DAT functions very differently depending upon how fast, how completely, and how long you engage it (compare Figures 11-35 pulsatile action with Figure 11-33 sustained action). That is, rapid and high degrees of DAT occupancy cause euphoria and lead to abuse and addiction (Figure 11-35; see also Chapter 13 and Figure 13-7). In fact, the more rapidly and completely the DATs are blocked, the more reinforcing and abusable a drug will be. This applies not only to methylphenidate, modafinil, and amphetamine as DAT blockers, but also to methamphetamine and cocaine that are also DAT blockers. Oral ingestion can get a DAT inhibitor to the brain, but not as fast as snorting nasally, and not as fast as intravenously, and certainly not as fast as smoking. High dosing especially by these other routes of administration provides complete, catastrophic, and sudden blockade of DATs. The rapid build-up of synaptic dopamine (Figure 11-35) is nothing like what is seen with more gradual, sustained, and lower levels of DAT occupancy (Figure 11-33). In fact, dopamine levels can build up so high that the DATs can actually be reversed to transport dopamine out of the presynaptic terminal to add to the

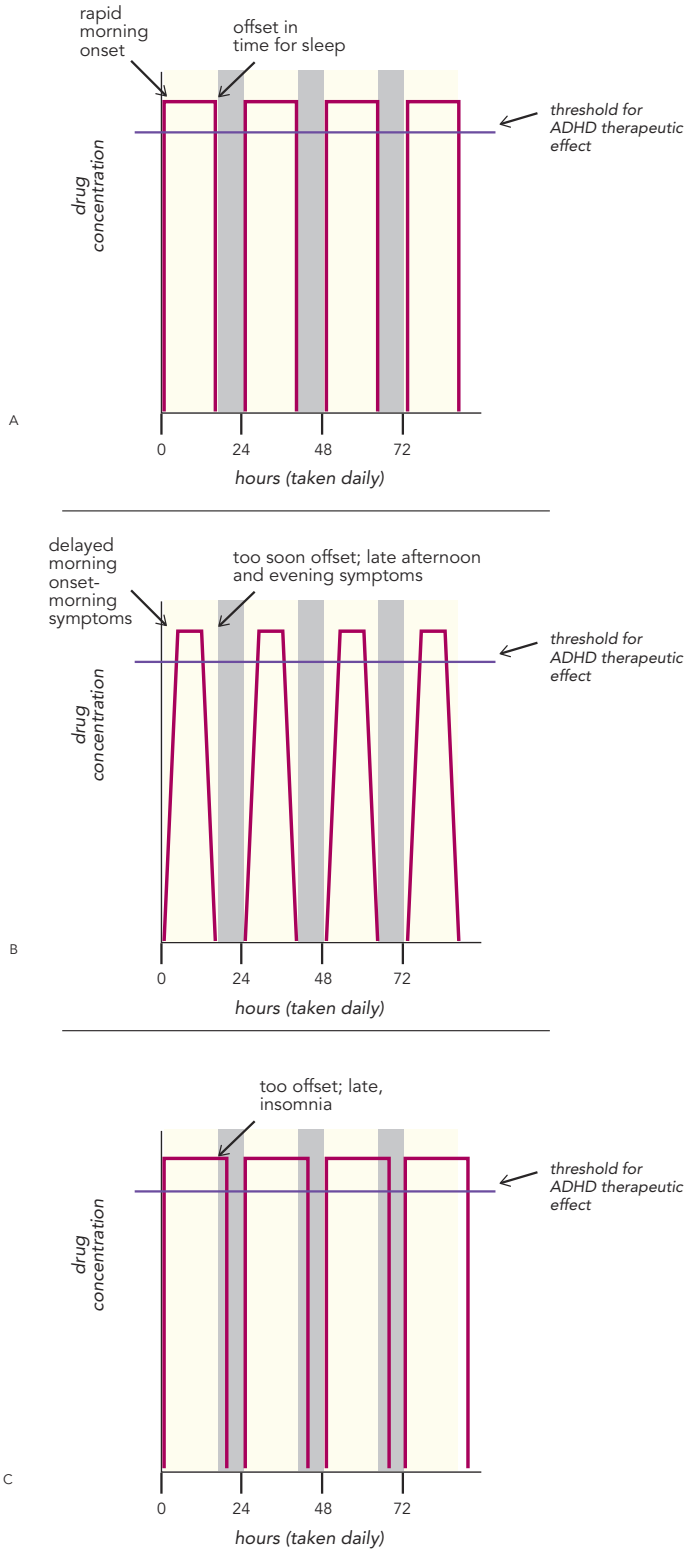
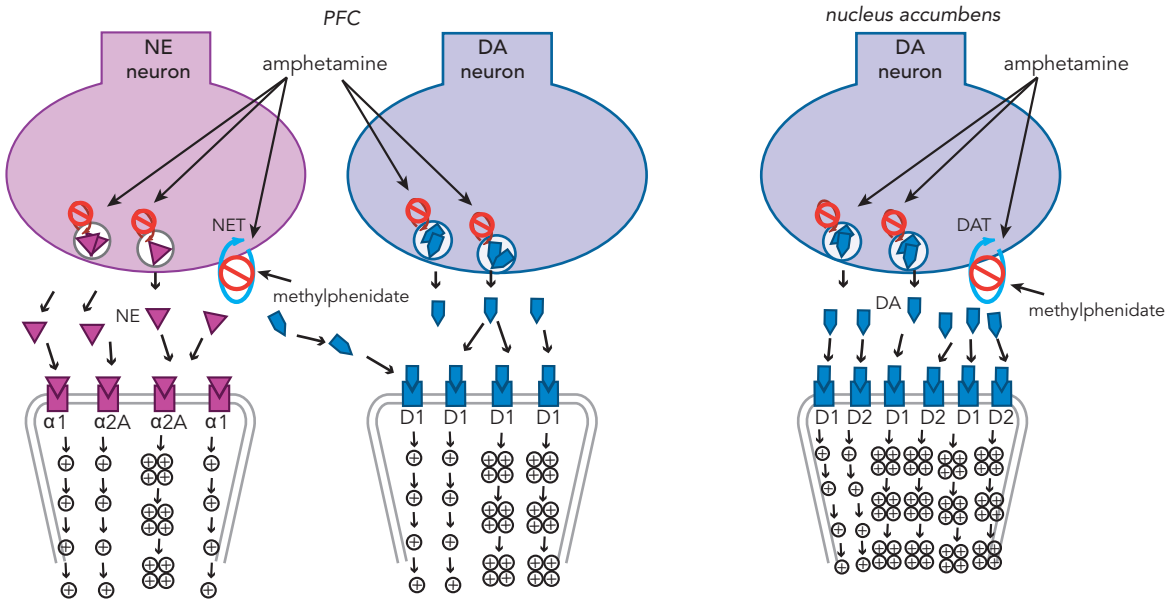


Figure 11-34 Dopamine transporter (DAT) occupancy levels and therapeutic effects. The therapeutic effects of DAT blockade are dependent upon attaining occupancy levels above a critical therapeutic threshold, with therapeutic action terminated as soon as occupancy falls below this threshold. The critical threshold of receptor occupancy for onset of therapeutic actions in ADHD is likely between 50% and 60%. Both the onset to achieving the threshold, and the duration of time above the threshold, are important for efficacy and tolerability. (A) Ideally, onset of achieving therapeutic DAT occupancy would be immediately upon waking, with levels maintained within the critical threshold throughout the day and dropping below the threshold in time for sleep. (B) Delayed onset of DAT blockade in the critical threshold can lead to morning symptoms, while inadequate duration of DAT blockade can cause evening symptoms. (C) If DAT blockade remains within the critical threshold for too long, this can result in evening side effects, notably insomnia.

Pulsatile Stimulants Amplify Tonic and Phasic NE and DA Signals



pulsatile stimulants

oral immediate-release, intravenous, intranasal, smoked, D-amphetamine, D,L amphetamine salts, methylphenidate, D-methylphenidate, cocaine, methamphetamine

Figure 11-35 Pulsatile stimulants amplify tonic and phasic norepinephrine (NE) and dopamine (DA) signals. Hypothetically, whether a drug has abuse potential depends on how it affects the DA pathway. In other words, the pharmacodynamic and pharmacokinetic properties of stimulants affect their therapeutic as well as their potential abuse profiles. Immediate-release oral stimulants – similarly to intravenous, smoked, or snorted stimulants (which are considered pulsatile stimulants) – lead to a rapid increase in NE and DA levels through blockade of the norepinephrine transporters (NETs) in the prefrontal cortex (PFC) and the DA transporters (DATs) in the nucleus accumbens. Rapidly amplifying the phasic neuronal firing of DA in the nucleus accumbens is associated with euphoria and abuse. The abuse potential of immediate-release formulations of methylphenidate and amphetamine may be due to increased phasic as well as tonic DA signaling.

massive release of dopamine from sudden, complete, and catastrophic DAT blockade (discussed earlier in this chapter and illustrated in Figure 11-32, bottom right). So, understanding how a more gentle and prudent administration of DAT inhibition can be therapeutic whereas the same drug can be disastrous can allow the best judicious administration of a DAT inhibitor. Be careful, and don't mess incorrectly with your DAT! Mystery solved.

Slow-Release Versus Fast-Release Stimulants

Based upon now having solved the mystery of the DAT, many drug delivery systems are not only designed to control how much DAT inhibition there is, and for how long, but also how quickly the DAT is inhibited, all to maximize therapeutic effects in ADHD and minimize abuse and side effects (Figure 11-36 and Tables 11-1 through 11-4). The goal is to enhance phasic DA neurotransmission with low to moderate, continuous drug delivery (Figure 11-36, top), trying to increase mostly tonic DA firing and only judiciously to increase phasic DA firing, recognizing that this may be playing a bit with fire. In order not to get burned, as happens with pulsatile drug delivery in drug abuse situations (see Figure 11-36, bottom), to achieve prudent and therapeutic improvement of tonic and phasic DA neurotransmission without disastrous increases in phasic DA neurotransmission, leading to abuse and

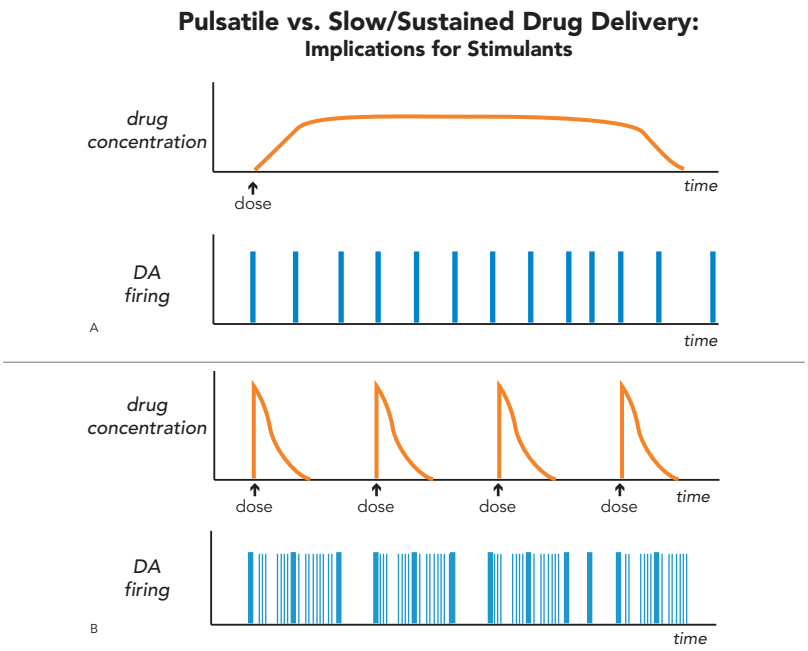


Figure 11-36 Pulsatile versus slow and sustained drug delivery. The difference between stimulants as treatments and stimulants as drugs of abuse lies less in their mechanism of action and more in the route of administration and dose, and thus the onset and duration of dopamine transporter (DAT) blockade. (A) When using stimulants to treat a patient it may be preferable to obtain a slow-rising, constant, steady-state level of the drug. Under those circumstances the firing pattern of DA will be tonic, regular, and not at the mercy of fluctuating levels of DA. (B) While some pulsatile firing can be beneficial, especially when involved in reinforcing learning and salience, higher doses of DA will mimic the actions of DA in stress and mimic drug abuse at the highest doses. Unlike a constant administration of DA, pulsatile administration of DA may lead to the highly reinforcing pleasurable effects of drugs of abuse and lead to compulsive use and addiction.

addiction, sustained delivery is what is wanted. Thus, controlled-release preparations for stimulants result in slowly rising, constant, steady-state levels of the drug (Figures 11-33, 11-34A; 11-35, top). Under those circumstances the firing pattern of DA will theoretically be mostly tonic, regular, and not at the mercy of fluctuating levels of DA. Some pulsatile firing is fine, especially when involved in reinforcing learning and salience (Figure 11-10). However, as seen in Figures 11-15 and 11-16, DA stimulation follows an inverted U-shaped curve, such that somewhat excessive DA will mimic the actions of DA in stress (Figure 11-14) and, at much higher doses, mimic drug abuse (Figure 11-36B). Thus, pulsatile drug administration that causes immediate release of DA, unlike controlled-release preparations, could potentially lead to the highly reinforcing pleasurable effects of drug abuse, especially at high enough doses and rapid enough administration. For this reason, using immediate-release stimulants, especially in adolescents and adults, is increasingly being avoided.

Just as importantly, the "slow-dose" stimulants, shown in Figure 11-33, optimize the rate, the amount, and the length of time that a stimulant occupies not only DATs for therapeutic use in ADHD, but also exploits the slow-dose occupancy of NETs for therapeutic actions in ADHD. Best pharmacological use of stimulants in ADHD (and sleepiness) targets both NETs and DATs rather than raising the dose to get predominantly DAT effects, many of which will be unwanted. Optimization for ADHD means not only targeting DATs, but also targeting NETs to occupy enough of these NETs in the prefrontal cortex at a slow enough onset and a long enough duration of action to enhance tonic NE signaling there via α_{2A} receptors (see discussion in Chapter 7 and Figure 7-33 for how NET inhibition leads to enhanced NE action). NET inhibition can also increase tonic DA signaling in the prefrontal cortex via D_1 receptors, as explained in Chapter 7 and illustrated in Figure 7-33. This allows good therapeutic effects in ADHD while occupying carefully a lower number of mysterious DAT targets, especially in the nucleus accumbens, so as not to increase phasic signaling there via D_2 receptors (Figures 11-35 and 11-36).

In summary, it appears that ADHD patients have their therapeutic improvement by stimulants at the mercy of how quickly, how much, and how long stimulants occupy NETs and DATs. When this is done in an ideal manner with slow onset, robust but sub-saturating levels of transporter blockade, together with a long duration of action before declining and wearing off, the patient ideally benefits with improved ADHD symptoms, hours of relief, and no euphoria (Figures 11-34 and 11-36).

Noradrenergic Treatment of ADHD

Atomoxetine

Atomoxetine (Figure 11-37) is a selective norepinephrine reuptake inhibitor (NRI). Sometimes called NET inhibitors, the selective NRIs have known antidepressant properties (discussed in Chapter 7). In terms of their mechanism of therapeutic action in ADHD, it is the same as just discussed for stimulants acting at the NETs here in Chapter 11, and as previously discussed for drugs used to treat depression in Chapter 7 and illustrated in Figure 7-33. Blocking NETs in the prefrontal cortex increases both DA and NE in the prefrontal cortex (Figure 11-38) and is why NET inhibitors are thought to work in ADHD. However, since there are few NE neurons and NETs in nucleus accumbens, inhibiting NET does not lead to an increase in either NE or DA there (Figure 11-38) and is why NET inhibitors are thought not to have reinforcing, abuse, or addiction potential.

Bupropion is a weak NRI and also a weak DAT inhibitor known as a norepinephrine–dopamine reuptake inhibitor (NDRI), and was previously discussed as a treatment for depression in Chapter 7 and illustrated in Figures 7-34 through 7-36; see also Figure 11-37). Several tricyclic antidepressants (TCAs) have notable NRI actions, such as desipramine and nortriptyline. All of these agents with NRI properties have been utilized in the treatment of ADHD, with varying amounts of success, but only atomoxetine is well-investigated and approved for this use in children and adults.

Atomoxetine's hypothetical actions in ADHD patients with stress and comorbidity states, presumably linked to excessive and phasic DA and NE release, are shown conceptually by comparing the untreated states in Figures 11-11 and 11-12 with the changes that theoretically follow chronic treatment with atomoxetine in Figure 11-39. That is, ADHD linked to conditions that are associated with chronic stress and comorbidities is theoretically caused by overly active NE and DA circuits in the prefrontal cortex, resulting in an excess of phasic NE and DA activity (Figure 11-13). When slow onset, long duration, and essentially perpetual NET inhibition occurs in the prefrontal cortex due to atomoxetine, this theoretically restores tonic postsynaptic D_1 and α_{2A}-adrenergic signaling, downregulates phasic NE and DA actions, and desensitizes postsynaptic NE and DA receptors (Figure 11-39). The possible consequence of this is to reduce stress as ADHD symptoms are improved. If so, decreases in ADHD symptoms could potentially be accompanied by decreases in anxiety, depression, and heavy drinking. Unlike stimulant use, where the therapeutic actions are at the mercy of plasma drug levels and momentary NET/DAT occupancies, actions from long-term NRI actions give 24-hour symptom relief, in much the same manner as do SSRIs (selective serotonin reuptake inhibitors) and SNRIs (serotonin–norepinephrine reuptake inhibitors) for the treatment of depression and anxiety. Selective NRIs generally have smaller effect sizes for reducing ADHD symptoms than stimulants in short-term trials, especially in patients without comorbidity. However, NRIs are not necessarily inferior in ADHD patients who

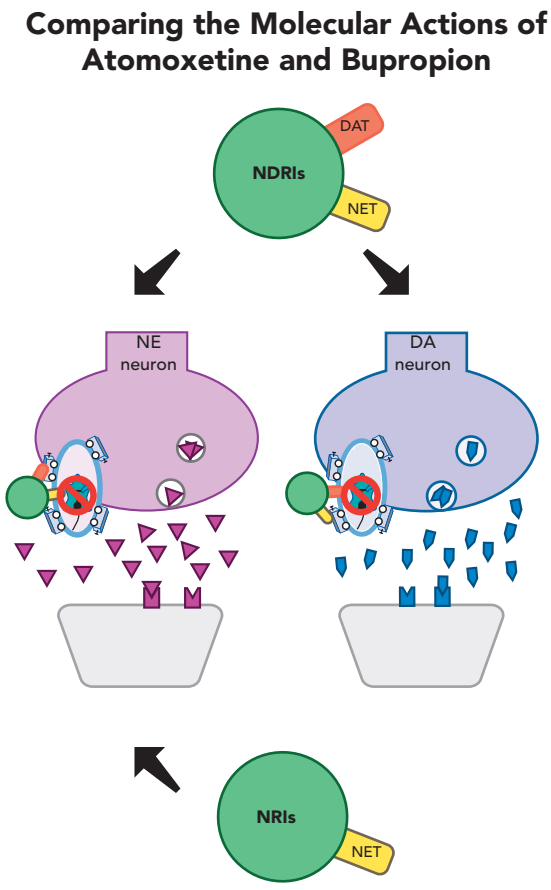


Figure 11-37 Comparing the molecular actions of atomoxetine and bupropion. Atomoxetine is a selective norepinephrine reuptake inhibitor (NRI), while bupropion is a norepinephrine–dopamine reuptake inhibitor (NDRI). Both agents block the norepinephrine transporters (NETs) in the prefrontal cortex, which leads to an increase in both norepinephrine (NE) and dopamine (DA) there (because NETs also transport dopamine). NDRIs also block the dopamine transporters (DATs), which are not present in the prefrontal cortex but are present in the nucleus accumbens.

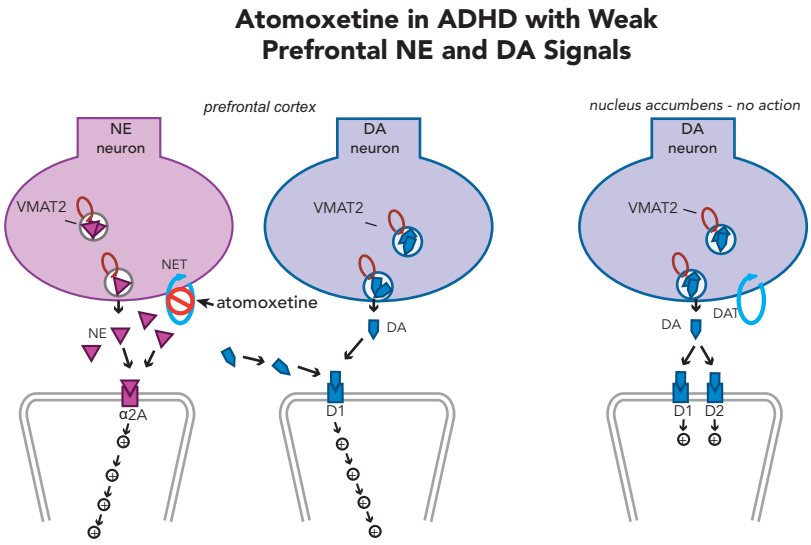


Figure 11-38 **Atomoxetine in ADHD with weak prefrontal norepinephrine (NE) and dopamine (DA) signals.** Through its blockade of norepinephrine transporters (NETs), atomoxetine causes NE and DA levels to increase in the prefrontal cortex, where inactivation of both of these neurotransmitters is largely due to NETs (on the left). At the same time, the relative lack of NETs in the nucleus accumbens prevents atomoxetine from increasing NE or DA levels in that brain area, thus reducing the risk of abuse (on the right). Other NET inhibitors would be expected to have the same effects.

NET inhibitors

atomoxetine (NRI), reboxetine (NRI), bupropion (NDRI), venlafaxine (SNRI), duloxetine (SNRI), desvenlafaxine (SNRI), milnacipran (SNRI), desipramine (TCA), nortriptyline (TCA)

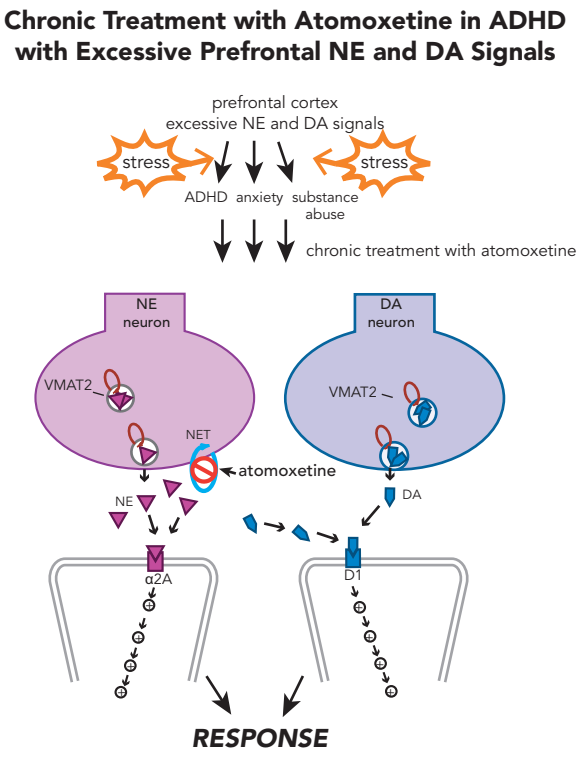


Figure 11-39 **Chronic treatment with atomoxetine in ADHD with excessive signals.** ADHD linked to conditions that are associated with chronic stress and comorbidities is theoretically caused by overly active NE and DA circuits. Continuous blockade of NETs could restore tonic postsynaptic D_1 and α_{2A}-adrenergic signaling, downregulate phasic NE and DA actions, and desensitize postsynaptic NE and DA receptors.

have not been previously treated with stimulants, nor in ADHD patients who have been treated long term (more than 8–11 weeks). NRIs may actually be preferred to stimulants in patients with complex comorbidities, side effects, or lack of response to stimulants.

Alpha-2A-Adrenergic Agonists

Norepinephrine receptors are discussed in Chapter 6 and illustrated in Figures 6-14 through 6-16. There are numerous subtypes of α-adrenergic receptors, from presynaptic autoreceptors, generally of the α_{2A} subtype (Figure 6-14) to postsynaptic α_{2A}, α_{2B}, α_{2C}, and α_1 subtypes α_{1A}, α_{1B}, and α_{1D} (Figures 6-14 through 6-16). Alpha-2A receptors are widely distributed throughout the central nervous system, with high levels in the cortex and locus coeruleus. These receptors are thought to be the primary mediators of the effects of NE in the prefrontal cortex, regulating symptoms of inattention, hyperactivity, and impulsivity in ADHD. Alpha-2B receptors are in high concentrations in the thalamus and may be important in mediating sedating actions of NE, while α_{2C} receptors are densest in striatum. Alpha-1 receptors generally have opposing actions to α_2 receptors, with α_2 mechanisms predominating when NE release is low or moderate (i.e., for normal attention), but with α_1 mechanisms predominating at NE synapses when NE release is high (e.g., associated with stress and comorbidity) and contributing to cognitive impairment. Thus, selective NRIs at low doses will first increase activity at α_{2A}

postsynaptic receptors to enhance cognitive performance, but at high doses may swamp the synapse with too much NE and cause sedation, cognitive impairment, or both. Patients with these responses to selective NRIs may benefit from lowering the dose. Alpha-2-adrenergic receptors are present in high concentrations in the prefrontal cortex, but only in low concentrations in the nucleus accumbens.

There are two direct-acting agonists for α_2 receptors used to treat ADHD, guanfacine (Figure 11-40) and clonidine (Figure 11-41). Guanfacine is relatively more selective for α_{2A} receptors (Figure 11-40). It has been formulated into a controlled-release product, guanfacine ER, that allows once-daily administration, and lower peak-dose side effects than immediate-release guanfacine. Only the controlled-release version of guanfacine is approved for treatment of ADHD. Clonidine is a relatively nonselective agonist at α_2 receptors, with actions on α_{2A}, α_{2B}, and α_{2C} receptors (Figure 11-41). In addition, clonidine has actions on imidazoline receptors, thought to be responsible for some of clonidine's sedating and hypotensive actions (Figure 11-41). Although the actions of clonidine at α_{2A} receptors exhibit therapeutic potential for ADHD, its actions at other receptors may increase side effects. Clonidine is approved for the treatment of hypertension, but only the controlled-release version of clonidine is approved for treatment of ADHD. Both clonidine and guanfacine, especially in the controlled-release formulations, are used "off-label" for the treatment of conduct disorder, oppositional defiant disorder, and Tourette syndrome. Unlike clonidine, guanfacine is 15–60 times more selective for α_{2A} receptors than for α_{2B} and α_{2C} receptors. Additionally, guanfacine is 10 times weaker than clonidine at inducing sedation and lowering blood pressure, yet it is 25 times more potent in enhancing prefrontal cortical function. The therapeutic benefits of both clonidine and guanfacine are hypothetically related to direct effects on postsynaptic receptors in the prefrontal cortex, which lead to the strengthening of network inputs, and to behavioral improvements, as seen in Figures 11-42 and 11-43.

Who are the best candidates for monotherapy with an α_2 agonist? Hypothetically, the symptoms of ADHD could be caused in some patients by NE levels being low in the prefrontal cortex, without additional impairments in DA neurotransmission (Figure 11-43A). This would lead to scrambled signals lost within the background noise, which could be seen behaviorally as hyperactivity, impulsivity, and inattention (Figure 11-43A). In this instance, treatment with a selective α_{2A} agonist would lead to an increased signal via direct stimulation of

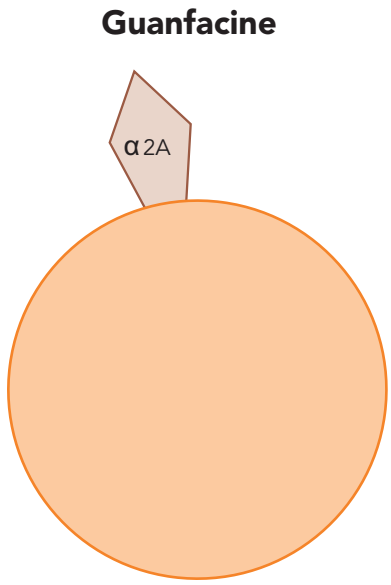


Figure 11-40 Guanfacine. Guanfacine is a selective α_{2A} receptor agonist. Specifically, guanfacine is 15–60 times more selective for α_{2A} receptors than for α_{2B} and α_{2C} receptors.

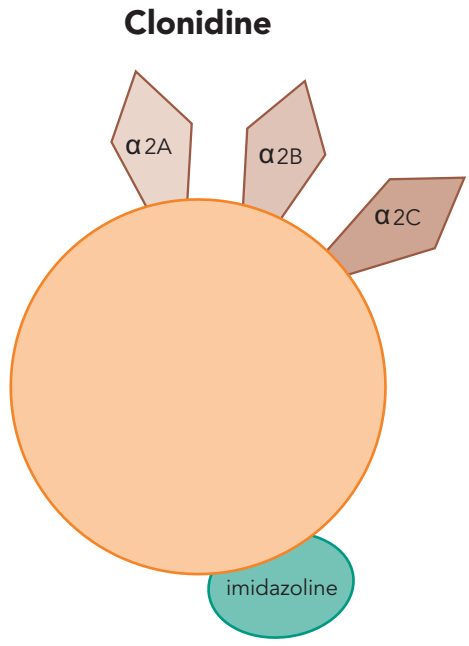


Figure 11-41 Clonidine. Clonidine is an α_2 receptor agonist. It is nonselective and thus binds to α_{2A}, α_{2B}, and α_{2C} receptors. Clonidine also binds to imidazoline receptors, which contributes to its sedating and hypotensive effects.

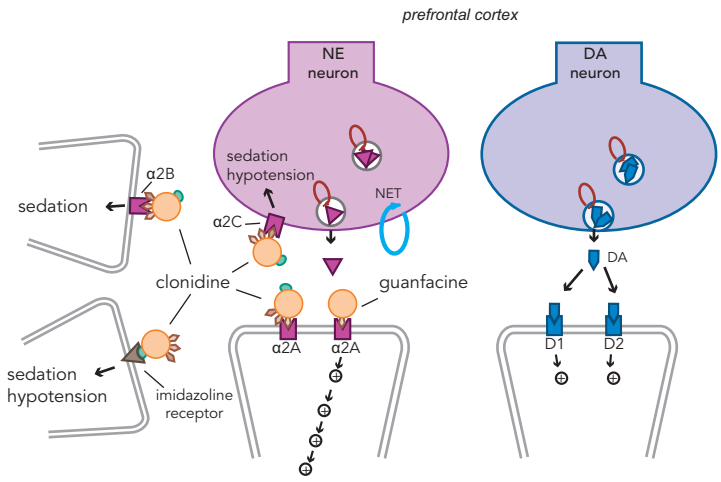


Figure 11-42 Mechanism of action of clonidine and guanfacine. Alpha-2-adrenergic receptors are present in high concentrations in the prefrontal cortex, but only in low concentrations in the nucleus accumbens. There are three types of α_2 receptors: α_{2A}, α_{2B}, and α_{2C}. The most prevalent subtype in the prefrontal cortex is the α_{2A} receptor. Alpha-2B receptors are mainly located in the thalamus and are associated with sedative effects. Alpha-2C receptors are located in the locus coeruleus, with few in the prefrontal cortex. Besides being associated with hypotensive effects, they also have sedative actions. In ADHD, clonidine and guanfacine – by stimulating postsynaptic receptors – can increase NE signaling to normal levels. The lack of action at postsynaptic DA receptors parallels their lack of abuse potential.

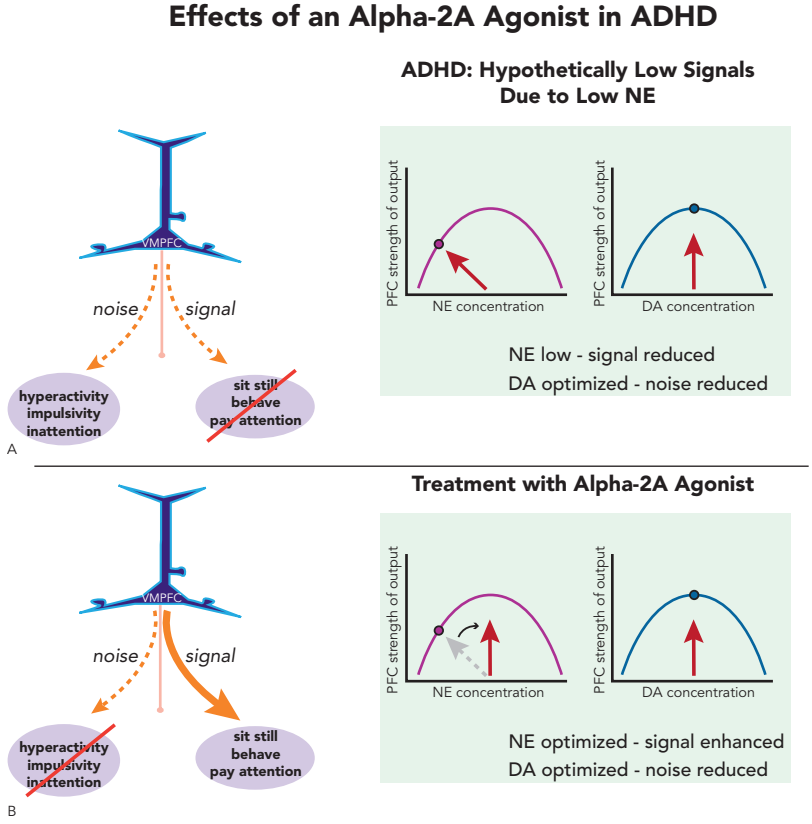


Figure 11-43 Effects of an α_{2A} agonist in ADHD. (A) The symptoms of ADHD could hypothetically be due to low norepinephrine (NE) levels in the prefrontal cortex (PFC), without additional impairments in dopamine (DA) neurotransmission. The resulting scrambled signals may manifest as hyperactivity, impulsivity, and inattention. (B) Treatment with a selective α_{2A} agonist would lead to increased signal via direct stimulation of postsynaptic receptors, resulting in an increased ability to sit still and focus. VMPFC: ventromedial prefrontal cortex.

postsynaptic receptors, and this would translate into the patient being able to focus, sit still, and behave adequately (Figure 11-43B). There is currently no way to identify these patients in advance, other than by an empiric trial of guanfacine ER.

Patients suffering from ADHD and oppositional symptoms can be argumentative, disobedient, aggressive, and exhibit temper tantrums (Figures 11-8 and 11-44A). These behaviors are hypothetically linked to very low levels of NE and low levels of DA in the ventromedial prefrontal cortex (VMPFC), thus leading to much reduced signal and increased noise (Figure 11-44A). While treatment with a stimulant will improve the situation by reducing the noise, it would not solve any strong hypothetical NE deficiencies (Figure 11-44B), therefore only partially improving behavior.

Augmenting a stimulant with an α_{2A} agonist (Figure 11-44C) could hypothetically solve the problem by optimizing the levels of NE, thus enhancing the signal, in the presence of an already optimized DA output. Behaviorally, this could hypothetically result in a patient cooperating and behaving appropriately. Guanfacine ER has been approved as an augmenting agent for patients inadequately responsive to stimulants, and may be especially helpful in patients with oppositional symptoms.

Future Treatments for ADHD

There are ever-evolving new technologies for drug delivery of amphetamine and methylphenidate and more of these are in development, partly because they allow customization of the duration of desired therapeutic

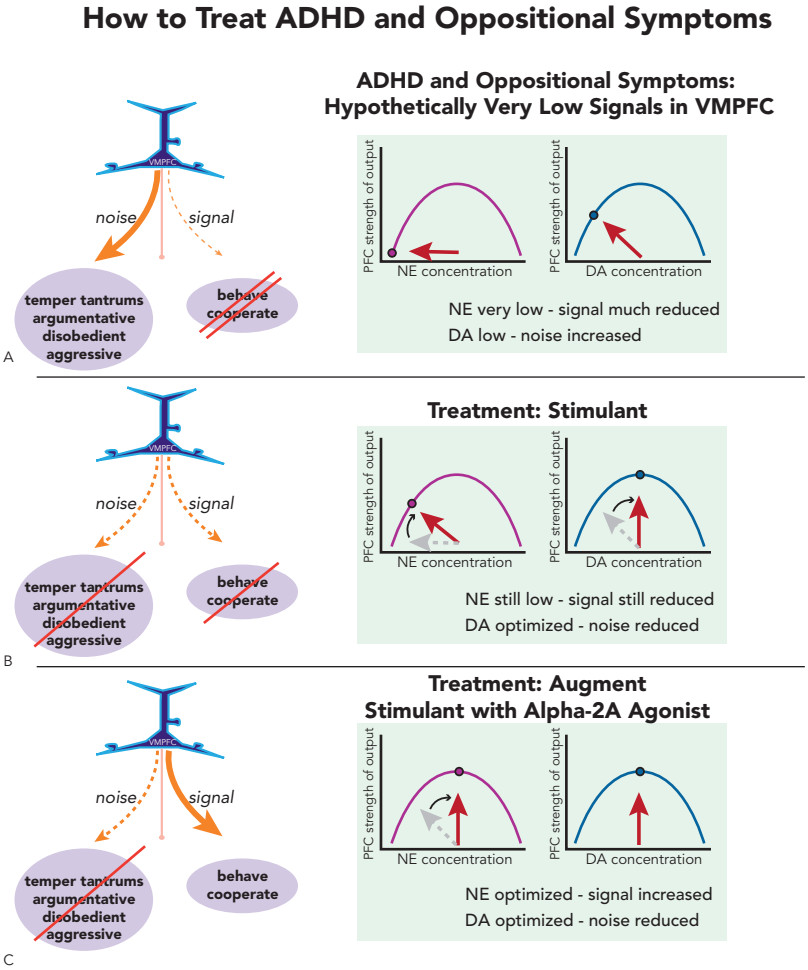


Figure 11-44 How to treat ADHD and oppositional symptoms. Argumentative, disobedient, and aggressive behaviors are often seen in patients suffering from ADHD and oppositional symptoms. (A) These behaviors could theoretically be due to very low levels of norepinephrine (NE) and low levels of dopamine (DA) in the ventromedial prefrontal cortex (VMPFC), leading to much reduced signal and increased noise. (B) While treatment with a stimulant may reduce the noise, it will not solve the strong NE deficiencies, therefore only partially improving behavior. (C) The augmentation of a stimulant with an α_{2A} agonist could optimize the levels of NE, thus enhancing the signal in the presence of an already optimized DA output.

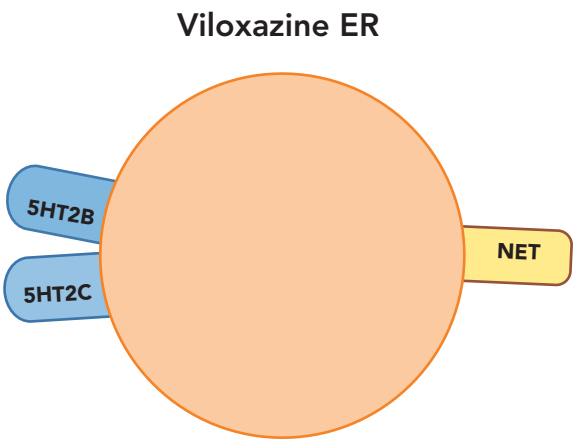


Figure 11-45 Viloxazine ER. Viloxazine is an inhibitor of the norepinephrine transporter (NET) and also has actions at serotonin 2B ($5HT_{2B}$) and $5HT_{2C}$ receptors. A controlled-release formulation is in late-stage clinical development for ADHD.

action, and partially because they are patentable and commercializable. One newer aspect of controlled-release formulations is the potential to make them in a matrix that resists attempts to powderize for inhaling, snorting, smoking, or injecting.

A selective NRI called viloxazine (Figure 11-45), once marketed abroad for the treatment of depression but never marketed in the US, has been repurposed in a controlled-release formulation for use in ADHD, and is now in late-stage clinical development for ADHD.

The DAT inhibitor mazindol, once approved for appetite suppression, is in testing and so is a triple (5HT–NE–DA) reuptake inhibitor centanafadine.

SUMMARY

ADHD has core symptoms of inattentiveness, impulsivity, and hyperactivity, linked theoretically to specific malfunctioning neuronal circuits in the prefrontal cortex. ADHD can also be conceptualized as a disorder of dysregulation of norepinephrine and dopamine in the prefrontal cortex, including some patients with deficient norepinephrine and dopamine and others with excessive norepinephrine and dopamine. Treatments theoretically return patients to normal efficiency of information processing in prefrontal circuits. There are differences between children and adults with ADHD, and special considerations exist for how to treat these two populations. The mechanisms of action, both in terms of pharmacodynamics and pharmacokinetics, for stimulant treatments of ADHD are discussed in detail. The goal is to amplify tonic but not phasic norepinephrine and dopamine actions in ADHD by controlling the rate of stimulant drug delivery, the degree of transporter occupancy, and the duration of transporter occupancy. Theoretical mechanisms of action of selective norepinephrine reuptake inhibitors such as atomoxetine and their possible advantages in adults with chronic stress and comorbidities are discussed. Actions of α_{2A}-adrenergic agonists are also presented.

12 Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine

Dementia: Diagnosis and Causes 487
What Is Dementia? 487
What Is Mild Cognitive Impairment (MCI)? 487
Four Major Causes of Dementia 488
Pursuit of Disease-Modifying Therapies by Targeting Aβ in Alzheimer Disease 496
The Amyloid Cascade Hypothesis 496
Current Status of the Amyloid Cascade Hypothesis and Treatments Targeting Aβ 499
Diagnosing Alzheimer Disease Before It Is Too Late 499
Presymptomatic Stage 1 499
MCI Stage 2 500
Dementia Stage 3 502
Overview of Symptomatic Treatments for Dementia 503
Targeting Acetylcholine for the Symptomatic Treatment of Memory and Cognition in Alzheimer Disease 505
Acetylcholine: Synthesis, Metabolism, Receptors, and Pathways 505
Symptomatic Treatment of Memory and Cognition in Alzheimer Disease by Inhibiting Acetylcholinesterase 509
Targeting Glutamate for the Symptomatic Treatment of Memory and Cognition in Alzheimer Disease 515
Memantine 516
Targeting the Behavioral Symptoms of Dementia 521
Defining Agitation and Psychosis in Alzheimer Disease 521
Pharmacological Treatment of Psychosis and Agitation in Dementia 523
Targeting Serotonin for the Symptomatic Treatment of Dementia-Related Psychosis 524
Neuronal Networks of Agitation in Alzheimer Disease 528
Targeting Multimodal Neurotransmitters (Norepinephrine, Serotonin, and Dopamine) for the Symptomatic Treatment of Agitation in Alzheimer Disease 530
Targeting Glutamate for the Symptomatic Treatment of Agitation in Alzheimer Disease 533
Treating Depression in Dementia 534
Pseudobulbar Affect (Pathological Laughing and Crying) 535
Apathy 536
Other Treatments for the Behavioral Symptoms of Dementia 537
Summary 537

This chapter will provide a brief overview of the various causes of dementia and their pathologies, including the most recent diagnostic criteria, and how biomarkers are beginning to be integrated into clinical practice, especially for Alzheimer disease (AD). Full clinical and pathological descriptions and formal criteria for how to diagnose the numerous known dementias should be obtained by consulting standard reference sources. The discussion here will emphasize how various pathological mechanisms in different dementias disrupt brain circuits and their neurotransmitters. We will also show how disruption of these brain circuits is linked to various symptoms of dementia, and how drugs targeting these brain circuits and their neurotransmitters lead to symptomatic improvement, emphasizing memory, psychosis, and agitation. The goal of this chapter is to acquaint the reader with ideas about the clinical and biological aspects of dementia and its current management with various approved drugs as well as novel agents on the horizon. Although hopes have faded for the early development of disease-modifying treatments that could slow, halt, or reverse the pathological processes underlying dementia, several new treatments improve behavioral symptoms of dementia such as psychosis and agitation, which are becoming more problematic as the number of patients with dementia explodes. Thus, the emphasis here is on the biological basis of symptoms of dementia and of their relief by psychopharmacological agents, as well as the mechanism of action of drugs that treat these symptoms. For details of doses, side effects, drug interactions, and other issues relevant to the prescribing of these drugs in clinical practice, the reader should consult

standard drug handbooks (such as *Stahl's Essential Psychopharmacology: the Prescriber's Guide*).

DEMENTIA: DIAGNOSIS AND CAUSES

What Is Dementia?

The term "dementia" describes cognitive and neuropsychiatric symptoms severe enough to interfere with the ability to perform usual activities, causing definite decline from previous levels of functioning (Table 12-1). These symptoms include cognitive dysfunction, memory loss, reasoning impairment, visual spatial impairment, language and communication issues, and behavioral symptoms such as psychosis and agitation (Table 12-1).

What Is Mild Cognitive Impairment (MCI)?

Mild cognitive impairment (MCI) is often confused with dementia and is often a precursor of dementia but MCI itself is not dementia (Figure 12-1 and Table 12-2). Instead, MCI represents only mild cognitive decline that does not (yet) significantly affect the ability to carry out activities of daily living. Not all patients with MCI will go on to develop dementia. In fact, there is great debate about what MCI is versus "normal aging."

Table 12-1 All-cause dementia diagnosis

All-cause dementia
• Cognitive/neurospsychiatric symptoms that interfere with ability to perform usual activities • Decline from previous levels of functioning • Not attributable to delirium or a major psychiatric disorder • Cognitive impairment diagnosed through neuropsychological testing or patient informant • Cognitive impairment involves two of the following: o Impaired ability to acquire/retain new information o Reasoning impairment o Visuospatial impairment o Changes in personality or behavior

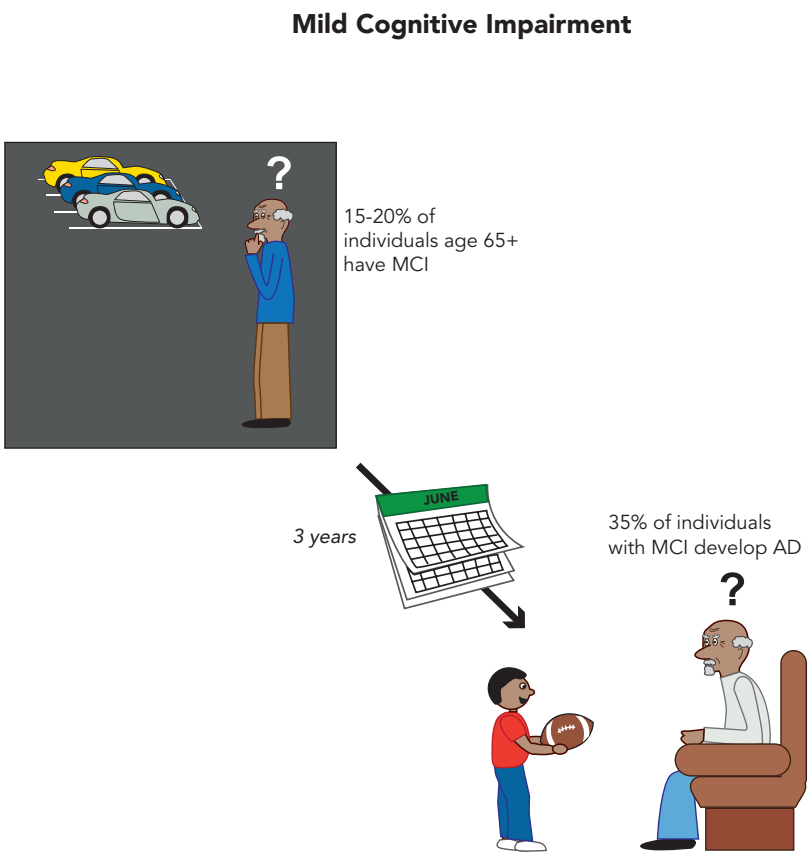


Figure 12-1 Mild cognitive impairment (MCI). Many older adults have subjective memory complaints. A subset of those adults has mild cognitive impairment (MCI), which denotes the presence of mild cognitive decline that does not significantly affect the ability to carry out activities of daily living and does not meet the threshold for dementia. Although MCI is evident in the early, prodromal stages of Alzheimer disease (AD), not all patients with MCI will go on to develop AD. In fact, many individuals with cognitive impairment may actually have a psychiatric disorder (e.g., depression) or a sleep disorder. Within 3 years, approximately 35% of individuals with MCI develop AD.

Hopefully, the study of biomarkers and neuroimaging will be able to settle this in the future. From a purely clinical perspective, over half of elderly residents living in the community have four common subjective memory complaints (SMCs). Compared to their functioning of 5 or 10 years ago, they experience diminished ability (1) to remember names, (2) to find the correct word, (3) to remember where objects are located, and (4) to concentrate. When such complaints occur in the absence of overt dementia, depression, anxiety disorder, sleep/wake disorder, pain disorder, or ADHD (attention deficit hyperactivity disorder), they are called MCI by many experts. Others reserve the term MCI only for those in the earliest stages of AD ("predementia AD," "MCI due to AD," or "prodromal AD"), but at this time it is not possible to determine those with SMCs who are destined to progress to AD and those who are not. Thus, MCI tends to be used as a general term encompassing all causes of subjective memory complaints. Attempts are being made to use biomarkers to distinguish those with normal aging from those with reversible conditions such as depression, from those destined to progress to AD or another dementia. On clinical grounds alone and without biomarkers, studies show that between 6% and 15% of MCI patients convert to a diagnosis of dementia every year; after 5 years about half meet the criteria for dementia; after 10 years or autopsy, up to 80% will prove to have AD. Thus, MCI is not always a prodrome of dementia, but it often is. Reversible and treatable causes of MCI should be pursued vigorously, properly diagnosed, and treated whenever possible.

Four Major Causes of Dementia

Over 35 million individuals worldwide have some form of dementia and this number is growing rapidly. There are numerous causes of dementia with many different pathological origins, but these all have both overlapping as well as distinctive clinical characteristics (Table 12-2) and neuroimaging findings (Table 12-3). The four major causes are AD, vascular dementia, Lewy body dementias (LBD), and frontotemporal dementia (FTD) (Table 12-2 and Table 12-3).

Alzheimer Disease (AD)

Alzheimer disease (AD) is the most common cause of dementia and arguably the most devastating age-related disorder, with profound consequences to patients, family members, caregivers, and the economy. An estimated 5.4 million Americans currently have AD and, in the absence of any disease-modifying treatment, cases will more than double to 14 million by 2050. The three pathological hallmarks of AD seen in the brain at autopsy are: (1) amyloid-beta (Aβ), aggregated into plaques; (2) neurofibrillary tangles composed of hyperphosphorylated tau protein; and (3) substantial neuronal cell loss (Figure 12-2). The loss of neurons is often so profound that it can be seen with the naked eye upon postmortem examination of the brain (Figure 12-3).

Table 12-2 Differential diagnosis: clinical presentation

Mild cognitive impairment (MCI)	Alzheimer disease (AD)	Vascular dementia	Lewy body dementias (LBD)	Frontotemporal degeneration (FTD)
Reduced speed of mental processing and choice reaction times Benign forgetfulness that is mild, inconsistent, and not associated with functional impairment	Short-term memory loss Impaired executive function Difficulty with activities of daily living Time and spatial disorientation Language impairment, personality changes	Impaired abstraction, mental flexibility, processing speed, and working memory Verbal memory is better preserved Slower cognitive decline Dementia occurs within several months of a stroke	Visual hallucinations Spontaneous parkinsonism Cognitive fluctuations Visuospatial, attention, and executive function deficits are worse Memory impairment is not as severe Earlier presentation of psychosis and personality changes Rapid eye movement (REM) sleep disturbances	Progressive behavioral and personality changes that impair social conduct (apathy, disinhibition, etc.) Language impairment Possibly preserved episodic memory

Table 12-3 Differential diagnosis: neural imaging

	Alzheimer disease (AD)	Vascular dementia	Lewy body dementias (LBD)	Frontotemporal degeneration (FTD)
MRI	Medial temporal lobe atrophy	Medial temporal lobe atrophy; white matter abnormalities	Medial temporal lobe atrophy	Medial temporal lobe atrophy
FDG PET	Temporo-parietal cortices	Fronto-subcortical networks	Parieto-occipital and temporo-parietal cortices	Frontotemporal cortices

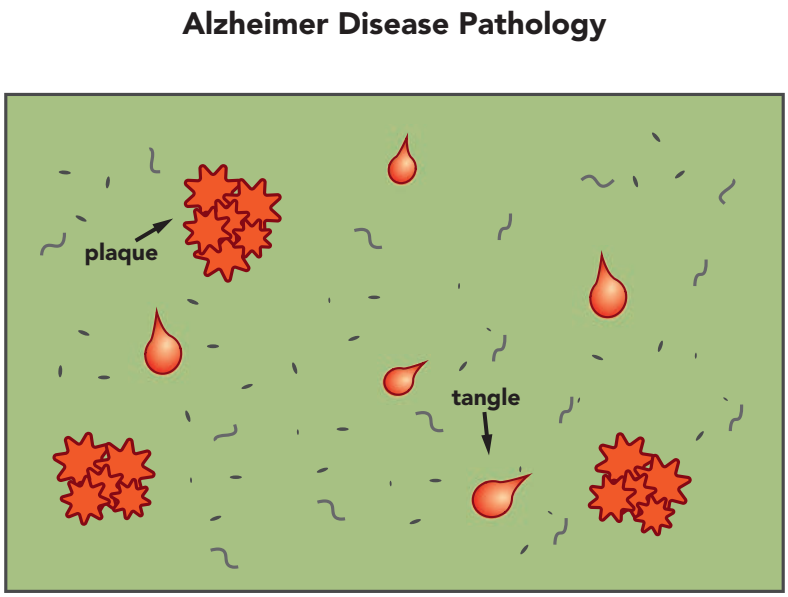


Figure 12-2 Alzheimer disease pathology. Two of the major pathological hallmarks seen in the Alzheimer disease brain at autopsy are plaques composed of Aβ and neurofibrillary tangles composed of hyperphosphorylated tau protein.

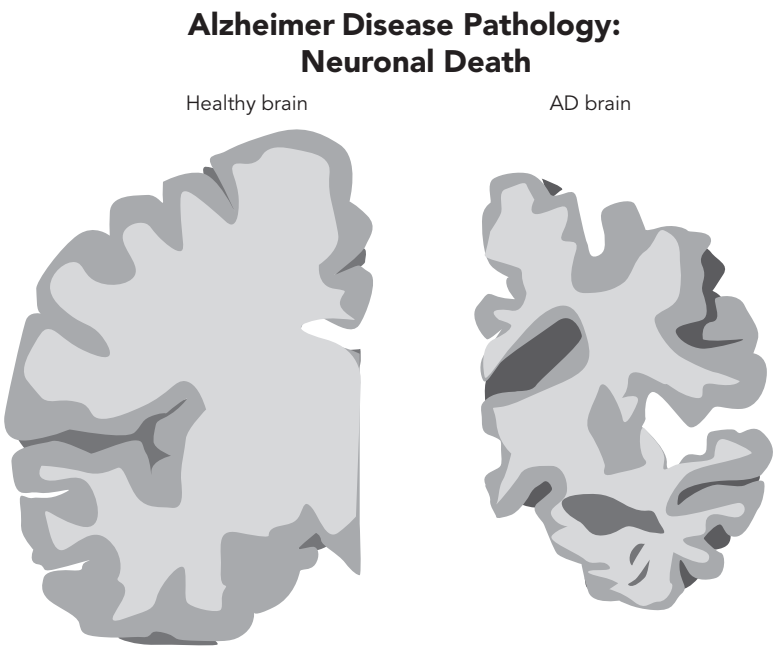


Figure 12-3 Alzheimer disease pathology: neuronal death. The third major pathological hallmark seen in the Alzheimer disease (AD) brain at autopsy is neuronal cell loss; it is often so profound that it can be seen with the naked eye on postmortem examination. Loss of neurons occurs in limbic and cortical regions and profoundly affects cholinergic neurons, although other neurotransmitter systems are also impacted.

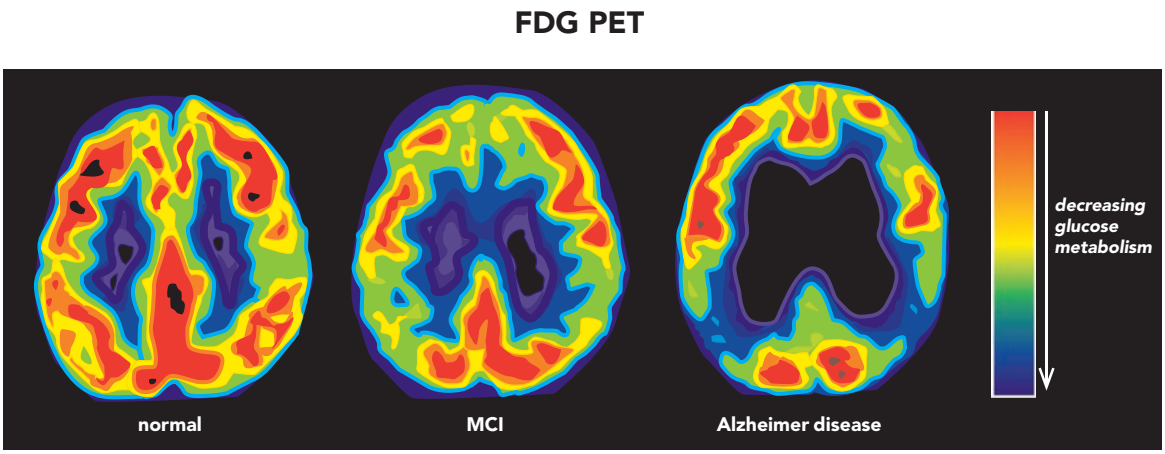


Figure 12-4 FDG PET. In living brains, neuronal loss in Alzheimer disease can be detected using ^{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET), which measures glucose metabolism in the brain. In the normal brain, glucose metabolism is robust. In mild cognitive impairment (MCI), reductions in glucose metabolism are evident in more posterior brain regions such as the temporo-parietal cortex. In Alzheimer disease (AD), glucose hypometabolism in posterior regions becomes even more evident. The FDG PET abnormalities seen in patients with AD are believed to reflect accumulating neurodegeneration. FDG PET results can be informative but are not diagnostic for AD.

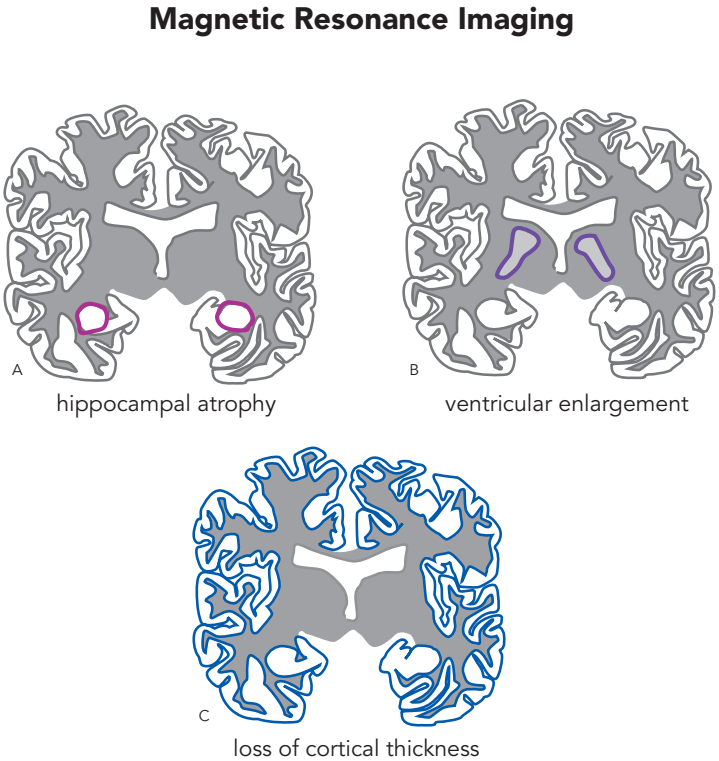


Figure 12-5 Magnetic resonance imaging. In living brains, neuronal loss in Alzheimer disease (AD) can be detected using magnetic resonance imaging (MRI), particularly in the medial temporal lobes; changes that have been seen include hippocampal atrophy (A), ventricular enlargement (B), and loss of cortical thickness (C). MRI results can be informative but are not diagnostic for AD.

Neuronal loss in AD can be detected in living patients by measuring brain glucose utilization, using fluorodeoxyglucose positron emission tomography (FDG PET) (Figure 12-4). The brains of normal, healthy controls show robust glucose metabolism throughout the brain, but in mild cognitive impairment (MCI) there can be reduction in brain glucose metabolism in more posterior brain regions such as temporo-parietal cortex (Figure 12-4). As the disease progresses to full-blown AD, brain glucose hypometabolism in posterior areas becomes more and more evident on FDG PET (Figure 12-4). The worsening of glucose metabolism with the progression of AD is believed

to reflect accumulating neurodegeneration, especially in key brain areas such as temporo-parietal cortices.

Magnetic resonance imaging (MRI) can also detect loss of neurons in living patients with AD, particularly in the medial temporal lobes (Figure 12-5). Even patients with mild AD may have 20–30% loss of entorhinal cortex volume, 15–25% loss of hippocampal volume, as well as ventricular enlargement (Figure 12-5). By the time a patient begins to exhibit even mild signs of dementia due to AD, damage to the brain may already be extensive and irreversible.

Vascular Dementia

Vascular dementia is the second most common form of dementia and accounts for about 20% of dementia cases (Figure 12-6). Vascular dementia is essentially a

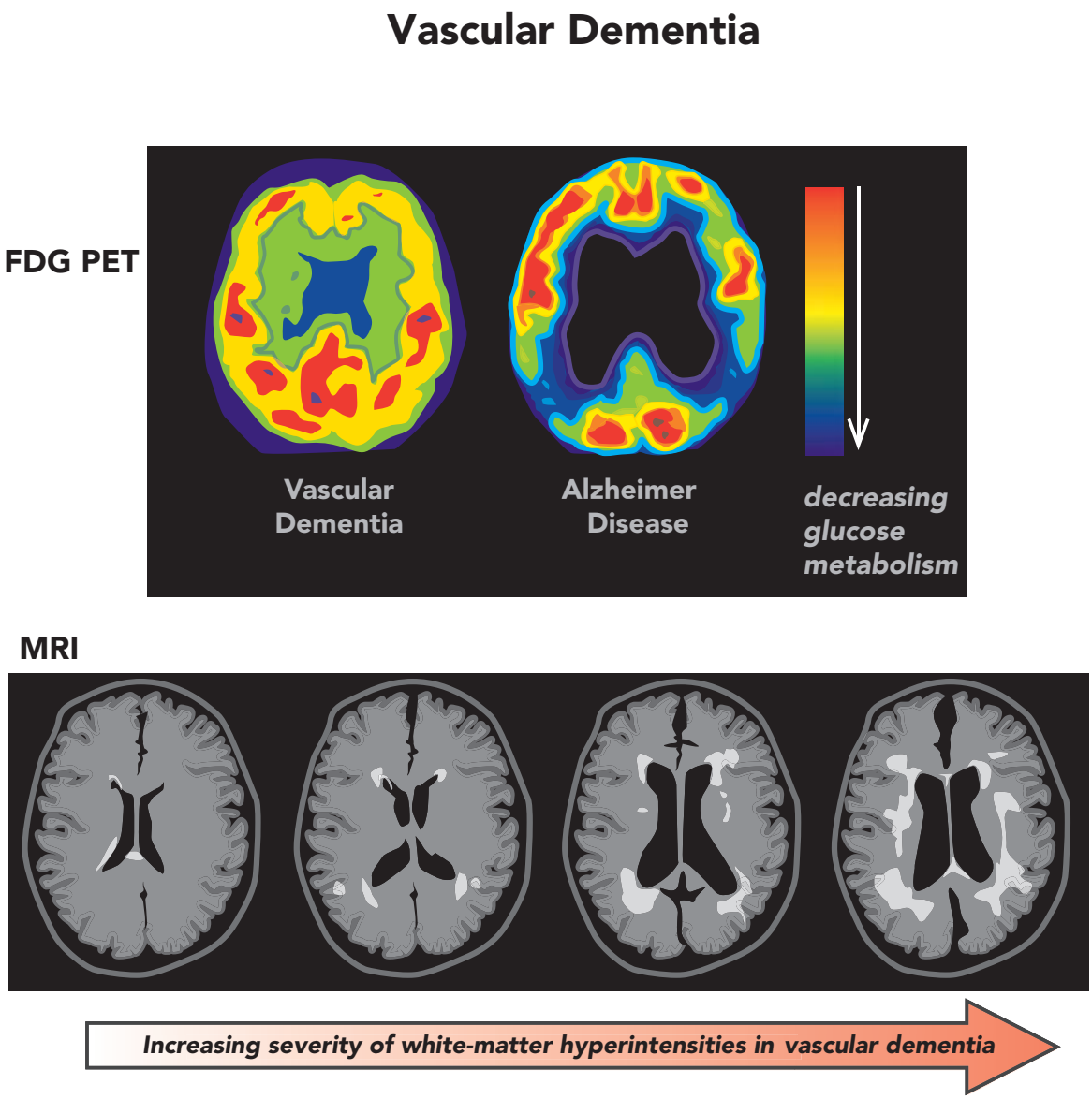


Figure 12-6 Vascular dementia. Vascular dementia is a neurological manifestation of cardiovascular disease, with decreased cerebral blood flow attributable to myriad pathologies including atherosclerosis, arteriosclerosis, infarcts, white-matter changes, and microbleeds, as well as deposition of Aβ into cerebral blood vessels. Vascular dementia and Alzheimer disease (AD) frequently overlap. In "pure" vascular dementia, the pattern of hypoperfusion on FDG PET is different than that for AD, with hypometabolism in the sensorimotor and subcortical areas and a relative sparing of the association cortex. On MRI, patients with vascular dementia show increasing severity of white-matter hyperintensities.

Alzheimer Disease/Vascular Dementia Comorbidity

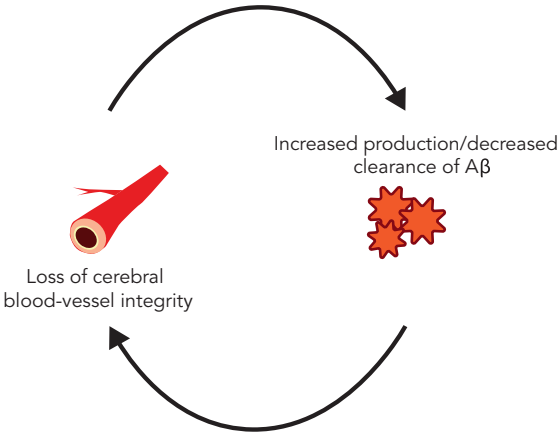


Figure 12-7 Alzheimer disease/vascular dementia comorbidity. A large portion of individuals with Alzheimer disease have comorbid vascular dementia pathology. This is hypothesized to occur due to a dynamic relationship between Aβ metabolism and cerebral vasculature integrity. That is, the deposition of Aβ into cerebral blood vessels hypothetically increases risk for vascular dementia; conversely, loss of integrity and increased permeability of the blood–brain barrier hypothetically increases production or decreases clearance of Aβ.

neurological manifestation of cardiovascular disease, with decreased cerebral blood flow attributable to atherosclerosis, infarcts, white-matter changes, and microbleeds, as well as deposition of Aβ into cerebral blood vessels (Figure 12-6). In fact, approximately 30% of elderly individuals who have a stroke will experience post-stroke cognitive impairment and/or dementia. Many of the risk factors associated with peripheral cardiovascular disease (e.g., hypertension, smoking, heart disease, high cholesterol, diabetes) are also linked with vascular dementia.

Vascular dementia and AD frequently overlap. Relatively "pure" vascular dementia cases show a different pattern of hypoperfusion (diminished blood flow) on FDG PET than AD (Figure 12-6). In vascular dementia, FDG PET indicates hypometabolism in sensorimotor and subcortical areas, with relative sparing of the association cortex whereas – as mentioned above – in AD, FDG-PET scans show reduction in brain glucose metabolism in more posterior brain regions such as the temporo-parietal cortex (Figures 12-4 and 12-6).

A large portion of individuals with AD, however, also have comorbid vascular dementia pathology, and this overlap may occur in part due to a dynamic relationship between Aβ metabolism and cerebral vasculature integrity (Figure 12-7). That is, deposition of Aβ into cerebral blood vessels hypothetically increases the risk for vascular dementia and, conversely, loss of integrity and increased permeability of the blood–brain barrier hypothetically increases production or reduces clearance of Aβ from the brain (Figure 12-7).

Lewy Bodies and Lewy Neurites

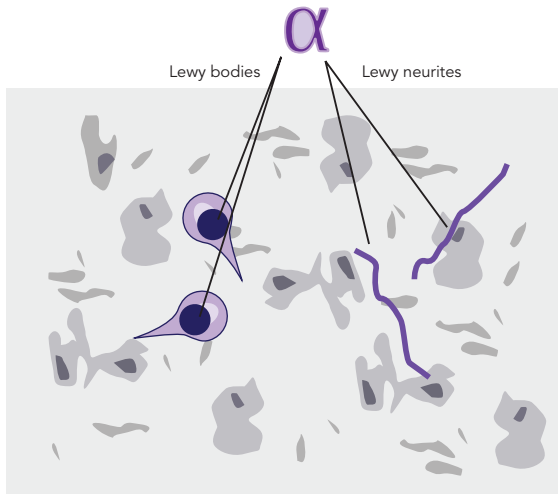


Figure 12-8 Lewy bodies and Lewy neurites. The pathology of both dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) includes the abnormal accumulation of a protein called α-synuclein. These aggregates form Lewy bodies and Lewy neurites, which are observable upon histopathological staining. In addition to α-synuclein, Lewy bodies and Lewy neurites may also contain various other proteins, such as neurofilaments, parkin, and ubiquitin.

Lewy Body Dementias (LBD)

Dementia with Lewy bodies (DLB) and the related Parkinson's disease dementia (PDD) are collectively known as Lewy body dementias (LBD), and account for about 10–15% of all cases of dementia. However, only an estimated 20% of LBD patients have "pure" LBD since approximately 80% of LBD patients will also have pathological features of other dementias, especially AD

Table 12-4 Dementia with Lewy bodies (DLB): diagnosis

Presence of Dementia
CORE FEATURES • Fluctuating attention and concentration • Recurrent well-formed visual hallucinations • Spontaneous parkinsonism
SUGGESTIVE CLINICAL FEATURES • Rapid eye movement (REM) sleep behavior disorder • Severe neuroleptic sensitivity • Low dopamine transporters uptake in basal ganglia on SPECT or PET
SUPPORTIVE CLINICAL FEATURES • Repeated falls • Transient loss of consciousness • Hallucinations in other sensory modalities • Severe autonomic dysfunction • Depression • Delusions • Syncope
FACTORS THAT MAKE DLB DIAGNOSIS LESS LIKELY • Presence of cerebrovascular disease • Presence of any other physical illness or brain disorder that may account in part or in total for the clinical picture • Parkinsonism appears for the first time at a stage of severe dementia

pathology. DLB and PDD share pathological links to the abnormal accumulation of a protein called α-synuclein, and thus both are also called "synucleinopathies." In LBD, for unknown reasons, α-synuclein proteins aggregate to form oligomers, eventually turning into "Lewy bodies" and Lewy neurites, as neurons degenerate (Figure 12-8).

The diagnostic criteria for the diagnosis of probable DLB and for possible DLB are given in Table 12-4. In terms of PDD, the majority (~80%) of patients with Parkinson's disease (PD) will develop cognitive dysfunction from one cause or another as the disease progresses, with the average time from diagnosis of PD to onset of dementia being 10 years. PDD is associated with increased morbidity and death ultimately occurring, on average, 4 years after PDD onset. As with AD, the harbinger of dementia in PD is often MCI. Symptoms of PDD include impairments in memory (including recognition), executive dysfunction, deficits in attention, and altered visual perception. The pathological basis for PDD is hypothesized to be neuronal degeneration and atrophy occurring in the thalamus, caudate nucleus, and hippocampus, as Lewy bodies and Lewy neurites accumulate there (Figure 12-9). Lewy body pathology is also often found in neocortical areas; however, the

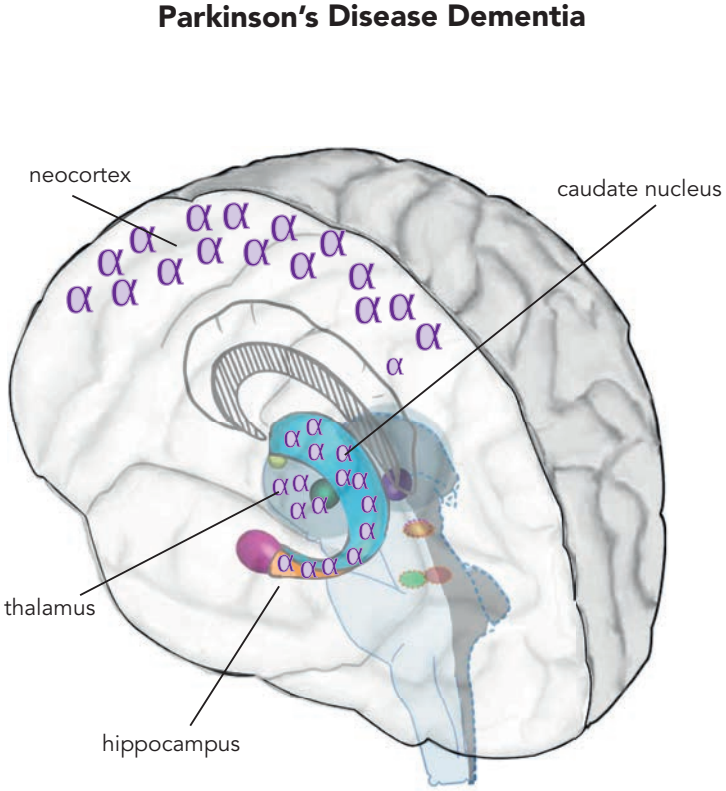


Figure 12-9 Parkinson's disease dementia. The pathological basis for Parkinson's disease dementia (PDD) is hypothesized to be neuronal degeneration and atrophy occurring in the thalamus, caudate nucleus, and hippocampus. Lewy body pathology is also often found in neocortical areas; however, the severity of dementia in Parkinson's disease correlates with the severity of α-synuclein (as well as amyloid and tau) pathology in limbic regions.

severity of α-synuclein (as well as amyloid and tau) pathology in limbic regions correlates with the severity of dementia in PDD. There is much debate over whether DLB and PDD are actually the same disease with slightly different clinical expression and progression, or two distinct diseases (Figure 12-10). Certainly, PDD and DLB share many pathophysiological and clinical characteristics, and the differential diagnosis between DLB and PDD relies mainly on when there is onset of motor symptoms versus when there is onset of dementia. That is, if motor symptoms precede dementia by 1 year or more, the diagnosis is PDD; however, if dementia occurs at the same time or precedes the onset of parkinsonism, the diagnosis is DLB. Many argue that this "1-year rule" is arbitrary and offers little in terms of treatment guidance.

Although AD and PD have historically been viewed as two distinct entities, the overlap between the disorders has increasingly been recognized. As many as 70% of patients with AD eventually show extrapyramidal and parkinsonian symptoms, and Lewy bodies are seen in ~30% of patients with AD. Likewise, ~50% of patients with PD develop dementia and often have Alzheimer-type pathology. DLB shares many neuropsychiatric features with AD as well as many motor features (albeit often less severe) with PD. Due to this overlap in pathology and clinical presentation, some now propose that AD and PD may lie on opposite ends of a spectrum, with DLB falling somewhere between AD and PD (Figure 12-11). It has been proposed that an individual's neuropsychiatric and physical clinical presentation may be a result of the unique combination of pathological proteins present in the brain as well as the particular brain regions most affected (i.e., more or less AD pathology plus more or less PD pathology combined with a cortical versus subcortical abundance of pathology determines where they land on the spectrum.)

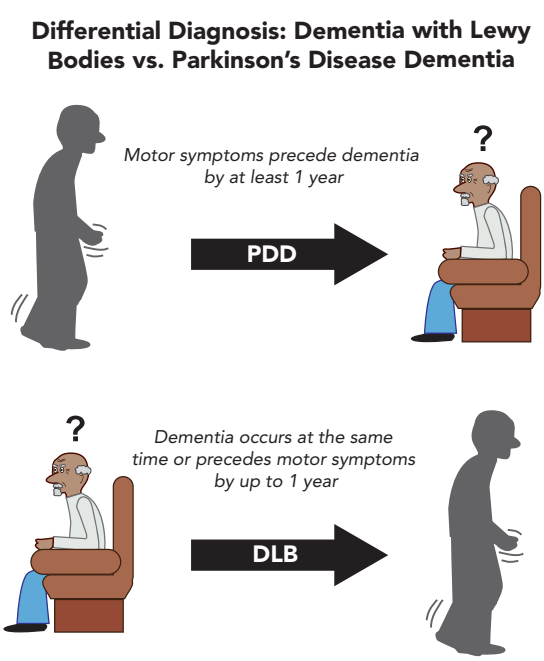


Figure 12-10 Dementia with Lewy bodies versus Parkinson's disease dementia. Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) share many pathophysiological and clinical characteristics. The differential diagnosis relies mainly on the onset of motor symptoms versus the onset of dementia. If motor symptoms precede dementia by 1 year or more, the diagnosis is PDD. If dementia occurs at the same time or precedes the onset of parkinsonism, the diagnosis is DLB. Many argue that this "1-year rule" is arbitrary and offers little in terms of treatment guidance.

Frontotemporal Dementia

Frontotemporal dementia (FTD) is about as common as LBD, with a worldwide prevalence of 3–26% in individuals aged 65 years and older and an average age of onset of 50–65 years. FTD (Figure 12-12) is divided into four subtypes: a behavioral variant (bvFTD) (Table 12-5), and three primary progressive aphasia variants (Figure 12-12). The behavioral variant, bvFTD, the most common of the FTD subtypes, usually presents with gradual and progressive personality changes (such as disinhibition, apathy, and loss of sympathy and empathy), hyperorality, perseverative or compulsive behaviors, and, eventually, cognitive deficits with a general sparing of visuospatial abilities. Patients with bvFTD are often unaware of their inappropriate behaviors, and contrary to patients with AD, do not typically have rapid memory loss and may do fairly well in memory tasks if provided cues. Pathologically, bvFTD is characterized by frontal and anterior temporal cortex atrophy, particularly the prefrontal cortex, insula, anterior cingulate, striatum, and thalamus, with the non-dominant hemisphere typically more affected. The diagnosis of FTD can be somewhat complex as clinical presentation and pathology often overlap with those of several other dementias, and many patients exhibit parkinsonian-like features. FTD can often be differentiated from AD by the absence of AD biomarkers.

Frontotemporal lobar degeneration (FTLD) is an umbrella term describing a group of different disorders with varying clinical presentations, genetics, and pathophysiology. We have already mentioned that aggregation of phosphorylated tau into neurofibrillary tangles is a hallmark feature of AD (Figure 12-2). Mutations in the gene coding for the tau protein (microtubule-associated protein tau; *MAPT*) is actually not associated with AD but with several forms of FTLD that may have aggregation and progression of tau pathology (Figure 12-13).

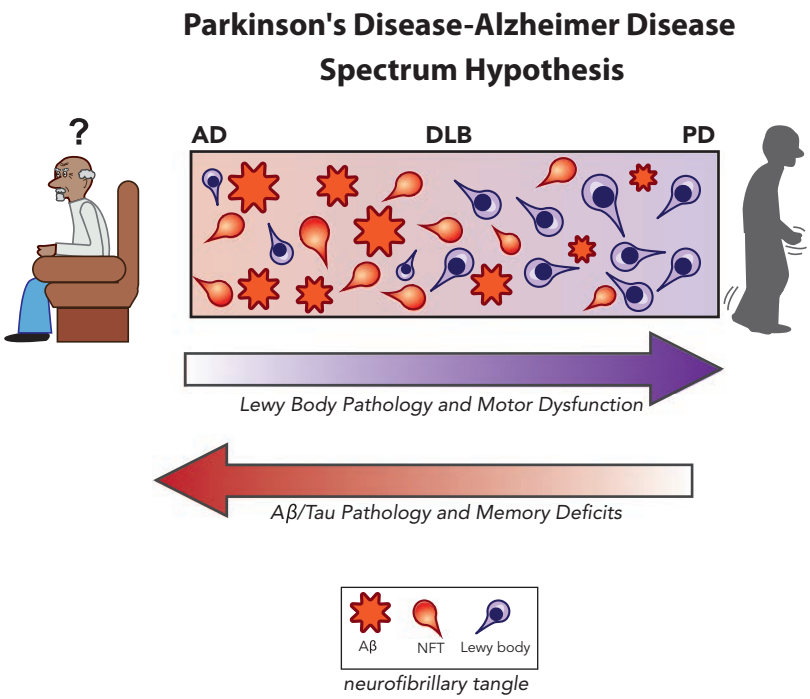


Figure 12-11 Parkinson's disease–Alzheimer disease spectrum hypothesis. There are clinical and pathological overlaps between Parkinson's disease (PD) and Alzheimer disease (AD). As many as 70% of patients with AD eventually show extrapyramidal and parkinsonian symptoms, and Lewy bodies are seen in approximately 30% of patients with AD. Likewise, approximately half of patients with PD develop dementia and often have Alzheimer-type pathology. Dementia with Lewy bodies (DLB) shares many neuropsychiatric features with AD as well as many motor features (albeit often less severe) with PD. Due to this overlap in pathology and clinical presentation, some now propose that AD and PD may lie on opposite ends of a spectrum, with DLB falling somewhere between AD and PD. It has been proposed that an individual's clinical presentation may be a result of the unique combination of pathological proteins present in the brain as well as the particular brain regions most affected.

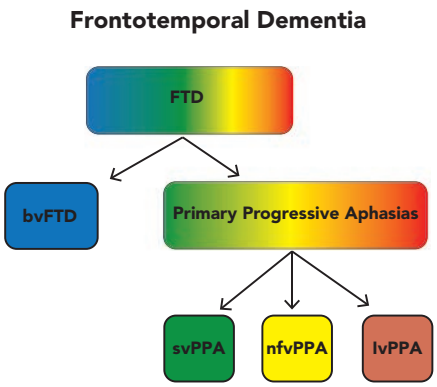


Figure 12-12 Frontotemporal dementia. Frontotemporal dementia (FTD) is divided into four subtypes: behavioral variant FTD (bvFTD) and three primary progressive aphasias (semantic variant primary progressive aphasia [svPPA], non-fluent variant primary progressive aphasia [nfvPPA]), and logopenic variant primary progressive aphasia [lvPPA]); bvFTD is the most common subtype. The diagnosis of FTD can be somewhat complex as clinical presentation and pathology often overlap with that of other dementias. FTD can often be differentiated from Alzheimer disease (AD) by the absence of AD biomarkers.

Table 12-5 Behavioral variant frontotemporal dementia (bvFTD)

Clinical presentation
Progressive personality changes: • disinhibition • apathy • loss of sympathy/empathy Hyperorality Perseverative/compulsive behaviors Cognitive deficits Cued memory and visuospatial abilities spared
Pathological presentation
Atrophy in: • prefrontal cortex • insula • anterior cingulate • striatum • thalamus Non-dominant hemisphere more affected

Mixed Dementia

As can be seen from our discussion so far, many individuals present with the clinical, neuroimaging, and pathological characteristics of more than one dementia (i.e., "mixed dementia"), making distinctions amongst the various causes of dementia often very difficult in clinical practice (Figure 12-14). Postmortem analyses indeed reveal that most dementia patients exhibit mixed pathology, comprising various combinations of abnormal protein aggregates plus vascular changes (Figure 12-14).

If each dementia were not complicated enough, combinations of dementia in a single individual

compound the complexity of diagnosis and eventually will compound the complexity of treatment. For example, in one study of community-dwelling adults, 56% of dementia patients were diagnosed with multiple underlying pathologies (AD in combination with either LBD, cerebrovascular injuries, or both). After adjusting for age, individuals with multiple diagnoses were deemed to be nearly three times more likely to develop dementia as those with a single underlying pathology. In another study, 59–68% of patients with AD neuropathology also displayed Lewy body pathology or vascular brain injury. Differential diagnosis of the various dementias during life will become more important when specific treatments for specific forms of dementia become available. However, most patients will have more than one cause of dementia and ultimately may require more than one type of treatment.

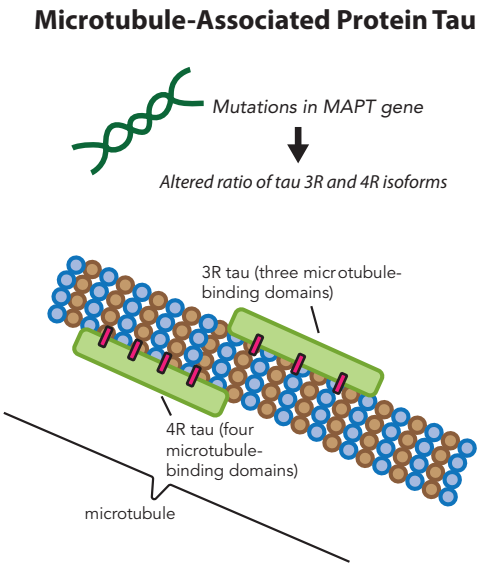


Figure 12-13 Microtubule-associated protein tau. Mutations in the gene coding for the tau protein (microtubule-associated protein tau; *MAPT*) are associated with several forms of frontotemporal lobar degeneration. Typically, these mutations change the ratio of tau 3R and 4R isoforms, leading to an accumulation of pathological tau.

PURSUIT OF DISEASE-MODIFYING THERAPIES BY TARGETING Aß IN ALZHEIMER DISEASE

The Amyloid Cascade Hypothesis

According to this hypothesis, Alzheimer disease (AD) is caused by the accumulation of toxic Aβ, which form into plaques, hyperphosphorylation of tau, neurofibrillary tangle formation, synaptic dysfunction, and ultimately neuron loss with memory loss and dementia (Figure 12-15). This notion is somewhat analogous to how abnormal deposition of cholesterol in blood vessels is thought to cause atherosclerosis. A corollary to the amyloid cascade

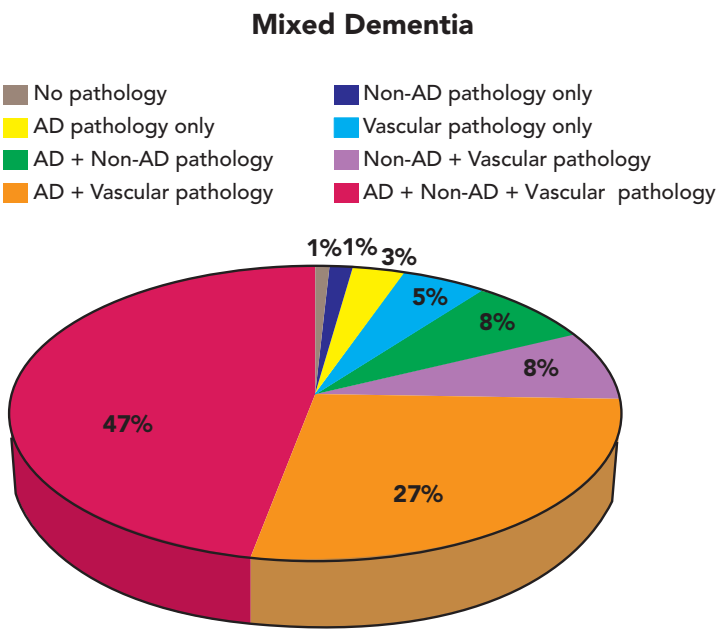


Figure 12-14 Mixed dementia. Dementias with only one type of pathology are likely the exception rather than the rule. Postmortem pathological analyses reveal that most patients with dementia have mixed pathology, comprising various combinations of abnormal protein aggregates and vascular changes.

hypothesis is that if the cascade could be blocked and Aβ prevented from forming, aggregating, and creating plaques and tangles, AD would be prevented, halted, or even reversed.

Aβ is formed when a precursor protein (amyloid precursor protein or APP) is cut by enzymes into smaller peptides (Figures 12-16 and 12-17). There are two enzymatic cleavage pathways by which APP may be processed: the non-amyloidogenic and the amyloidogenic pathways. In the non-amyloidogenic pathway, APP is cleaved by the enzyme α-secretase directly in the portion of APP where Aβ sits; thus, processing of APP by α-secretase thereby precludes production of Aβ. In the amyloidogenic pathway, APP is first cleaved by β-secretase and then by γ-secretase (Figure 12-16). Gamma-secretase cuts APP into several Aβ peptides, ranging from 38 to 43 amino acids long (Figure 12-17). The Aβ40 isoform is the most common form; however, the Aβ42 isoform is more prone to aggregation into oligomers and is considered the more toxic form of Aβ peptides. The Aβ43 isoform is relatively rare but is thought to be even more prone to aggregation than Aβ42. The Aβ-processing enzymes α-, β-, and γ-secretase have all been the targets of novel potential treatments for AD in the hopes that by preventing the processing of APP into amyloidogenic peptides, this would prevent AD (Table 12-6). Unfortunately, to date, these therapeutic approaches have been ineffective, unsafe, or both.

Table 12-6 Potential disease-modifying treatments for Alzheimer disease

Agents targeting Aß pathology
Anti-amyloid antibodies
Active Aβ immunization
ß-secretase inhibitors
γ-secretase inhibitors
α-secretase promoters
Aβ aggregation inhibitors
Agents targeting tau pathology
Anti-tau antibodies
Active tau immunization
Tau aggregation inhibitors
Microtubule stabilizers
Tau phosphorylation inhibitors

Mutations in several genes associated with AD lead to increased processing of APP via the amyloidogenic pathway, supporting the amyloid cascade hypothesis. Another genetic factor related to Aβ processing that is linked to AD is the gene (called *APOE*) for a protein called apolipoprotein E (ApoE), which transports the cholesterol needed by neurons for synapse development, dendrite formation, long-term potentiation, and axonal guidance. ApoE protein is also hypothesized to have an intricate relationship with Aβ metabolism, aggregation, and deposition in the brain. There are several forms of the *APOE* gene (Figure 12-18). Inheritance of even one copy of the *APOE4* gene results in a threefold increase in

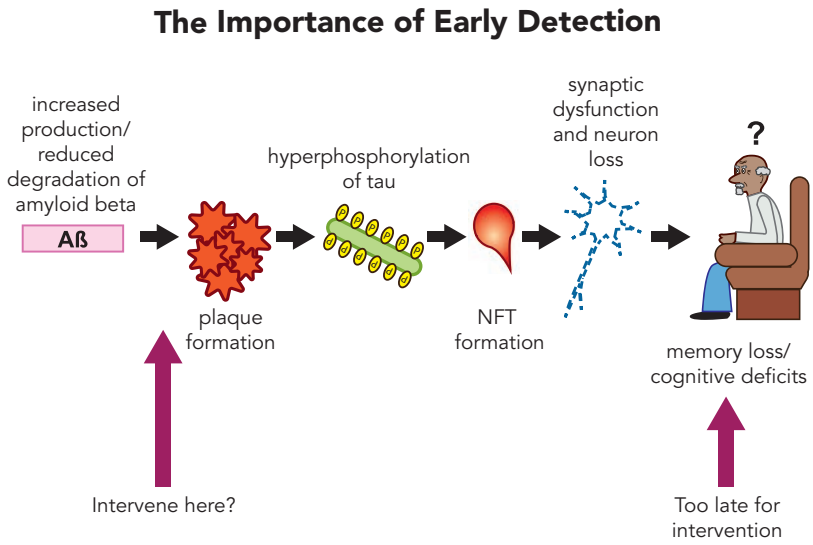


Figure 12-15 Importance of early detection. Alzheimer disease is hypothesized to be caused by increased production and/or reduced degradation of Aβ leading to plaque formation, hyperphosphorylation of tau, and neurofibrillary tangle (NFT) formation, synaptic dysfunction, and ultimately neuronal cell loss that presents with memory loss and cognitive deficits. Intervention at the stage of obvious memory loss and cognitive decline may be too late, as neurodegeneration has already occurred. If intervention were possible much earlier, then perhaps the cascade of toxic events could be avoided.

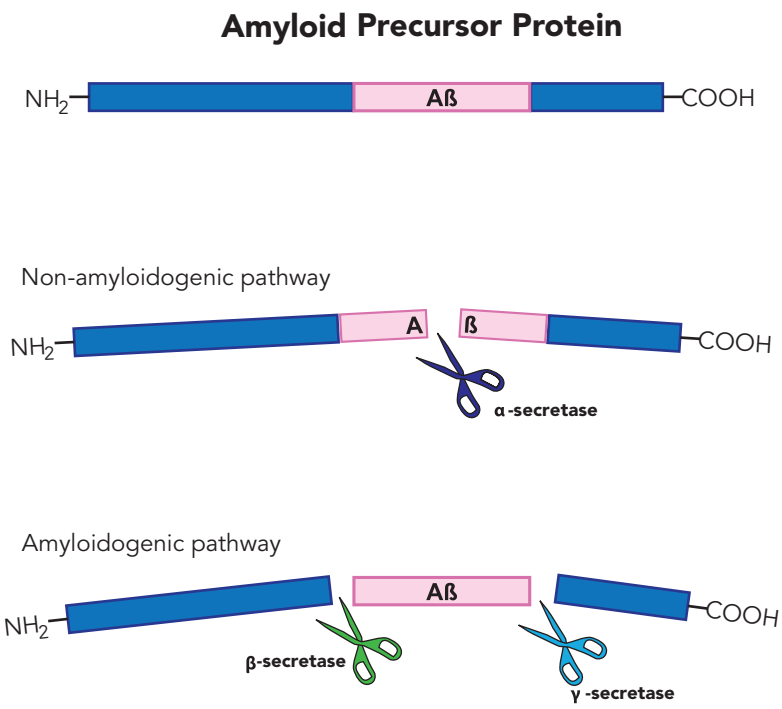


Figure 12-16 **Amyloid precursor protein.** The Aβ peptide is cut from a larger protein called the amyloid precursor protein (APP). There are two cleavage pathways by which APP may be processed: the non-amyloidogenic and the amyloidogenic pathways. In the non-amyloidogenic pathway, APP is cleaved by an enzyme termed α-secretase directly in the portion of APP where Aβ sits; processing of APP by α-secretase thereby precludes production of Aβ. In the amyloidogenic pathway, APP is first cleaved by β-secretase at the amino (NH_2) border of Aβ and then by γ-secretase.

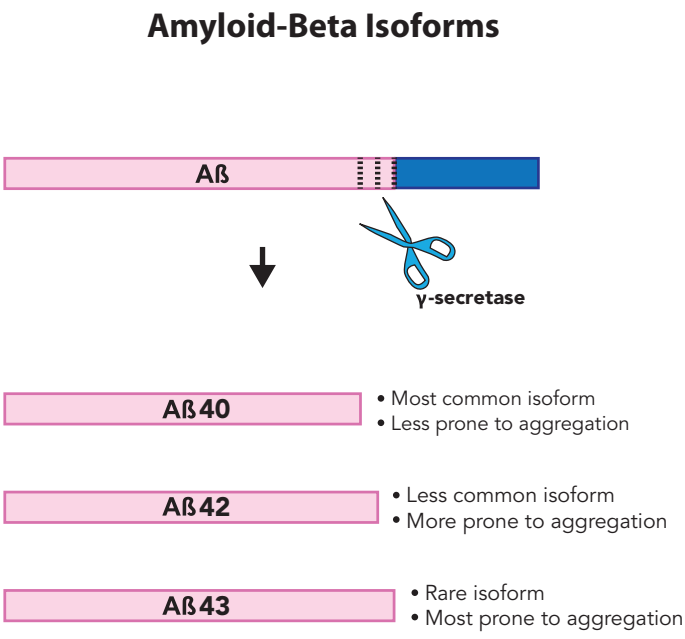


Figure 12-17 **Aβ isoforms.** Gamma-secretase cuts APP into several Aβ peptides, ranging from 38 to 43 amino acids long. The Aβ40 isoform is the most common form; however, the Aβ42 isoform is more prone to aggregation into oligomers. The Aβ43 isoform is relatively rare but is thought to be even more prone to aggregation than the Aβ42 isoform.

the risk of developing AD; inheritance of two copies of *APOE4* leads to a tenfold increased AD risk. Conversely, the *APOE2* gene appears to offer some protection from AD whereas the *APOE3* gene (the most common form of the *APOE* gene) conveys a risk that falls between *APOE2* and *APOE4*. Approximately 15% of individuals in the general population carry the *APOE4* allele (Figure 12-18). However, amongst individuals with AD, 44% carry the *APOE4* allele.

Current Status of the Amyloid Cascade Hypothesis and Treatments Targeting Aß

The amyloid cascade hypothesis has dominated thinking about the pathogenesis of AD for over 30 years, and has led to a several-decades-long pursuit of treatments targeting Aβ in the hope that this would prevent, halt, or even reverse AD. Although numerous drugs have been developed that successfully engage Aβ-related targets, none has (yet) been shown to have therapeutic benefit in AD (Table 12-6). Given the many failures of treatments that target Aβ in AD, not all experts are convinced any more that the amyloid cascade hypothesis is correct. An alternate theory is that Aβ formation is an epiphenomenon in AD that occurs simultaneously alongside neurodegeneration and thus is only a "tombstone" serving as a marker of neuronal death, but is not the cause of neurodegeneration. Just as eliminating all tombstones will not halt people from dying, eliminating Aβ will not necessarily prevent neurons from degenerating in AD.

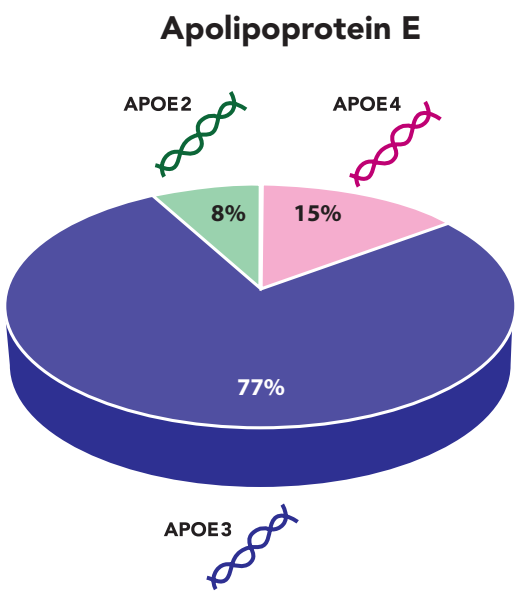


Figure 12-18 Apolipoprotein E. Of the genetic factors that contribute to the risk of developing Alzheimer disease (AD), the gene for apolipoprotein E (ApoE) appears to have the greatest influence. ApoE is a protein that transports the cholesterol needed by neurons for synapse development, dendrite formation, long-term potentiation, and axonal guidance. ApoE is also hypothesized to affect Aβ metabolism, aggregation, and deposition in the brain. Inheritance of even one copy of the *APOE4* allele results in a threefold increase in the risk of developing AD; inheritance of two copies of *APOE4* leads to a tenfold increased risk of developing AD. Approximately 15% of individuals in the general population carry the *APOE4* allele; however, among individuals with AD, 44% carry the *APOE4* allele. Conversely, the *APOE2* allele appears to offer some protection from AD, whereas the *APOE3* allele (the most common form of the *APOE* gene) conveys a risk that falls between *APOE2* and *APOE4*.

On the other hand, remaining proponents of the amyloid cascade hypothesis claim that previous anti-Aβ clinical trials have failed not because the hypothesis is wrong, but because the subjects enrolled in such trials have progressed too far in terms of irreversible damage to the brain (Figure 12-15). The many negative trials of Aβ-targeting therapies have all enrolled patients with clinically diagnosable AD or MCI and supporters of the amyloid cascade hypothesis theorize that once the amyloid cascade is set into motion, the detrimental effects (including oxidative stress, inflammation, the formation of neurofibrillary tangles, and synaptic dysfunction) may become a self-perpetuating cycle of destruction whereby further Aβ accumulation becomes irrelevant (Figure 12-15). Accordingly, these proponents believe that anti-Aβ therapies must be initiated at the earliest sign of Aβ accumulation possible – before the amyloid cascade is irreversibly set into motion and consequently before clinical signs of AD or even MCI are evident. Thus, for successful future treatment, there is the need to be able to diagnose AD in the asymptomatic stage. To that end, a great deal of research has focused on diagnosing AD not only long before death but also long before neurodegeneration sets in. Thus, AD is now conceptualized as occurring in three stages: presymptomatic, MCI, and dementia stages (Figure 12-19).

DIAGNOSING ALZHEIMER DISEASE BEFORE IT IS TOO LATE

Presymptomatic Stage 1

The presymptomatic stage 1 of AD (Figure 12-19) is also called asymptomatic amyloidosis. The neurodegenerative process in AD appears to start silently as Aβ accumulates in the brain. Aβ is detectable at the presymptomatic stage of AD using PET scans and radioactive neuroimaging tracers that label Aβ plaques (Figure 12-20). It is rarely detected in the brains of individuals under the age of 50 and although most cognitively normal healthy elderly people show no

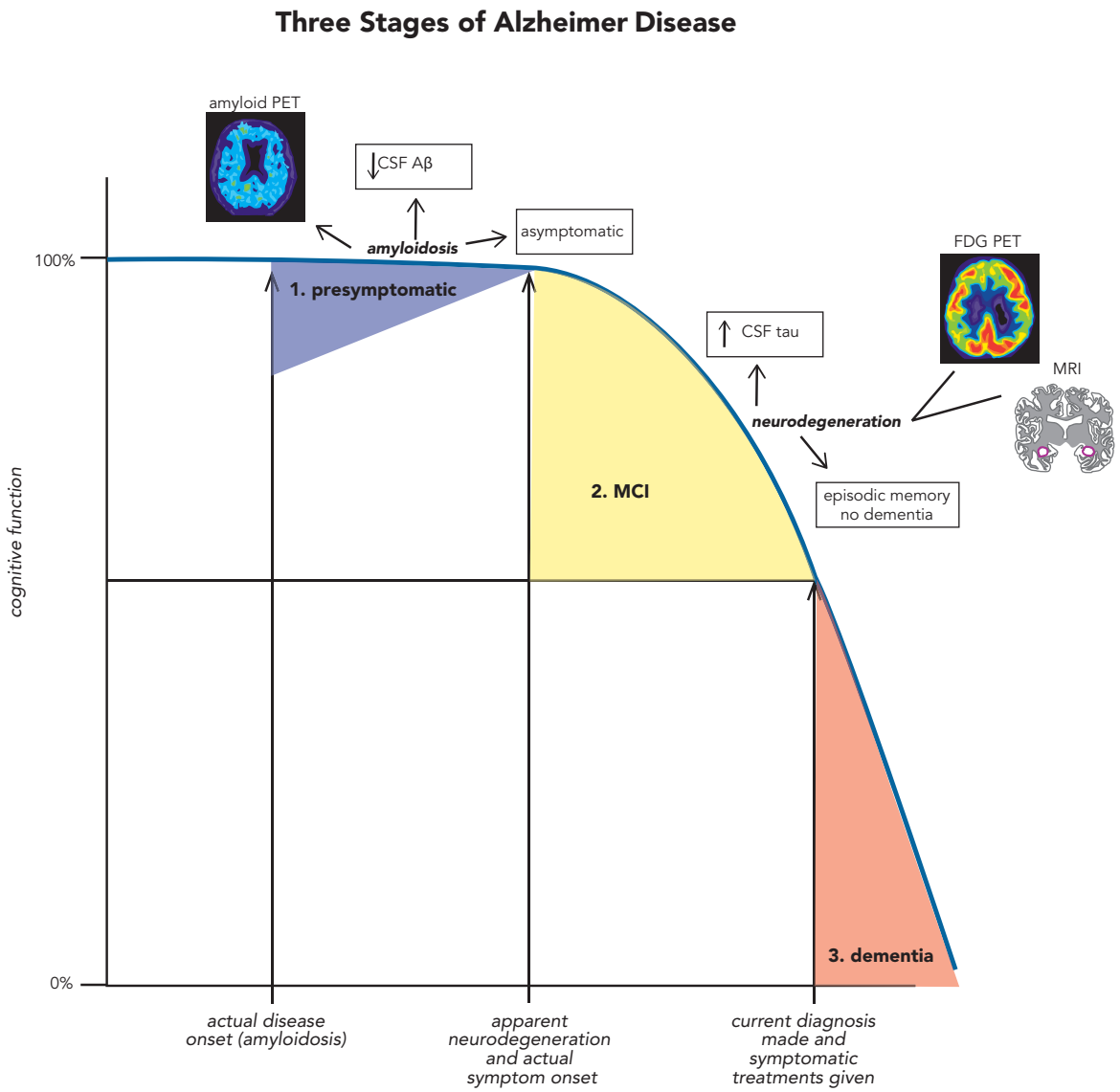


Figure 12-19 The three stages of Alzheimer disease. Stage 1 of Alzheimer disease (AD) is called presymptomatic or asymptomatic amyloidosis. During stage 1, cognition is intact despite elevated levels of Aβ in the brain as evidenced by both positive Aβ positron emission tomography (PET) and reduced levels of Aβ toxic peptides in cerebrospinal fluid (CSF). In the second stage, clinical signs of cognitive impairment in the form of episodic memory deficits begin to manifest. The onset of clinical symptoms in stage 2 appears to be correlated with neurodegeneration, as evidenced by elevated CSF tau, brain glucose hypometabolism on fluorodeoxyglucose positron emission tomography (FDG PET) scans, and volume loss in key brain regions on magnetic resonance imaging (MRI) scans. During stage 3 of AD (dementia), cognitive deficits can be severe. Currently, treatment of AD symptoms does not typically begin until stage 3, long after the actual disease onset.

evidence of Aβ deposition (Figure 12-20A), about a quarter of cognitively normal elderly controls are Aβ positive (Figure 12-20B and Figure 12-21), and are thus considered to have presymptomatic AD. Seeing Aβ on a PET scan may mean that the fuse is already lit for the development of AD even if there are no symptoms yet. Cerebrospinal fluid (CSF) levels of Aβ are also *low* at this stage of the illness because Aβ is being deposited in the brain instead of leaving the brain (Figure 12-19).

MCI Stage 2

The second stage of AD is called "predementia AD," or "MCI due to AD," or even "prodromal AD." These patients

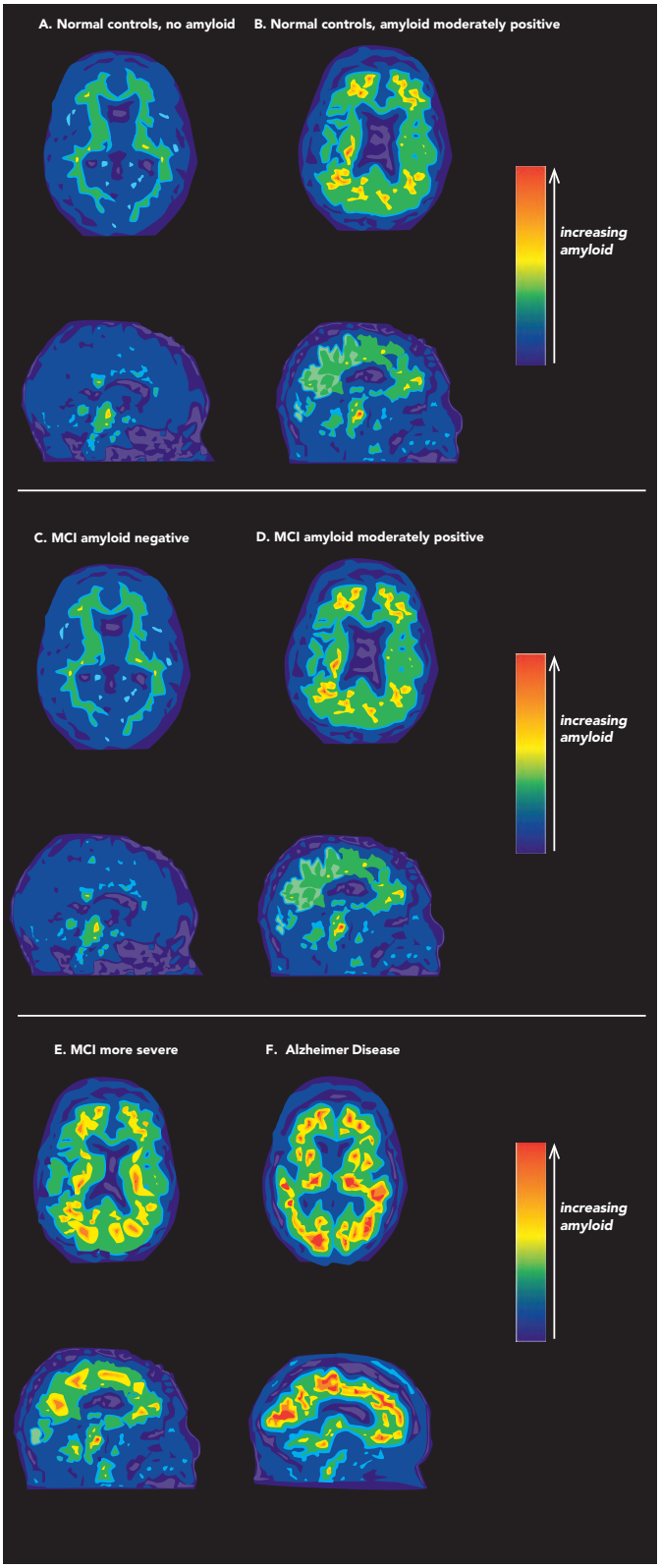


Figure 12-20 **Aβ PET imaging.** Positron emission tomography (PET) using Aβ tracers can be used to detect the presence of Aβ during the progression of Alzheimer disease (AD). (A) In most cognitively normal controls, Aβ PET imaging shows the absence of Aβ. (B) Individuals who are cognitively normal but have moderate accumulation of Aβ are likely in the presymptomatic first stage of AD. (C) Although mild cognitive impairment (MCI) is often present in the prodromal second stage of AD, not all patients with MCI have brain Aβ deposition. In such cases, the clinical presence of cognitive impairments is likely attributable to a cause other than AD. (D) Unfortunately, MCI is often a harbinger of impending AD. In these cases, Aβ deposition accompanies cognitive impairments. (E) Both Aβ accumulation and clinical symptoms of MCI worsen as AD progresses. (F) In the third and final stage of AD, when full-blown dementia is clinically evident, a large accumulation of brain Aβ can readily be seen.

have progressed from asymptomatic amyloidosis and stage 1 AD to stage 2 AD by manifesting both the clinical symptoms of MCI and the signs of neurodegeneration. Neurodegeneration is demonstrated by the presence of elevated tau protein levels in CSF, by atrophy on MRI or by the presence of neurofilament light (NfL) in CSF or possibly plasma. Tau is a microtubule-associated binding protein and, in its nonpathological form, binds to and stabilizes microtubules within axonal projections (Figure 12-22A). Synaptic vesicles carrying neurotransmitters are normally transported along these microtubules to the synapse (Figure 12-22A). When hyperphosphorylated, tau is no longer able to bind microtubules, so microtubules become destabilized and synaptic dysfunction results (Figure 12-22B). Hyperphosphorylated tau also forms paired helical filaments which aggregate into neurofibrillary tangles (NFTs), one of the hallmarks of AD (Figure 12-22C). As neurodegeneration and neuronal loss progresses, tau levels rise in CSF. Neuroimaging can also show neurodegeneration on MRI (Figure 12-5) or FDG PET (Figure 12-4). Hypometabolic FDG PET in MCI subjects predicts progression to dementia of up to 80–90% within 1–1.5 years.

Stage 2 AD now is symptomatic with MCI, but not all MCI patients have measurable amyloidosis (Figure 12-20C, D, and E). All MCI patients are presumed therefore not to be on a trajectory towards AD. In fact, about half of patients with MCI show no evidence of Aβ deposition (Figure 12-20C), and presumably have a cause of their mild cognitive symptoms other than AD, including depression or another dementia-causing disorder (Table 12-2). The other half of MCI patients do indeed show either moderate (Figure 12-20D) or severe Aβ deposition (Figure 12-20E) and almost 100% of patients with clinically probable AD (stage 3 AD with dementia) show heavy Aβ deposition (Figure 12-20F). About half of Aβ-positive MCI patients progress to dementia within a year, and 80% may progress to dementia within 3 years. However, it is really neurodegeneration and not amyloidosis that is thought to drive stage 1 AD to stage 2 with MCI symptoms, as well as to drive stage 2 AD to stage 3 dementia.

Dementia Stage 3

The final stage of AD is dementia (Figure 12-19). To diagnose probable AD by clinical criteria, the patient must first meet the diagnostic criteria for all-cause dementia (see Table 12-1). In addition, the patient must have a dementia which is insidious in onset with clearly demonstrated worsening of cognition over time, and either an amnestic (problems with learning and recall) or a non-amnestic presentation (language, visuospatial, or executive dysfunction). Probable AD with evidence of the Alzheimer pathophysiological process includes clearly positive biomarker evidence either of brain Aβ deposition/amyloidosis (Figure 12-20), or of downstream neuronal degeneration (Figures 12-4 and 12-5).

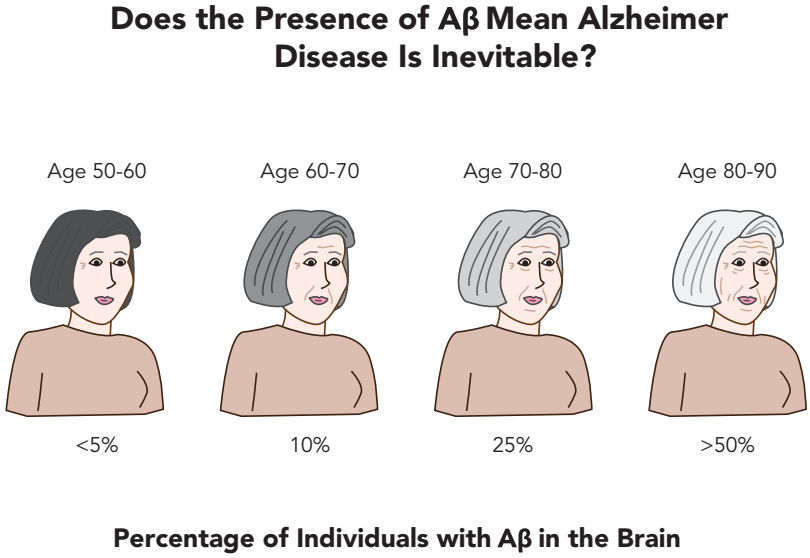


Figure 12-21 **Aβ and risk of Alzheimer disease.** Not all individuals with Aβ detectable in the brain have Alzheimer disease. Although the presence of Aβ has been associated with slightly poorer cognitive performance, approximately 25–35% of individuals with Aβ accumulation in the brain perform within normal limits on tests of cognition. Some hypothesize that such individuals may be in the preclinical or prodromal phases of dementia and will inevitably develop dementia should they live long enough.

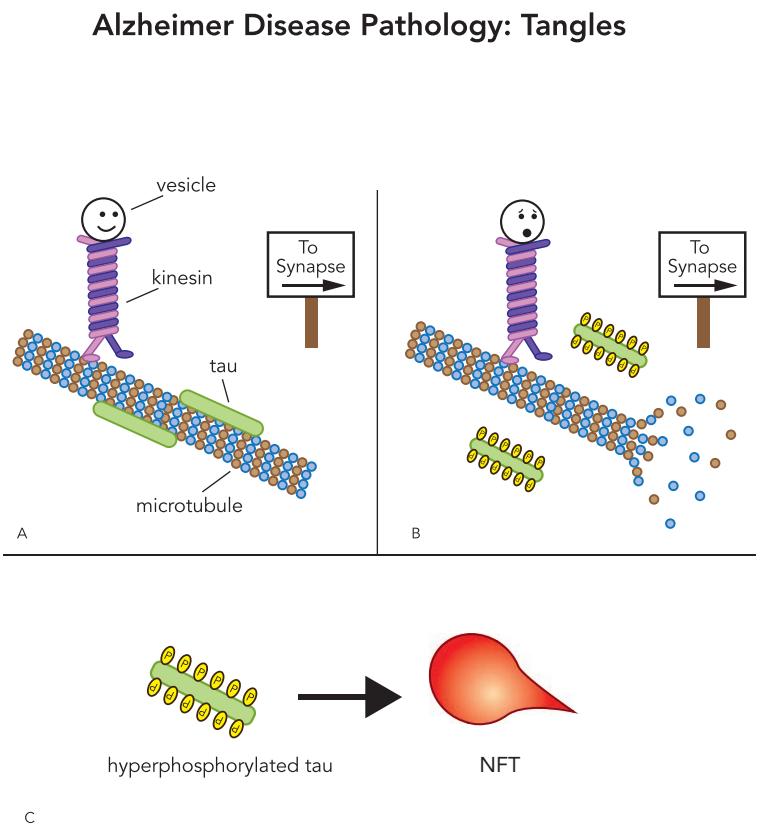


Figure 12-22 Alzheimer disease pathology: tangles. Tau is a microtubule-associated binding protein. (A) In its non-pathological form, it binds to and stabilizes microtubules within axonal projections. It is along these microtubules that synaptic vesicles carrying neurotransmitters are transported to the synapse. (B) When tau is hyperphosphorylated, it is no longer able to bind microtubules, which causes destabilization of microtubules and leads to synaptic dysfunction. (C) Hyperphosphorylated tau also forms paired helical filaments, which then aggregate into neurofibrillary tangles (NFTs).

OVERVIEW OF SYMPTOMATIC TREATMENTS FOR DEMENTIA

The first approved treatments for AD target the symptoms of cognitive and memory decline, but do not halt the relentless march of neurodegeneration. They are symptomatic treatments, but not disease-modifying treatments. As hopes fade for early development of treatments that can prevent, halt, or reverse AD, new drug development has pivoted back to treating the *symptoms* of dementia to improve the suffering of patients and to reduce the burden of their caregivers as the number of people who have dementia explodes. These treatments target neurotransmitters in different brain circuits that hypothetically regulate the different symptoms in dementia (Figure 12-23). This treatment approach is based upon the notion that different symptoms in dementia arise from different anatomical sites of neurodegeneration no matter what the cause of that neurodegeneration (Figure 12-23). This is the same concept developed throughout this book that behavioral symptoms in psychiatric disorders are topographically localized to hypothetically malfunctioning brain circuits, whether in psychosis, depression, mania, anxiety, sleep, pain, ADHD, or dementia. Furthermore, this point of view incorporates the possibility that the same symptom can appear in many different disorders if the same circuit is malfunctioning. Thus, for example, psychotic symptoms can appear in dementia as well as schizophrenia, hypothetically because the same circuit malfunctions in both conditions. Specifically, psychotic symptoms seem to be related to pathology in the neocortex, and like all symptoms in dementia (e.g. visual versus auditory hallucinations, delusions, disturbances in memory and cognition, agitation; Figure 12-23) each is likely to reflect damage to unique cortical areas.

Treatment strategies for symptoms in dementia likewise arise from this notion that each symptom is hypothetically regulated by a unique network or circuit of neurons. Each network connects specific glutamate, GABA (γ-aminobutyric acid), serotonin, and dopamine neurons at nodes (synapses) between these

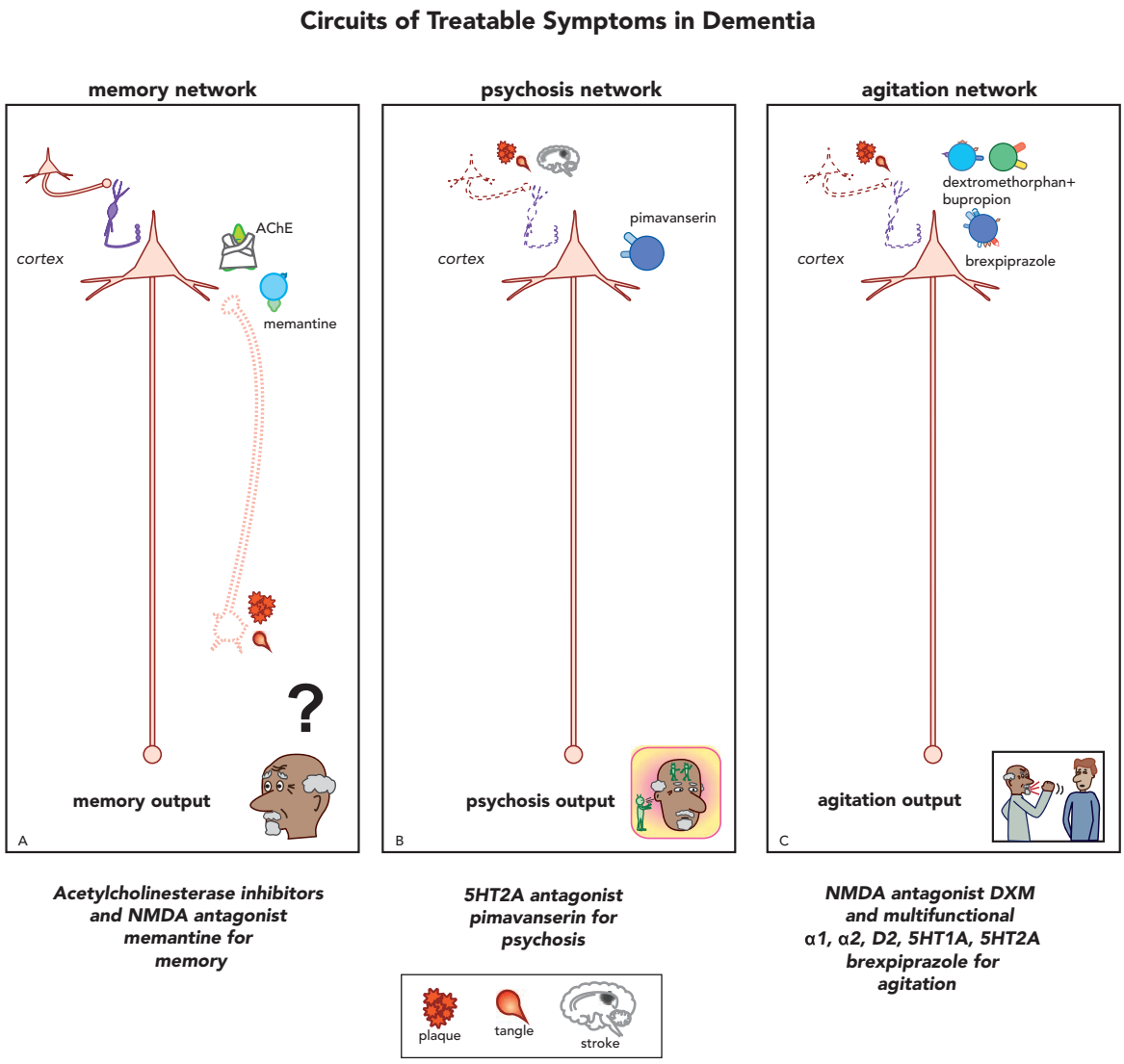


Figure 12-23 **Circuits of treatable symptoms in dementia.** Treatment of dementia is currently symptomatic rather than disease-modifying. There are three main treatable symptoms in dementia: memory problems, psychosis, and agitation. Treatment strategies for each of these symptoms arise from the notion that each symptom is hypothetically regulated by a unique network or circuit of neurons. Each network connects specific glutamate, GABA (γ-aminobutyric acid), serotonin, and dopamine neurons at nodes (synapses) between these different neurons that can influence not only the neuron being directly innervated but the entire network, via downstream effects set in motion at the node. (A) Acetylcholine and glutamate can be targeted by acetylcholinesterase (AChE) inhibitors and the NMDA (*N*-methyl-D-aspartate) antagonist memantine, respectively, to improve cognition in the memory network. (B) Psychosis can be targeted at the serotonin node as well as the dopamine node of the psychosis network. In particular, the $5HT_{2A}$ antagonist pimavanserin is approved to treat psychosis in Parkinson's disease. (C) Multimodal neurotransmitters (norepinephrine, serotonin, dopamine, and glutamate) can be targeted in the agitation network to improve the symptom of agitation in dementia. The NMDA antagonist dextromethorphan (DXM) in combination with bupropion and the multimodal agent brexpiprazole are both being studied for their use in agitation associated with dementia.

different neurons that can influence not only the neuron being directly innervated but the entire network, via downstream effects set in motion at the node. Nodes are the sites of potential therapeutic action by targeting them with drugs acting on the neurotransmitters normally working at that node. Thus, acetylcholine and glutamate can be targeted at different nodes to improve cognition in the memory network (Figure 12-23A). Similarly, we now know that psychosis can be therapeutically targeted at the serotonin node as well as the dopamine node of the psychosis network, since both are mutually

connected in the same neuronal network (see discussion in Chapter 4 and Figure 12-23B). Finally, multimodal neurotransmitters (norepinephrine, serotonin, dopamine, and glutamate) can be targeted in the agitation network to improve the symptom of agitation in dementia (Figure 12-23C). This strategy explains why treatment of the behavioral symptoms of dementia, particularly psychosis and agitation, have made notable progress recently, with several new drugs on the horizon.

TARGETING ACETYLCHOLINE FOR THE SYMPTOMATIC TREATMENT OF MEMORY AND COGNITION IN ALZHEIMER DISEASE

Degeneration of cholinergic neurons is thought to underlie in part some of the earliest symptoms of memory disturbance as MCI progresses to dementia in AD. Before discussing how targeting this hypothetical deficiency in acetylcholine neurotransmission underlies the symptomatic improvement in memory and cognition by various approved drugs for AD, it is important to understand acetylcholine neurotransmission, receptors, and brain circuits.

Acetylcholine: Synthesis, Metabolism, Receptors, and Pathways

Acetylcholine is formed in cholinergic neurons from two precursors: choline and acetyl coenzyme A (AcCoA) (Figure 12-24). Choline is derived from dietary and intraneuronal sources, and AcCoA is made from glucose in the mitochondria of the neuron. These two substrates interact with the synthetic enzyme choline acetyltransferase (ChAT) to produce the neurotransmitter acetylcholine (ACh). ACh's actions are terminated by one of two enzymes, either acetylcholinesterase (AChE) or butyrylcholinesterase (BuChE), sometimes also called "pseudocholinesterase" or "nonspecific cholinesterase" (Figure 12-25). Both enzymes convert ACh into choline, which is then transported back into the presynaptic cholinergic neuron for resynthesis into ACh (Figure 12-25). Although both AChE and BuChE can metabolize ACh, they are quite different in that they are encoded by separate genes and have different tissue distributions and substrate patterns. There may be different clinical effects of inhibiting these two enzymes as well. High levels of AChE are present in brain, especially in neurons that receive ACh input (Figure 12-25). BuChE is also present in brain, especially in glial cells (Figure 12-25). As will be discussed below, some cholinesterase inhibitors specifically inhibit AChE, whereas others inhibit both enzymes. It is AChE that is thought to be the key enzyme for inactivating ACh at cholinergic synapses (Figure 12-25), although BuChE can take on this activity if ACh diffuses to nearby glia. AChE is also present in the gut, skeletal muscle, red blood cells, lymphocytes, and platelets. BuChE is also present in the gut, plasma, skeletal muscle, placenta, and liver. BuChE may be present in some specific neurons, and it may also be present in Aβ plaques.

ACh released from central nervous system neurons is destroyed too quickly and too completely by AChE to be available for transport back into the presynaptic neuron; however, the choline that is formed by the breakdown of ACh is readily transported back into the presynaptic cholinergic nerve terminal by a transporter similar to the transporters for other neurotransmitters already discussed earlier in relationship to norepinephrine, dopamine, and serotonin neurons. Once back in the presynaptic nerve terminal, it can be recycled into new

Acetylcholine Is Produced

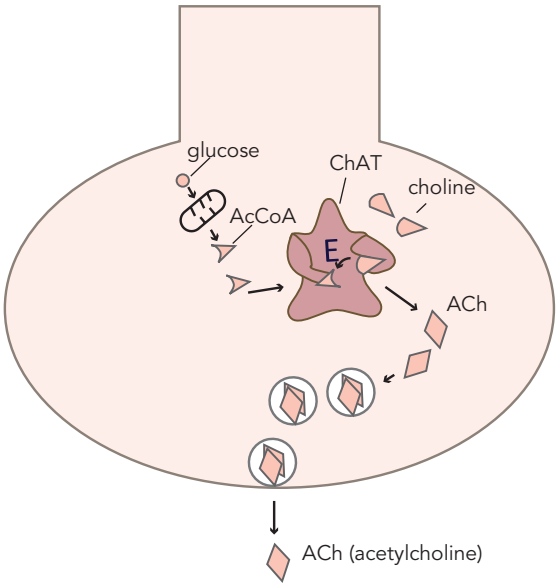


Figure 12-24 Acetylcholine is produced. Acetylcholine (ACh) is formed when two precursors – choline and acetyl coenzyme A (AcCoA) – interact with the enzyme choline acetyltransferase (ChAT). Choline is derived from dietary and intraneuronal sources and AcCoA is made from glucose in the mitochondria of the neuron.

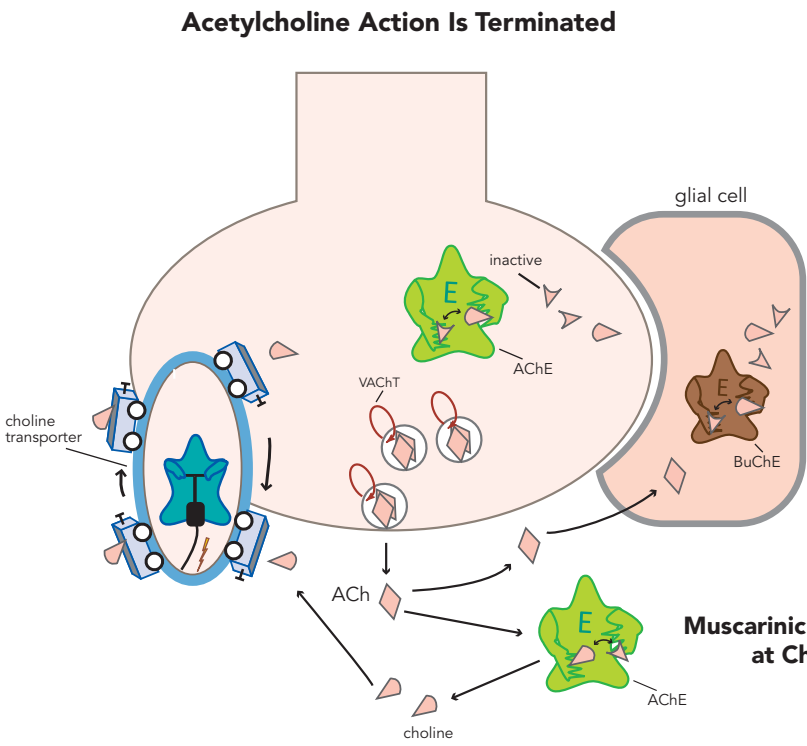


Figure 12-25 Acetylcholine's action is terminated. Acetylcholine's action can be terminated by two different enzymes: acetylcholinesterase (AChE), which is present both intra- and extracellularly, and butyrylcholinesterase (BuChE), which is particularly present in glial cells. Both enzymes convert acetylcholine into choline, which is then transported out of the synaptic cleft and back into the presynaptic neuron via the choline transporter. Once inside the presynaptic neuron, choline can be recycled into acetylcholine and then packaged into vesicles by the vesicular acetylcholine transporter (VAChT).

ACh synthesis (see Figure 12-25). Once synthesized in the presynaptic neuron, ACh is stored in synaptic vesicles after being transported into these vesicles by the vesicular transporter for ACh (VAChT), analogous to the vesicular transporters for the monoamines and other neurotransmitters.

There are numerous receptors for ACh (Figures 12-26 through 12-29). The major subtypes are nicotinic and muscarinic subtypes of cholinergic receptors. Classically, muscarinic receptors are stimulated by the mushroom alkaloid muscarine and nicotinic receptors by the tobacco alkaloid nicotine. Nicotinic receptors are all ligand-gated, rapid-onset, and excitatory ion channels blocked by curare. Muscarinic receptors, by contrast, are G-protein-linked, can be excitatory or inhibitory, and many are blocked by atropine, scopolamine, and other well-known so-called "anticholinergics" discussed throughout this text. Both nicotinic and muscarinic receptors have been further subdivided into numerous receptor subtypes.

Muscarinic receptors have five subtypes, M_1, M_2, M_3, M_4, and M_5 (Figure 12-26). M_1, M_3, and M_5 receptors are stimulatory to downstream second messengering, and are also postsynaptic at cholinergic synapses

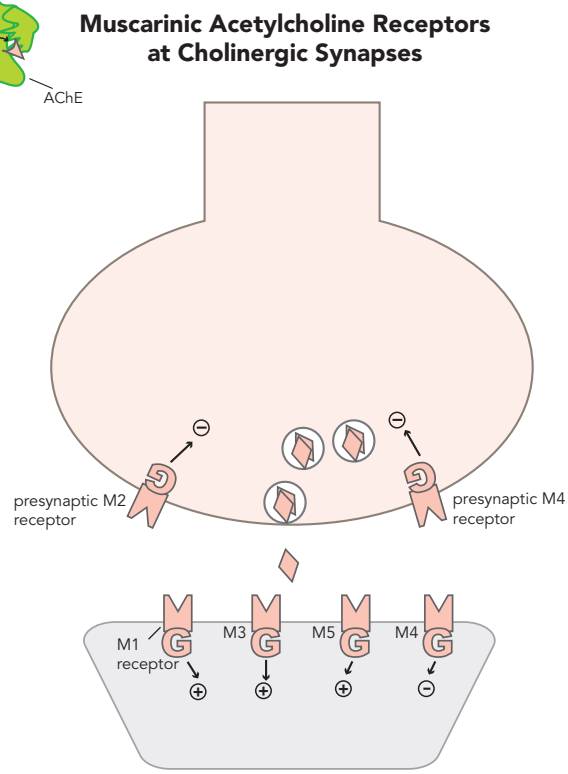


Figure 12-26 Muscarinic acetylcholine receptors. Muscarinic acetylcholine receptors are G-protein-linked and can be either excitatory or inhibitory. M_1, M_3, and M_5 receptors are excitatory postsynaptic receptors and stimulate downstream second messenging. M_2 and M_4 receptors are inhibitory presynaptic autoreceptors, preventing further release of acetylcholine. M_4 receptors are also thought to exist as inhibitory postsynaptic receptors.

(Figure 12-26). M_2 and M_4 receptors are inhibitory to downstream second messengering and are presynaptic, serving as autoreceptors, inhibiting the further release of acetylcholine once it builds up in the synapse (Figure 12-26). M_4 receptors are thought to be also postsynaptic in some brain areas (Figure 12-26).

The M_1 receptor is thought to be key to memory function in the hippocampus and neocortex, where it may facilitate dopamine release, whereas the M_4 receptor is thought to be involved in regulating the ventral tegmental dopamine neurons to inhibit dopamine release in the mesolimbic pathway and reduce psychosis. In Chapter 5, we briefly mentioned that preclinical and postmortem studies in patients with schizophrenia suggest that central cholinergic alterations may be key to the pathophysiology of both cognition and the positive symptoms of schizophrenia with M_4 receptor agonism reducing psychosis and with M_1 receptor agonism improving cognition. Xanomeline (see Chapter 5 and Figure 5-67), as an M_4/M_1 agonist, decreases dopamine cell firing in the ventral tegmental area in preclinical studies and improves positive symptoms of psychosis in early clinical studies of schizophrenia. This same drug or others working by similar mechanisms could theoretically reduce psychotic and cognitive symptoms in AD. Muscarinic M_2 and M_4 receptors can also be present on non-cholinergic neurons that release other neurotransmitters such as GABA and glutamate (Figure 12-27). When ACh diffuses away from its synapse to occupy these presynaptic heteroreceptors, it can block the release of the neurotransmitter there (e.g., GABA or glutamate) (see Figure 12-27).

A number of nicotinic receptor subtypes also exist in the brain, with different subtypes outside of the brain in skeletal muscle and ganglia. Two of the most important central nervouse system nicotinic cholinergic receptors are the subtype with all α_7 subunits, and the subtype with α_4 and β_2 subunits (Figure 12-28). The $\alpha_4\beta_2$ subtype is postsynaptic and plays an important role in regulating dopamine release in the nucleus accumbens. It is thought to be a primary target of nicotine in cigarettes, and to contribute to the reinforcing and addicting properties of tobacco. The $\alpha_4\beta_2$ subtypes of nicotinic cholinergic receptors are discussed in further detail in Chapter 13 on drug abuse.

Alpha-7 nicotinic cholinergic receptors can be either presynaptic or postsynaptic (Figures 12-28 and 12-29). When they are postsynaptic, they may be important

Presynaptic Muscarinic Heteroreceptors Inhibit GABA and Glutamate Release

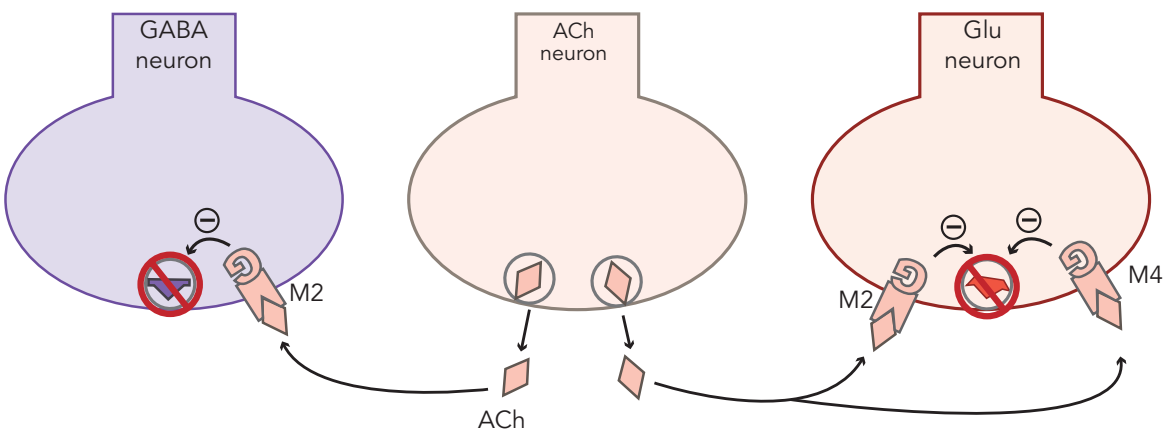


Figure 12-27 Presynaptic muscarinic heteroreceptors. M_2 and M_4 receptors can also be present presynaptically on non-cholinergic neurons such as GABA (γ-aminobutyric acid) and glutamate (Glu) neurons. When acetylcholine (ACh) diffuses away from the synapse and occupies these receptors, it can block the release of the neurotransmitter there.

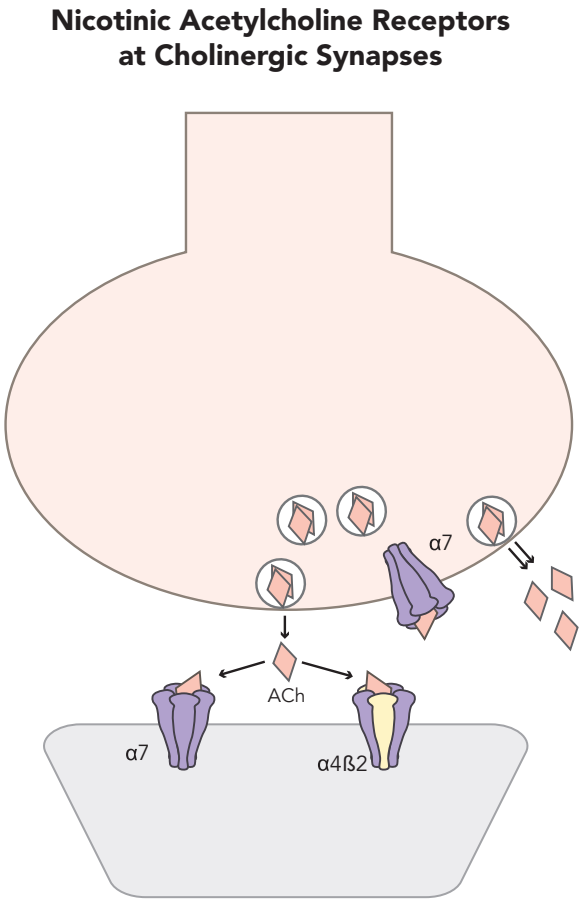


Figure 12-28 **Nicotinic acetylcholine receptors.** Acetylcholine neurotransmission can be regulated by ligand-gated excitatory ion channels known as nicotinic acetylcholine receptors, shown here. There are multiple subtypes of these receptors, defined by the subunits they contain. Two of the most important are those that contain all α_7 subunits and those that contain α_4 and β_2 subunits. Alpha-7 receptors can exist presynaptically, where they facilitate acetylcholine release, or postsynaptically, where they are important for regulating cognitive function in the prefrontal cortex. The $\alpha_4\beta_2$ receptors are postsynaptic and regulate release of dopamine in the nucleus accumbens.

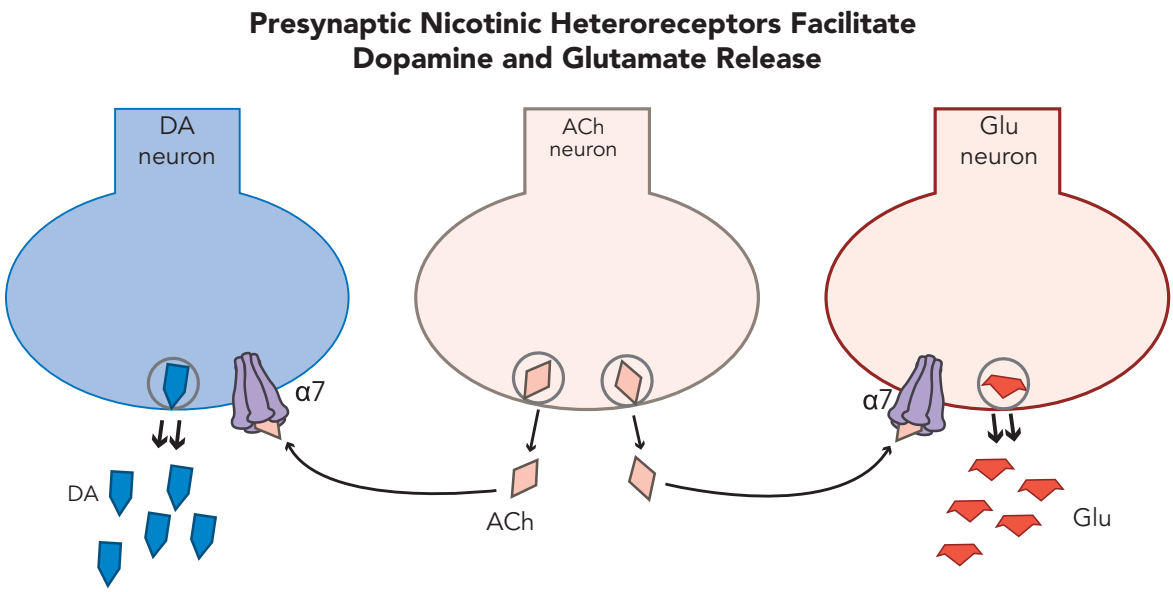


Figure 12-29 **Presynaptic nicotinic heteroreceptors.** Acetylcholine (ACh) that diffuses away from the synapse can bind to presynaptic α_7 nicotinic receptors on dopamine (DA) and glutamate (Glu) neurons, where it stimulates release of these neurotransmitters.

mediators of cognitive functioning in the prefrontal cortex. When they are presynaptic and on cholinergic neurons, they appear to mediate a "feed-forward" release process where ACh can facilitate its own release by occupying presynaptic α_7 nicotinic receptors (Figure 12-28). Furthermore, α_7 nicotinic receptors are present on neurons that release other neurotransmitters, such as dopamine and glutamate neurons (Figure 12-29). When ACh diffuses away from its synapse to occupy these presynaptic heteroreceptors, it facilitates the release of the neurotransmitter there (e.g., dopamine or glutamate) (see Figure 12-29).

Just as described in earlier chapters for other ligand-gated ion channels such as the $GABA_A$ receptor (in Chapter 6 on mood disorders; see Figures 6-20 and 6-21; see also Chapter 7 drugs for depression; Figure 7-56) and the NMDA (*N*-methyl-D-aspartate) receptor (see Chapter 4 on psychosis and Figure 4-30; and Chapter 10 on sleep and Figure 10-4), it appears that ligand-gated nicotinic cholinergic receptors are also regulated by allosteric modulators (Figure 12-30). Muscarinic receptors may also be modulated by positive allosteric modulators (not shown). Positive allosteric modulators (PAMs) have been well characterized for nicotinic receptors in brain; indeed, the cholinesterase inhibitor galantamine used in AD has a second therapeutic mechanism as a PAM for nicotinic receptors as described for this agent below.

The principle cholinergic pathways are illustrated in Figures 12-31 and 12-32. Cell bodies of some cholinergic pathways arise from the brainstem and project to many brain regions, including the prefrontal cortex, basal forebrain, thalamus, hypothalamus, amygdala, and hippocampus (Figure 12-31). Other cholinergic pathways have their cell bodies in the basal forebrain, project to the prefrontal cortex, amygdala, and hippocampus, and are thought to be particularly important for memory (Figure 12-32). Additional cholinergic fibers in the basal ganglia are not illustrated.

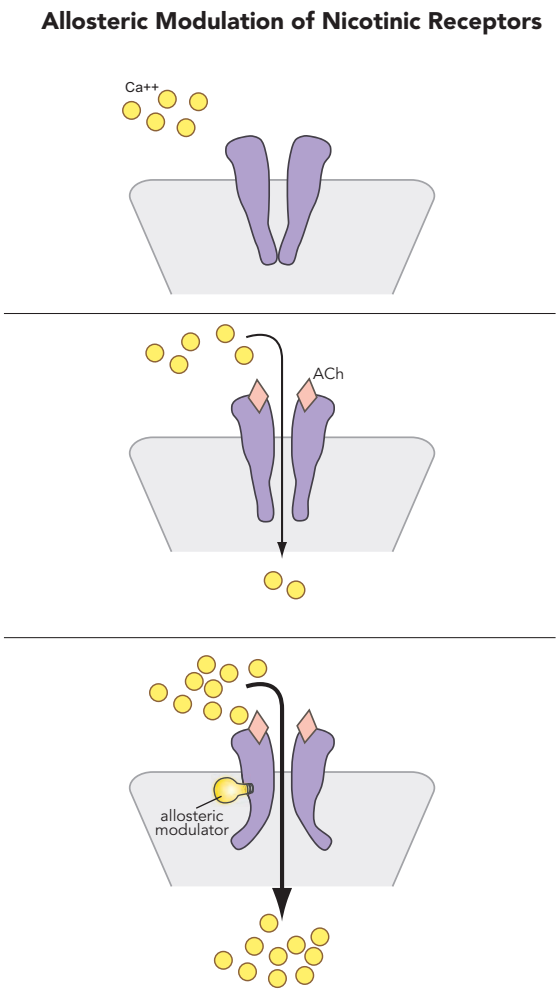


Figure 12-30 Allosteric modulation of nicotinic receptors. Nicotinic receptors can be regulated by allosteric modulators. These ligand-gated ion channels control the flow of calcium into the neuron (top panel). When acetylcholine is bound to these receptors, it allows calcium to pass into the neuron (middle panel). A positive allosteric modulator bound in the presence of acetylcholine increases the frequency of opening of the channel and thus can allow for more calcium to pass into the neuron (bottom panel).

Symptomatic Treatment of Memory and Cognition in Alzheimer Disease by Inhibiting Acetylcholinesterase

It is well established that cholinergic dysfunction accompanies age-related cognitive decline, hypothetically due to the early loss of cholinergic neurons from the nucleus basalis (compare Figure 12-33A normal cognition and 12-33B mild cognitive impairment). At this early stage of memory decline, cholinergic innervation is lost, but cholinergic postsynaptic targets remain (Figure 12-33B), so that stimulating postsynaptic cholinergic receptors by increasing ACh levels with acetylcholinesterase inhibition can hypothetically restore some of the lost function of degenerated cholinergic neurons (Figure 12-33C; effective cholinergic treatment of cognition in early AD). This model is analogous to Parkinson's disease treatment with levodopa restoring some of the lost function of degenerated dopamine neurons. However, as AD progresses from MCI and early dementia to later stages of dementia, there is progressive loss of neocortical and hippocampal neurons. In the

Cholinergic Projections from Brainstem

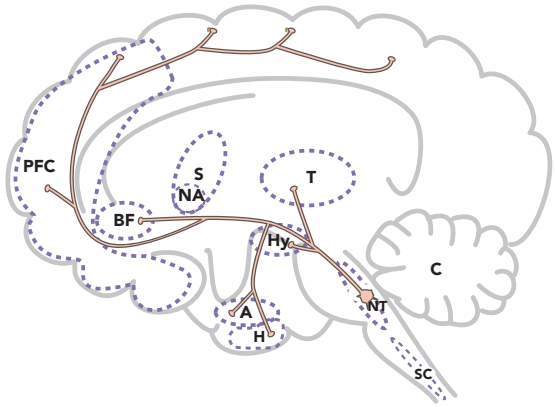


Figure 12-31 Cholinergic projections from the brainstem. The cell bodies of some cholinergic neurons are found in the brainstem and project to many different brain regions, including the basal forebrain (BF), prefrontal cortex (PFC), thalamus (T), hypothalamus (Hy), amygdala (A), and hippocampus (H).

Cholinergic Projections from Basal Forebrain

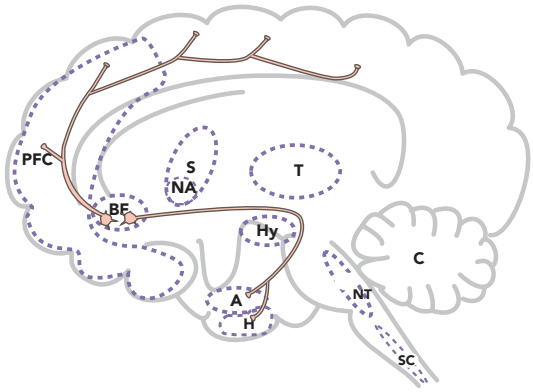


Figure 12-32 Cholinergic projections from the basal forebrain. The cell bodies of some cholinergic neurons are found in the basal forebrain (BF) and project to the prefrontal cortex (PFC), amygdala (A), and hippocampus (H). These projections may be particularly important for memory.

process, receptor targets of cholinergic therapies are also lost and symptomatic pro-cholinergic treatment with acetylcholinesterase inhibitors begins to lose its effectiveness (Figure 12-33D; progression of AD and loss of cholinergic treatment effectiveness).

Nevertheless, the most successful approach to the intermediate-term treatment of cognitive and memory symptoms in AD is to boost cholinergic functioning by stopping the destruction of ACh. This can be readily accomplished by inhibiting the enzyme acetylcholinesterase (Figure 12-23A and Figure 12-25). Inhibition of acetylcholinesterase causes the build-up of ACh because ACh's action can no longer be as efficiently terminated. Enhanced availability of ACh is proven to impact cognitive and memory symptoms in AD patients, sometimes enhancing memory, but more often helping to retain current levels of memory function and thus slowing the decline in memory.

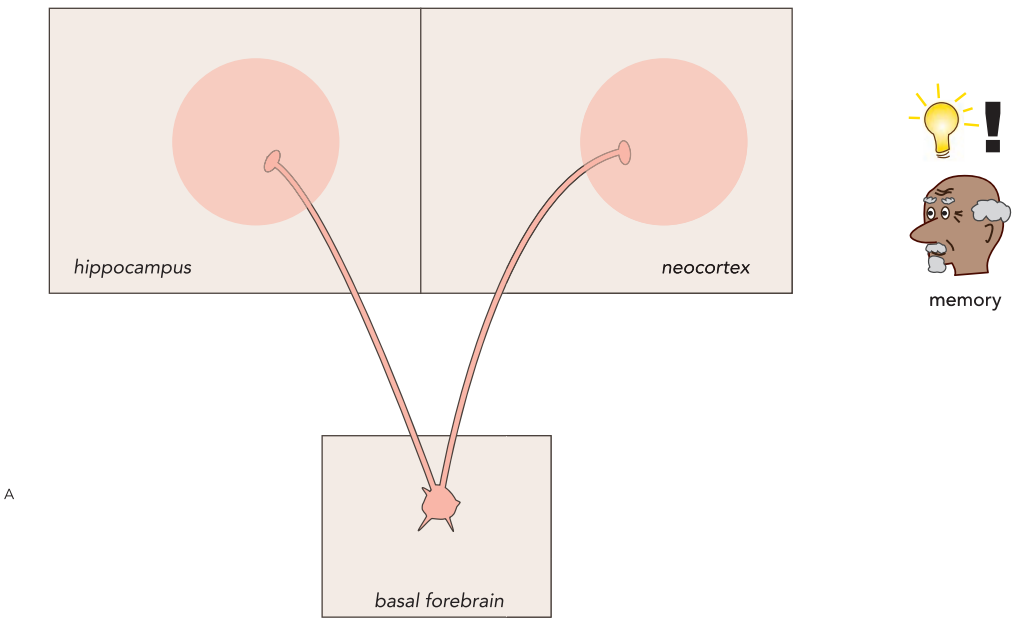
Donepezil

Donepezil is a reversible, long-acting, selective inhibitor of AChE without inhibition of BuChE (Figure 12-34). Donepezil inhibits AChE in pre- and postsynaptic cholinergic neurons, and in other areas of the central nervous system outside of cholinergic neurons where this enzyme is widespread (Figure 12-34A). Its central nervous system actions boost the availability of ACh at the remaining sites normally innervated by cholinergic neurons, but which are now suffering from a deficiency of ACh as presynaptic cholinergic neurons die off (Figures 12-33B and 12-33C). Donepezil also inhibits AChE in the periphery, where its actions in the gastrointestinal (GI) tract can produce GI side effects (Figure 12-34B). Donepezil is easy to dose, has mostly GI side effects, and these are mostly transient.

Rivastigmine

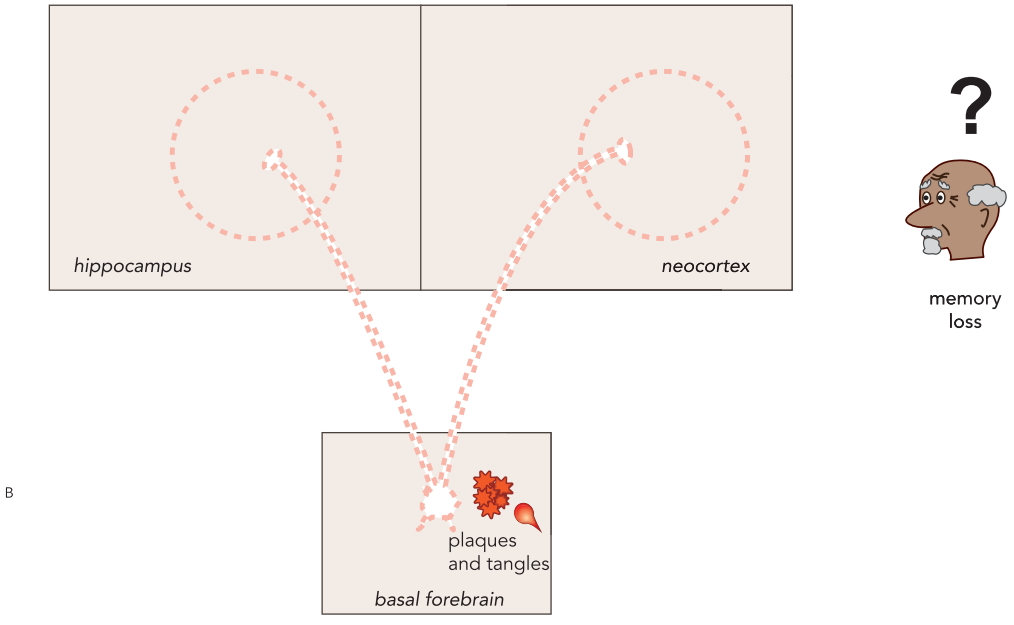
Rivastigmine is "pseudoirreversible" (which means it reverses itself over hours), intermediate-acting, not only selective for AChE over BuChE, but perhaps for AChE in the cortex and hippocampus over AChE in other areas of brain (Figure 12-35A). Rivastigmine also inhibits BuChE within glia, which may contribute somewhat to the enhancement of ACh levels within the central nervous system (Figure 12-35A). Inhibition of BuChE within glia may be even more important in patients with AD as they develop gliosis when cortical neurons die, because these glia contain BuChE, and inhibition of this increased enzyme activity may have a favorable action on increasing the availability of ACh to remaining cholinergic receptors via this second mechanism (Figure 12-35B). Rivastigmine appears to have comparable safety and efficacy to donepezil, although it may have more GI side effects when given orally, perhaps due to its pharmacokinetic profile, and perhaps due to inhibition of both AChE and BuChE in the periphery (Figure 12-35C). However, there is now a transdermal formulation of rivastigmine available that greatly reduces the peripheral

The Memory Network and Cholinergic Projections



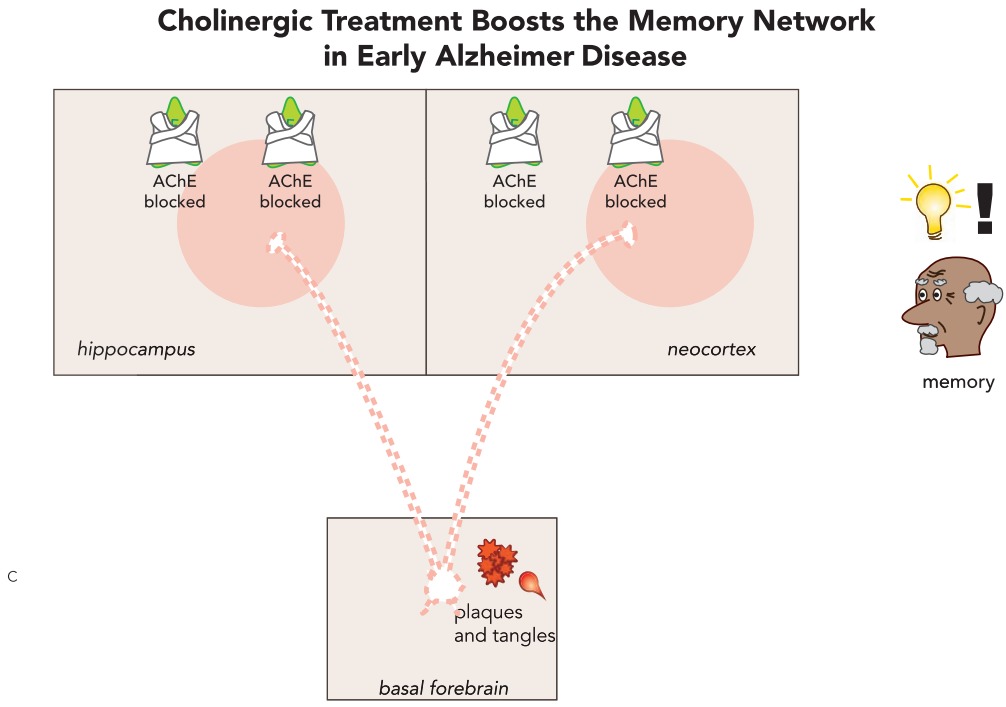
A

Loss of Cholinergic Projections and Preservation of Cholinergic Targets in the Memory Network in Mild Cognitive Impairment and Early Alzheimer Disease



B

Figure 12-33A, B Degeneration of cholinergic projections from the basal forebrain: impact on memory. (A) Cholinergic projections from the basal forebrain to the neocortex and to the hippocampus are thought to be particularly important for memory. (B) Accumulation of plaques and tangles in the brain can lead to neurodegeneration that may particularly affect these cholinergic projections and thus lead to memory loss. In early stages, although cholinergic innervation is lost, cholinergic postsynaptic targets remain.



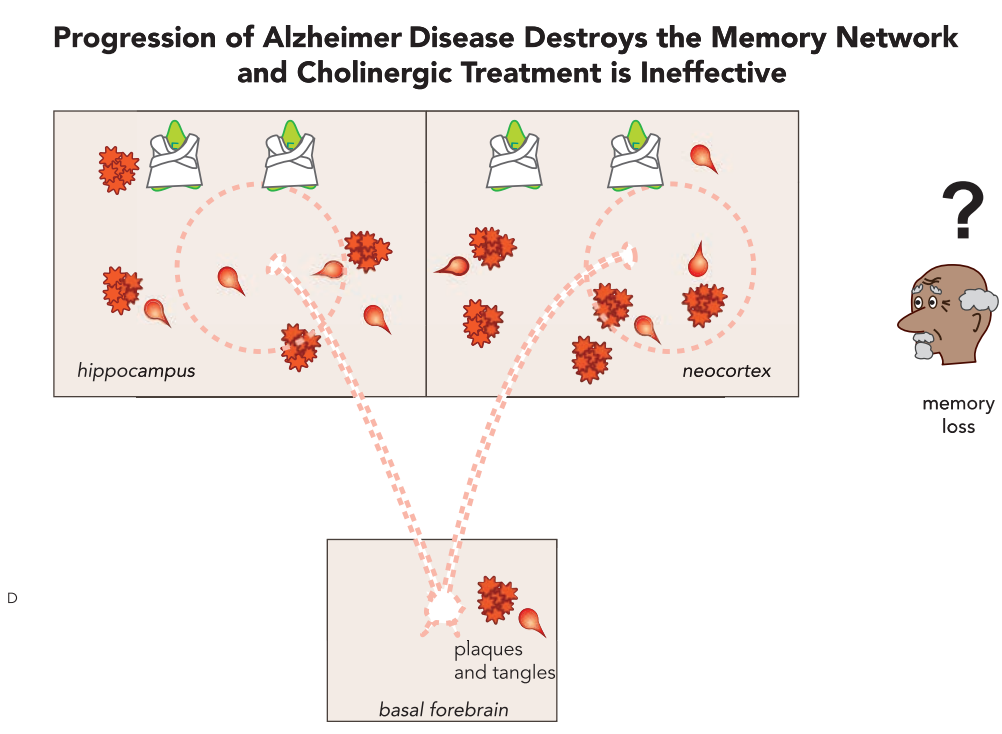
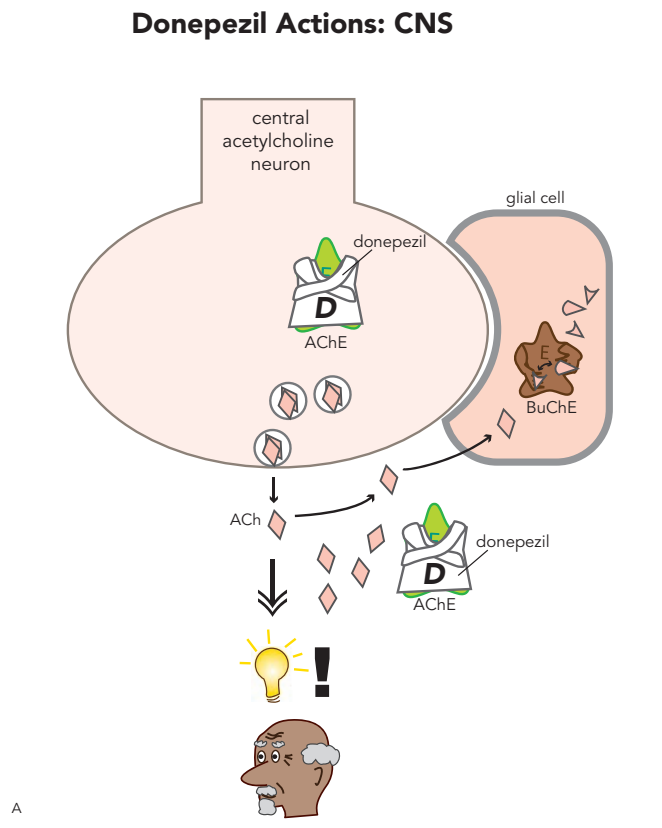


Figure 12-33C, D **Degeneration of cholinergic projections from the basal forebrain: impact of cholinergic treatment.** (C) In early stages of Alzheimer disease, although cholinergic innervation from the basal forebrain is lost, cholinergic postsynaptic targets remain. It is therefore possible to potentially improve memory by increasing acetylcholine levels in the hippocampus and neocortex. This can be achieved with agents that block the metabolism of acetylcholine, such as acetylcholinesterase (AChE) inhibitors. (D) As Alzheimer disease progresses, loss of neurons in the neocortex and hippocampus means that the receptor targets for acetylcholine are also lost, and thus AChE inhibitors lose their effectiveness.



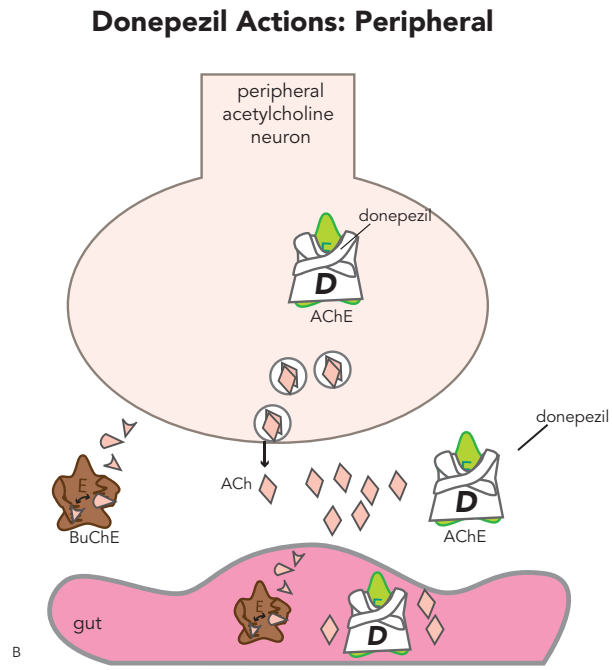


Figure 12-34 Donepezil actions. Donepezil is a reversible inhibitor of the enzyme acetylcholinesterase (AChE), which is present both in the central nervous system (CNS) and peripherally. (A) Central cholinergic neurons are important for regulation of memory; thus, in the CNS, the boost of acetylcholine (ACh) caused by AChE blockade contributes to improved cognitive functioning. (B) Peripheral cholinergic neurons in the gut are involved in gastrointestinal effects; thus the boost in peripheral acetylcholine caused by AChE blockade may contribute to gastrointestinal side effects.

side effects of oral rivastigmine, probably by optimizing drug delivery, and reducing peak drug concentrations.

Galantamine

Galantamine is a very interesting cholinesterase inhibitor found in snowdrops and daffodils! It has a dual mechanism of action, matching AChE inhibition (Figure 12-36A) with positive allosteric modulation of nicotinic cholinergic receptors (Figure 12-36B). Theoretically, the inhibition of AChE (Figure 12-36A) could be enhanced when joined by the second action of galantamine at nicotinic receptors (Figure 12-36B). Thus, raising ACh levels at nicotinic cholinergic receptors by AChE inhibition could be boosted by the positive allosteric modulating actions of galantamine (Figure 12-36B). However, it has not been proven that this theoretically advantageous second action as a nicotinic positive allosteric modulator (PAM) translates into clinical advantages.

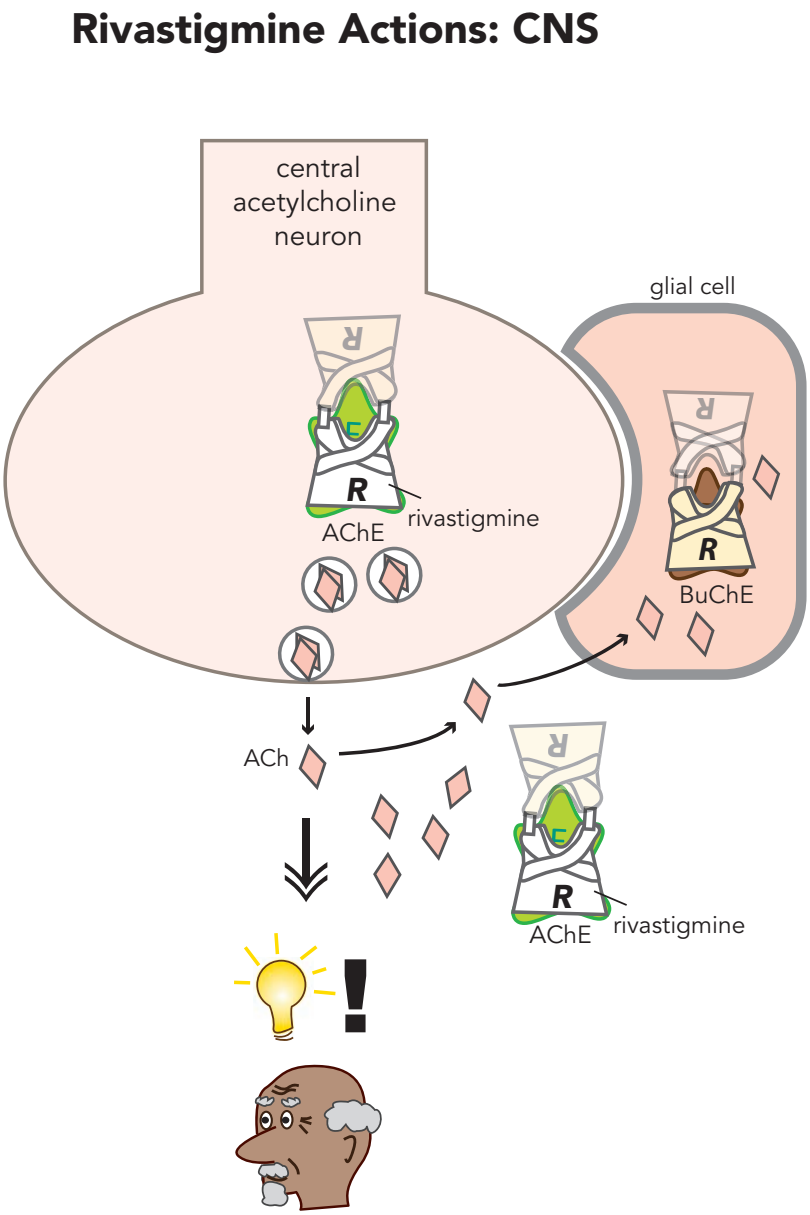


Figure 12-35A Rivastigmine actions, part one. Rivastigmine is a pseudoirreversible inhibitor (it reverses itself over hours) of the enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), which are present both in the central nervous system (CNS) and peripherally. Central cholinergic neurons are important for regulation of memory; thus, in the CNS, the boost of acetylcholine caused by AChE blockade contributes to improved cognitive functioning. In particular, rivastigmine appears to be somewhat selective for AChE in the cortex and hippocampus – two regions important for memory – over other areas of the brain. Rivastigmine's blockade of BuChE in glia may also contribute to enhanced acetylcholine levels.

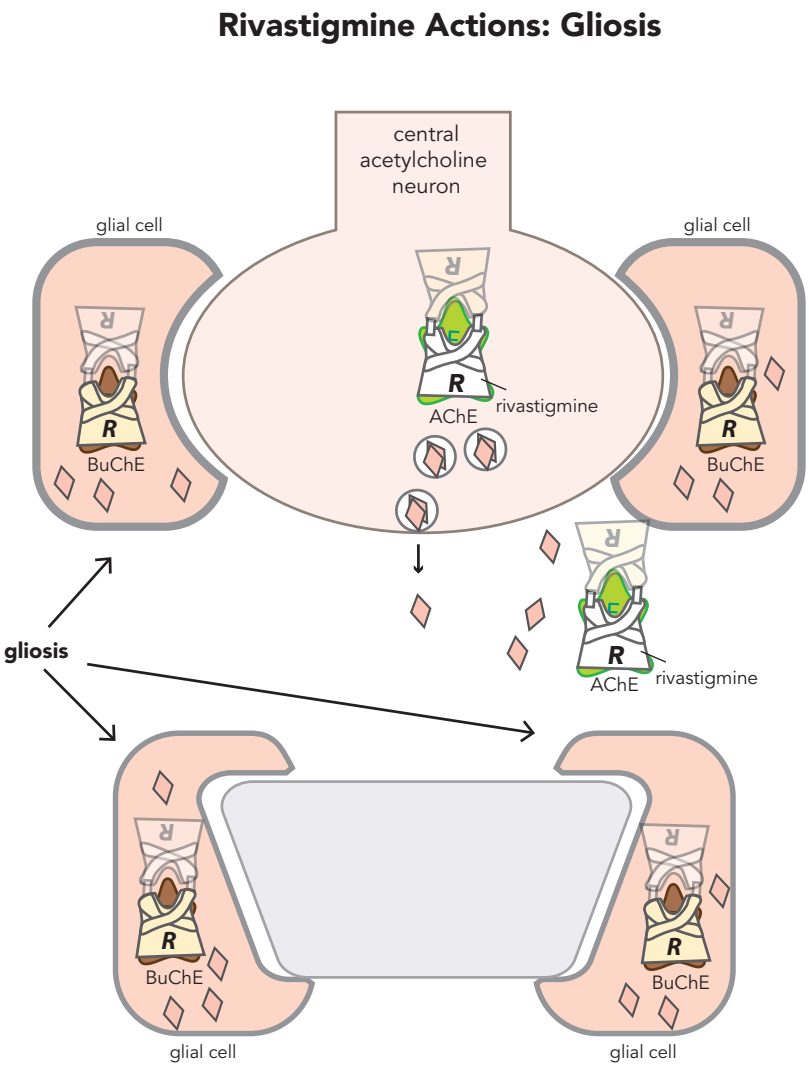


Figure 12-35B **Rivastigmine actions, part two.** Rivastigmine inhibits the enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), which are present both in the central nervous system (CNS) and peripherally. Inhibition of BuChE may be more important in later stages of disease, because as more cholinergic neurons die and gliosis occurs, BuChE activity increases.

TARGETING GLUTAMATE FOR THE SYMPTOMATIC TREATMENT OF MEMORY AND COGNITION IN ALZHEIMER DISEASE

Cholinergic dysfunction of course is not the only problem in AD, and there is progressive neurodegeneration of both cholinergic and glutamatergic circuits as patients transition from MCI to AD. Glutamate has been hypothesized to be released in excess once AD develops (see Figure 4-52D and discussion in Chapter 4; see also Figure 12-23A, left), perhaps in part triggered by neurotoxic Aβ plaques and neurofibrillary tangles that release glutamate from normal inhibition by GABA as GABA interneurons degenerate (see Chapter 4 and Figure 4-52D and also compare Figures 12-37A, 12-37B, and12-37C). That is, in the resting state, glutamate is normally quiet, and the NMDA receptor is physiologically blocked by magnesium ions (Figure 12-37A). When normal excitatory neurotransmission comes along, a flurry of glutamate is released (Figure 12-37B). The postsynaptic NMDA receptor is a "coincidence detector" and allows inflow of ions if three things happen at the same time: neuronal depolarization, often from activation

Rivastigmine Actions: Peripheral

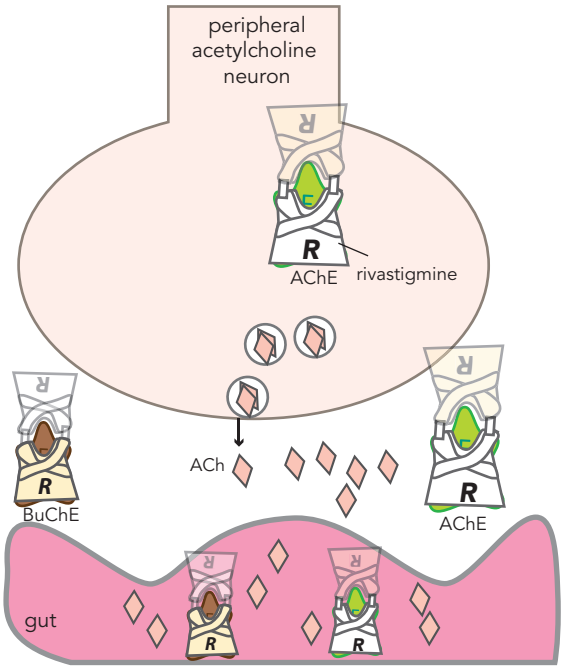


Figure 12-35C Rivastigmine actions, part three. Rivastigmine inhibits the enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), which are present both in the central nervous system (CNS) and peripherally. Peripheral cholinergic neurons in the gut are involved in gastrointestinal effects; thus the boost in peripheral acetylcholine caused by AChE and BuChE blockade may contribute to gastrointestinal side effects.

of nearby AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid) receptors; glutamate occupying its binding site on the NMDA receptor; and the cotransmitter glycine occupying its site on the NMDA receptor (Figure 12-37B). If plaques and tangles cause a steady "leak" of glutamate (see Chapter 4 and Figure 4-52D), this would theoretically interfere with the fine-tuning of glutamate neurotransmission, and possibly interfere with memory and learning, but not necessarily be damaging to neurons (Figure 12-37C). Hypothetically, as AD progresses, glutamate release could be increased to a level that is tonically bombarding the postsynaptic receptor, eventually killing off dendrites and then killing off full neurons due to excitotoxic cell death (Figure 12-23A and Figure 12-37C).

Memantine

The rationale for the use of memantine (Figure 12-38), a type of NMDA antagonist, is to reduce abnormal activation of glutamate neurotransmission and thus interfere with the pathophysiology of AD, improve cognitive function, and slow the rate of decline over time (Figure 12-23A and Figure 12-37D). Blocking NMDA receptors chronically would hypothetically interfere with memory formation and neuroplasticity. So what do you do to decrease the excessive and sustained but low level of excitotoxic activation of NMDA receptors, yet not interfere with learning, memory, and neuroplasticity, and without inducing a schizophrenia-like state?

The answer seems to be that you interfere with NMDA-mediated glutamatergic neurotransmission with a weak (low-affinity) NMDA antagonist that works at the same site, plugging the ion channel where the magnesium ion normally blocks this channel at rest (Figure 12-37D). That is, memantine is an uncompetitive open-channel NMDA receptor antagonist with low to moderate affinity, voltage dependence, and fast blocking and unblocking kinetics. That is a fancy way of saying that it only blocks the ion channel of the NMDA receptor when it is open. This is why it is called an open-channel antagonist and why it is dependent upon voltage: namely, to open the channel. It is also a fancy way of saying that memantine blocks the open channel quickly, but is readily and quickly reversible if a barrage of glutamate comes along from normal neurotransmission (Figure 12-37E).

This concept is illustrated in Figures 12-37C, 12-37D, and 12-37E. First, the hypothetical state of the glutamate neuron during Alzheimer excitotoxicity is illustrated in Figure 12-37C. Here, steady, tonic, and excessive amounts of glutamate are continuously released in a manner that interferes with the normal resting state of the glutamate neuron (Figure 12-37C), and in a manner that interferes with established memory functions, new learning, and normal neuronal plasticity in AD. Eventually, this leads to the activation of intracellular enzymes that produce toxic free radicals that damage the membranes of the postsynaptic dendrite and eventually destroy the entire neuron (Figure 12-37C). When memantine is given, it blocks this tonic glutamate release from having downstream effects, hypothetically returning the glutamate neuron to a new resting state, despite the continuous release of glutamate (Figure 12-37D). Theoretically, this stops the excessive glutamate from interfering with the resting glutamate neuron's physiological activity, therefore improving memory; it also theoretically stops the excessive glutamate from causing neurotoxicity, therefore slowing the rate of

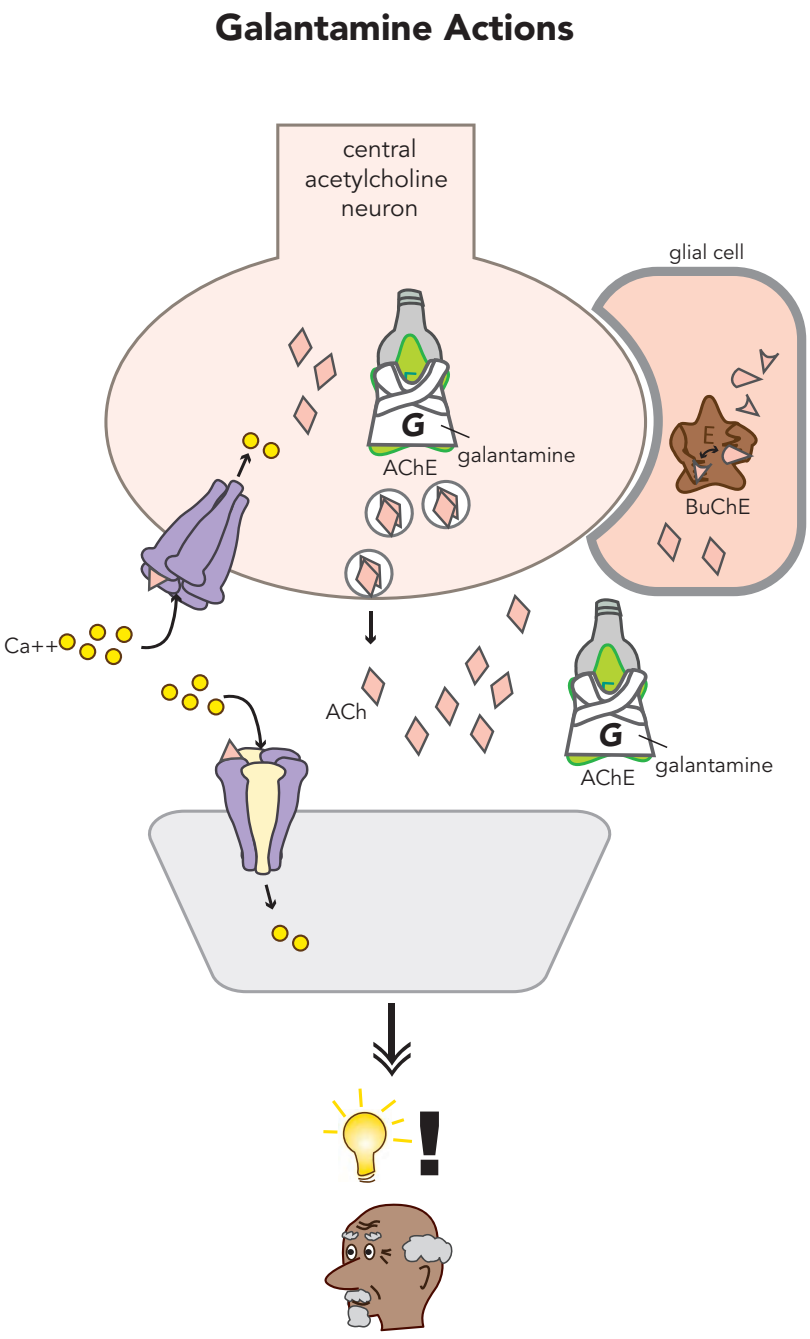


Figure 12-36A Galantamine actions, part one. Galantamine is an inhibitor of the enzyme acetylcholinesterase (AChE). Central cholinergic neurons are important for regulation of memory, and thus, in the central nervous system, the boost of acetylcholine caused by AChE blockade contributes to improved cognitive functioning.

neuronal death and also the associated cognitive decline that causes the progression in AD (Figure 12-37D).

However, at the same time, memantine is not so powerful a blocker of NMDA receptors that it stops all neurotransmission at glutamate synapses (Figure 12-37E). That is, when a phasic burst of glutamate is transiently released during normal glutamatergic neurotransmission, this causes a depolarization that is capable of reversing the memantine block, until the depolarization goes away (Figure 12-37E). For this

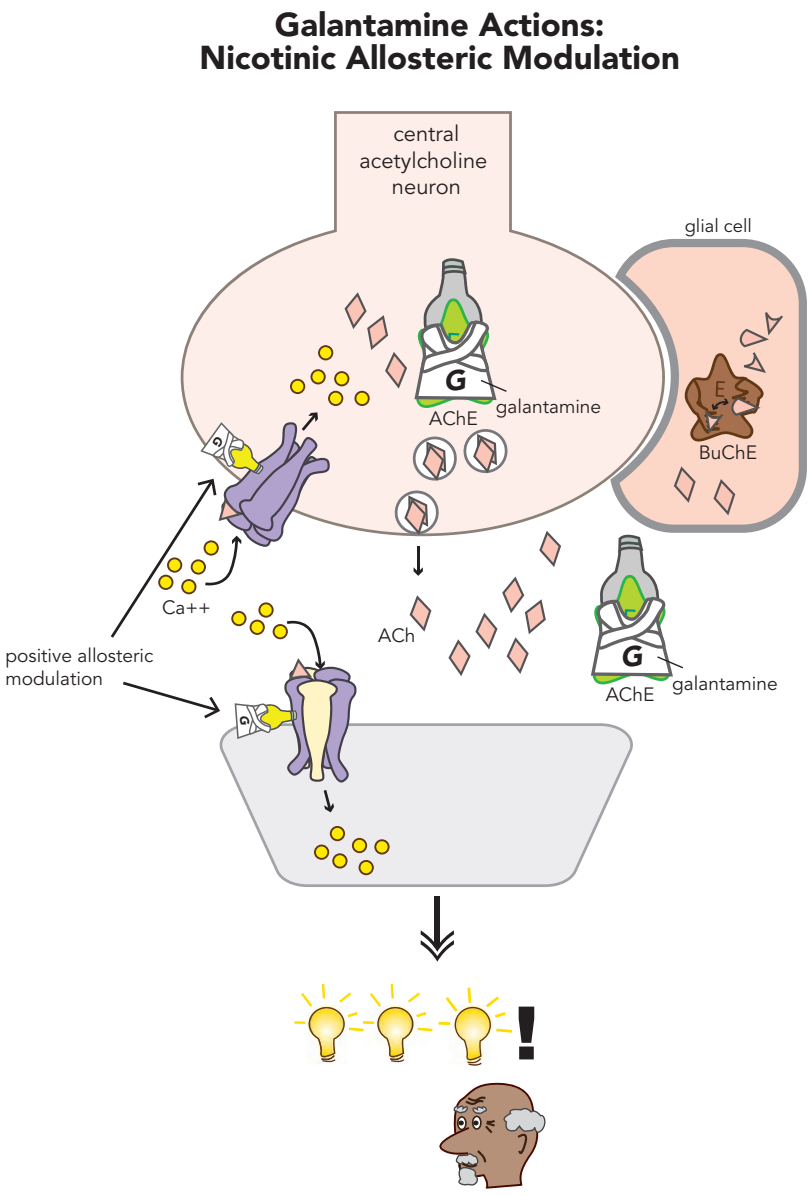


Figure 12-36B Galantamine actions, part two. Galantamine is unique among cholinesterase inhibitors in that it is also a positive allosteric modulator (PAM) at nicotinic cholinergic receptors, which means it can boost the effects of acetylcholine at these receptors. Galantamine's second action as a PAM at nicotinic receptors could theoretically enhance its primary action as a cholinesterase inhibitor.

reason, memantine does not have the psychotomimetic actions of other more powerful NMDA antagonists such as phencyclidine (PCP) and ketamine, and does not shut down new learning or the ability of normal neurotransmission to occur when necessary (Figure 12-37E). The blockade of NMDA receptors by memantine can be seen as a kind of "artificial magnesium," more effective than physiological blockade by magnesium, which is overwhelmed by excitotoxic glutamate release, but less effective than PCP or ketamine so that the glutamate system is not entirely shut down. Sort of like having your cake and eating it, too.

Memantine also has σ binding properties and weak $5HT_3$ antagonist properties (Figure 12-38), but it is not clear what these contribute to the actions of this agent in AD. Since its mechanism of action in AD is so different from cholinesterase inhibition, memantine is usually given concomitantly with a cholinesterase inhibitor to exploit the potential of both of these approaches and to get additive results in patients.

Glutamatergic Neurotransmission in AD: Part 1 - Resting State

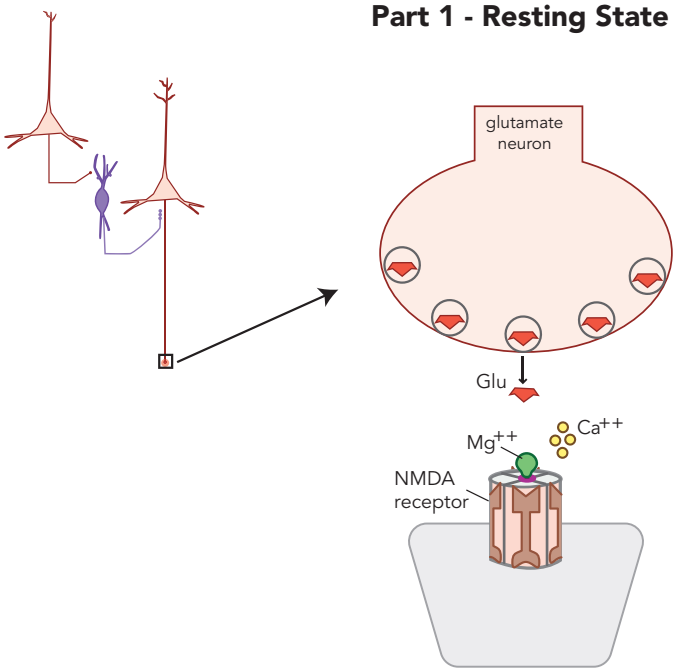


Figure 12-37A Glutamatergic neurotransmission in Alzheimer disease, part 1. In the resting state (absence of glutamate binding), the NMDA (*N*-methyl-D-aspartate) receptor is blocked by magnesium.

Glutamatergic Neurotransmission in AD: Part 2 - Normal Neurotransmission

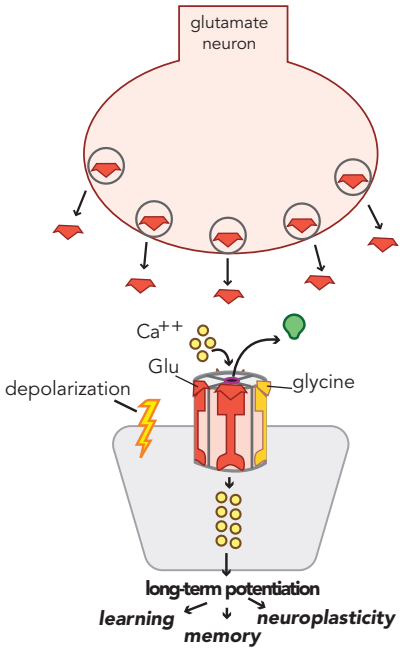


Figure 12-37B Glutamatergic neurotransmission in Alzheimer disease, part 2. With normal neurotransmission, glutamate is released and binds to the NMDA (*N*-methyl-D-aspartate) receptor. If the neuron is depolarized and glycine is simultaneously bound to the NMDA receptor, the channel opens and allows ion influx. This results in long-term potentiation.

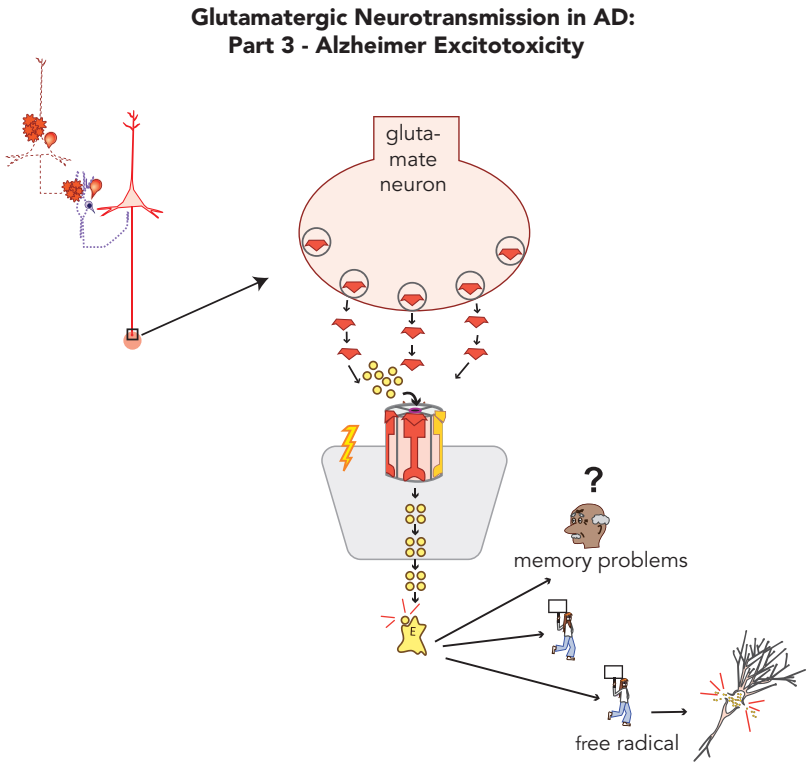


Figure 12-37C **Glutamatergic neurotransmission in Alzheimer disease, part 3.** Neurodegeneration caused by plaques and tangles could cause a steady leak of glutamate and result in excessive calcium influx in postsynaptic neurons, which in the short term may cause memory problems and in the long term may cause accumulation of free radicals and thus destruction of neurons.

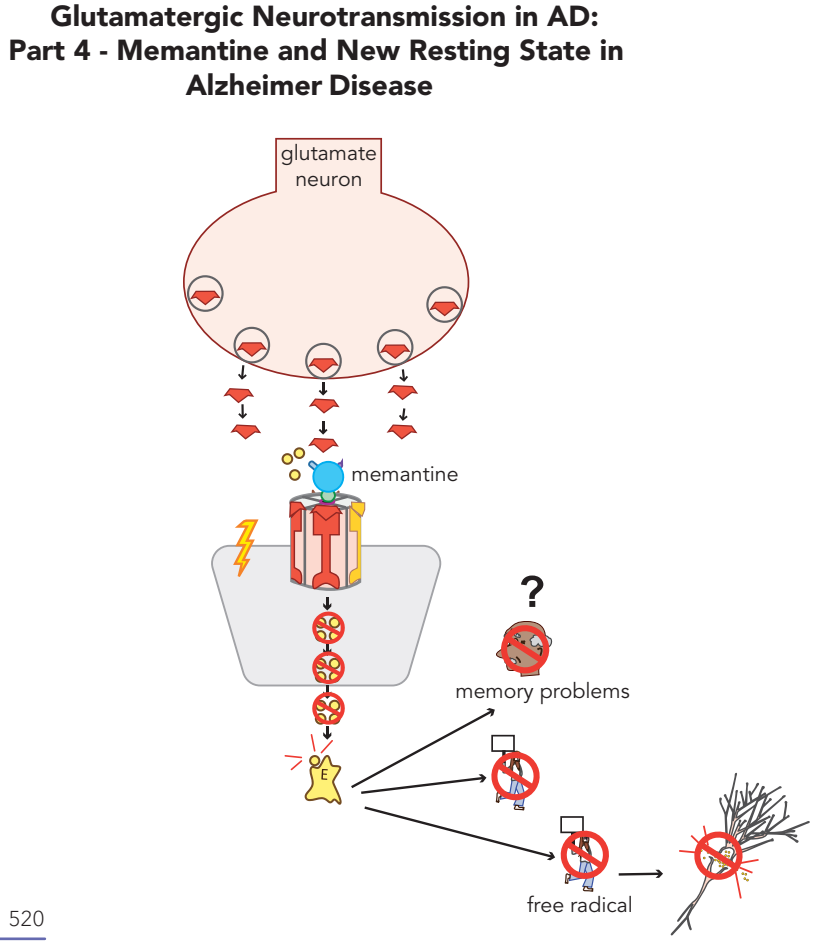


Figure 12-37D **Glutamatergic neurotransmission in Alzheimer disease, part 4.** Memantine is a noncompetitive, low-affinity NMDA (*N*-methyl-D-aspartate) receptor antagonist that binds to the magnesium site when the channel is open. Memantine thus blocks the downstream effects of excessive tonic glutamate release by "plugging" the NMDA ion channel, which may improve memory and prevent neuronal death due to glutamate excitotoxicity.

Glutamatergic Neurotransmission in AD: Part 5 - Normal Neurotransmission

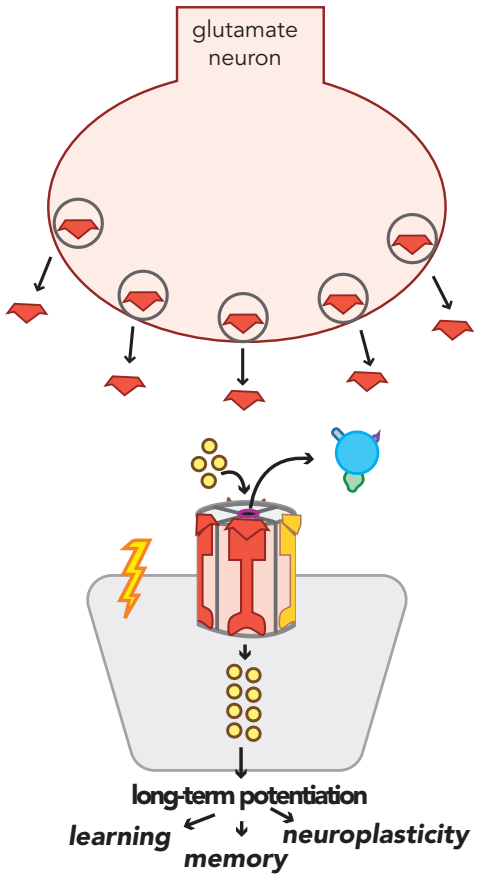


Figure 12-37E Glutamatergic neurotransmission in Alzheimer disease, part 5. Because memantine has low affinity, when there is a phasic burst of glutamate and depolarization occurs, this is enough to remove memantine from the ion channel and thus allow normal neurotransmission. This means that memantine does not have psychotomimetic effects or interfere with normal new learning.

TARGETING THE BEHAVIORAL SYMPTOMS OF DEMENTIA

Dementia is often seen as fundamentally a disorder of memory and cognition, but there are many important behavioral symptoms associated with dementia as well (Figure 12-39), each potentially regulated by separate neuronal networks (Figure 12-23). The prevalence of specific behavioral symptoms of dementia pooled from a large number of studies in AD is shown in Table 12-7. Treatment of dementia-related psychosis, agitation, depression, and apathy are all discussed here.

Defining Agitation and Psychosis in Alzheimer Disease

Perhaps no symptom of dementia raises alarm as much as agitation, especially when it turns into physical aggression with behaviors such as slamming doors, throwing objects, kicking, screaming, pushing, scratching, biting, wandering, intruding upon others, fidgeting, restlessness, pacing, refusing medications, refusing help with activities of daily living, and sexually inappropriate behavior (Table 12-8).

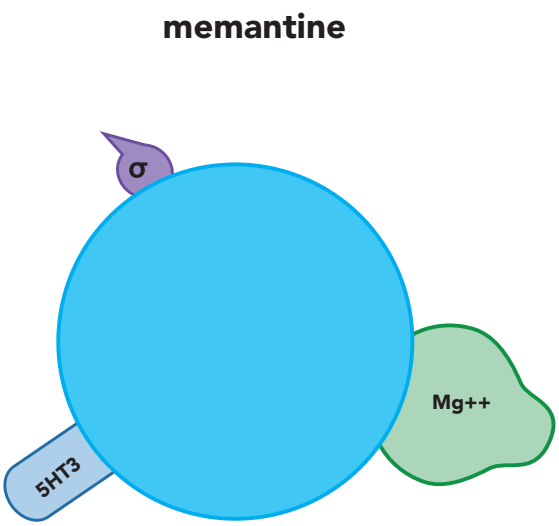


Figure 12-38 Memantine. Memantine is a noncompetitive, low-affinity NMDA (*N*-methyl-D-aspartate) receptor antagonist that binds to the magnesium site when the channel is open. It also has σ binding properties and weak $5HT_3$ antagonist properties.

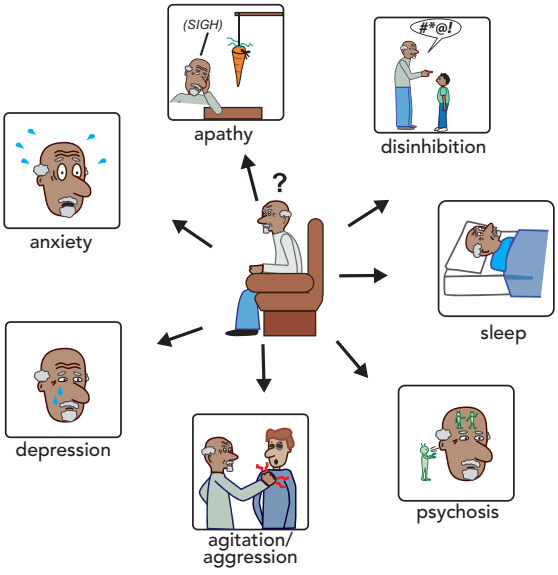


Figure 12-39 Behavioral symptoms in dementia. Patients with dementia can exhibit many symptoms in addition to cognitive and memory impairment, each of which is potentially regulated by separate neuronal networks.

Agitation is defined for clinical and research purposes by the Agitation Definition Work Group of the International Psychogeriatric Association as:

- occurring in patients with a cognitive impairment or dementia syndrome
- exhibiting behavior consistent with emotional distress
- manifesting excessive motor activity, verbal aggression, or physical aggression
- evidencing behaviors that cause excess disability and are not solely attributable to another disorder

In contrast, dementia-related psychosis as discussed above is defined by

- delusions or hallucinations occurring after the onset of cognitive decline
- persisting for at least one month
- not better explained by delirium or some other mental illness

Whereas psychosis and agitation can be rather readily distinguished from memory decline in AD, agitation and psychosis can easily be confused with each other. However, these two symptom domains of agitation and psychosis hypothetically arise from entirely separate malfunctioning neuronal networks in dementia (compare Figure 12-23B, C) and are giving rise to entirely separate treatments. Given that the new treatments on the horizon for psychosis and for agitation have distinct mechanisms that target these neuronal networks individually and differently, it is more important than ever to be able to distinguish agitation from psychosis in dementia. Furthermore, psychotic symptoms such as intrusive hallucinations and/or paranoid delusions can precipitate agitation or lead to aggressive behavior. Thus, some dementia patients will have both agitation and psychosis and require treatment for both.

Table 12-7 Prevalence of specific behavioral and psychological symptoms of dementia (BPSD)

Symptom	Percentage
Apathy	49
Depression	42
Aggression	40
Sleep disorder	39
Anxiety	39
Irritability	36
Appetite disorder	34
Aberrant motor behavior	32
Delusions	31
Disinhibition	17
Hallucinations	16
Euphoria	7

Estimates of prevalence are pooled from 48 studies of BPSD in Alzheimer disease, using the Neuropsychiatric Inventory.
Data are from Zhao et al. 2016.

Table 12-8 Assessing agitation

Cohen-Mansfield agitation inventory (CMAI)	
Physical/aggressive	Physical/non-aggressive
Hitting	Pacing, aimless wandering
Kicking	Inappropriate dress/disrobing
Grabbing	Trying to get to a different place
Pushing	Intentional falling
Throwing things	Eating/drinking inappropriate substances
Biting	Handling things inappropriately
Scratching	Hiding things
Spitting	Hoarding things
Hurting self or others	Performing repetitive mannerisms
Destroying property	General restlessness
Making physical sexual advances	
Verbal/aggressive	**Verbal/non-aggressive**
Screaming	Repetitive sentences or questions
Making verbal sexual advances	Strange noises
Cursing or verbal aggression	Complaining
	Negativism
	Constant unwarranted request for attention

Before using medications at all to treat agitation or psychosis in dementia, reversible precipitants particularly of agitation should be managed non-pharmacologically (Table 12-9):

- pain
- nicotine withdrawal
- medication side effects
- undiagnosed medical and neurological illnesses
- provocative environments that are either too stimulating or not stimulating enough

PHARMACOLOGICAL TREATMENT OF PSYCHOSIS AND AGITATION IN DEMENTIA

There is no pharmacological treatment for either psychosis or agitation in dementia yet approved although several agents are in late-stage trials. Up until now, psychosis versus agitation in dementia have not been differentiated particularly well clinically because they either remained untreated or were both nonspecifically and quite controversially treated with unapproved dopamine receptor blocking agents normally used to treat schizophrenia. No topic in the care of the behavioral symptoms of dementia has been more contentious than

Table 12-9 Non-pharmacological options for behavioral symptoms in dementia

- Address unmet needs (hunger, pain, thirst, boredom)
- Identify/modify environmental stressors
- Identify/modify daily routine stressors
- Caregiver support/training
- Behavior modification
- Group/individual therapy
- Problem solving
- Distraction
- Provide outlets for pent-up energy (exercise, activities)
- Avoid behavior triggers
- Increase social engagement
- Relaxation techniques
- Reminiscence therapy
- Music therapy
- Aromatherapy
- Pet therapy

the current management of agitation and psychosis in dementia, especially when it comes to the use of dopamine D_2 receptor blocking drugs.

Why are dopamine D_2 receptor blocking drugs controversial? This is due to many factors, including the potential for these drugs to act as "chemical straightjackets" and over-tranquilize patients. There are also major safety concerns and a "black box" warning, specifically about cardiovascular events such as stroke and death from using these drugs. Mortality risks may be due to stroke, thromboembolism, falls, cardiac complications of QT interval prolongations, and pneumonia, especially when sedated from drugs that increase the risk of aspiration (e.g., anticholinergics, sedative hypnotics, benzodiazepines, opioids, and alcohol).

On the other hand, efficacy of some dopamine receptor blockers coming from small trials or anecdotal observations from clinical practice often find greater efficacy than that reported in controlled trials that have high placebo response rates. Another consideration in the real world is that there are also risks of *non*-treatment of agitation, aggression, and psychosis in dementia, including the risks of early institutionalization and the dangers of such behaviors to the patient and others around them. Therefore, after careful consideration of the risks and the benefits to an individual dementia patient, some are treated cautiously "off-label" with dopamine blocking drugs, especially risperidone, olanzapine, and aripiprazole, as well as haloperidol, but not quetiapine or others (see Chapter 5 for extensive discussion of drugs for psychosis as well as each of these individual drugs).

The dilemma caused by necessity to treat yet the presence of a "black box" safety warning against the use of dopamine blockers has triggered the search for drugs proven effective for the treatment of psychosis and agitation, which have an adequate safety profile. Clinical trials are proceeding with several new therapeutic agents on the horizon that separately and more specifically target either the psychosis network (e.g., with the $5HT_{2A}$ antagonist pimavanserin) or the agitation network (with multimodal glutamate and monoamine agents such as brexpiprazole and dextromethorphan–bupropion). Thus, it is more important than ever to distinguish agitation from psychosis because treatments are directed to entirely different brain networks, with novel treatments for psychosis not proven effective for agitation and vice versa.

Targeting Serotonin for the Symptomatic Treatment of Dementia-Related Psychosis

Prevalence estimates for psychosis range from 10% for FTD to 75% for dementia with Lewy bodies (Table 12-10). In the US, it is estimated that over 2 million people suffer from dementia-related psychosis. Visual hallucinations are a prominent feature of psychosis in all forms of dementia, especially in dementia with Lewy bodies and Parkinson's disease dementia (Table 12-10 and Figures 12-40 and 12-41). Delusions are also observed in all forms of dementia, especially in AD (Figure 12-40), with the most common delusions being paranoid (e.g., theft or spousal infidelity) and misidentifications, though the latter is sometimes considered a type of memory deficit rather than psychosis. Psychosis in Parkinson's disease often heralds the emergence of dementia and vice versa. Up to 50–70% of patients with Parkinson's disease dementia report hallucinations compared to only 10% of patients with Parkinson's disease but no dementia (Figure 12-41 and Table 12-10). Approximately 85% of patients with Parkinson's disease psychosis

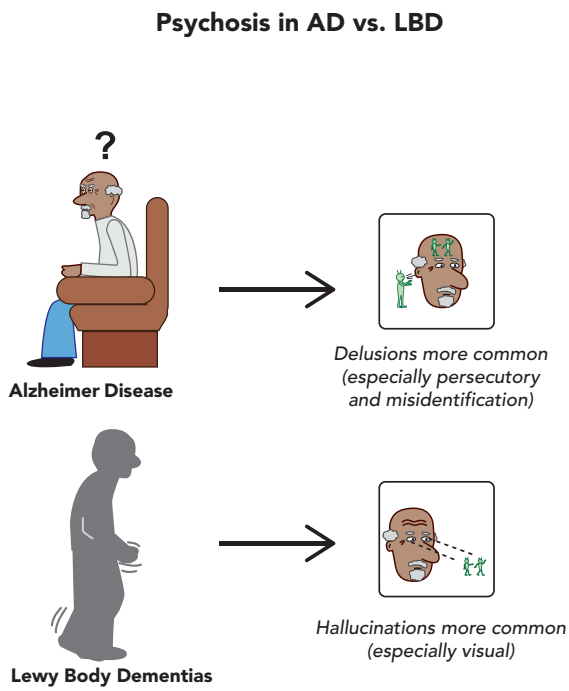


Figure 12-40 Psychosis in Alzheimer disease versus Lewy body dementias. In Alzheimer disease (AD), delusions are more common than hallucinations, and particularly delusions of persecution or misinformation. In Lewy body dementias (LBD), hallucinations are more common, particularly visual hallucinations.

Table 12-10 Prevalence ranges (%) for psychosis, delusions, and hallucinations in Alzheimer disease, vascular dementia, dementia with Lewy bodies, Parkinson's disease dementia, and frontotemporal dementia

	Alzheimer disease	Vascular dementia	Dementia with Lewy bodies	Parkinson's disease dementia	Frontotemporal dementia
Overall psychosis prevalence	30	15	75	50	10
Delusions prevalence	10–39	14–27	40–57	28–50	2.3–6
Hallucinations prevalence	11–17	5–14	55–78	32–63	1.2–13

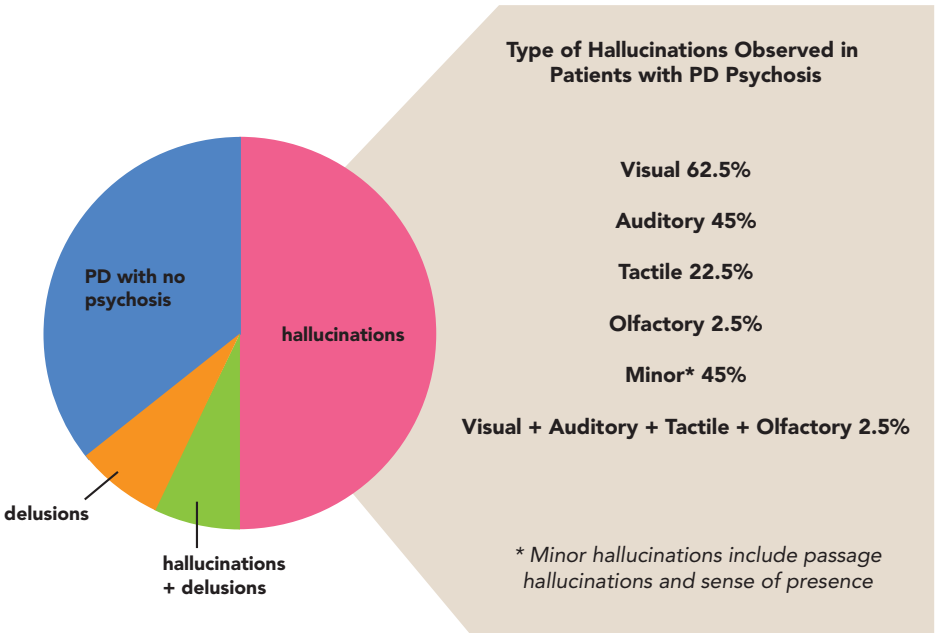


Figure 12-41 Psychosis in Parkinson's disease. Psychosis is commonly associated with Parkinson's disease (PD), and the presence of psychosis often heralds the emergence of dementia (and vice versa). The hallucinations reported by patients with PD are most often visual; however, other types of hallucinations may also be experienced.

experience hallucinations only, with 7.5% experiencing hallucinations and delusions and 7.5% experiencing delusions only (Figure 12-41). The severity of psychosis and the specific symptoms manifested also vary across the spectrum of dementias (Figures 12-40 and 12-41). The frequency of psychosis also varies across the time course and natural history of dementia, with psychosis being more frequently observed in patients with more advanced dementia. Psychotic symptoms in any form of dementia seem to be related to pathology in the neocortex, and like all symptoms in dementia, specific symptoms such as auditory versus visual hallucinations, versus delusions, are likely to reflect damage to specific cortical areas (Figures 12-23B and 12-42A through 12-42C). Dementia-related psychosis has consistently been associated with greater caregiver burden and more rapid progression to severe dementia, institutionalization, and death. Some questions that arise in understanding dementia-related psychosis include: How could so many different forms of dementia all have psychosis (Table 12-10) when their causes are so different? Also, why doesn't every patient with dementia have psychosis?

The answers to these questions may be found by grasping an understanding of the hypothetical brain circuits that mediate psychosis in dementia (Figures 12-23B and 12-42B; see also discussion on psychosis in Chapter 4 and illustrated in Figures 4-34, 4-52D, and 4-55). Psychosis is theoretically a symptom derived

from inefficient information processing in a different brain circuit from that which theoretically processes memory (compare Figures 12-23A and 12-42A). When the destructive process of any given dementia invades the psychosis network that regulates rational thinking and processing of sensory input (Figure 12-42A), the outcome is hypothetically psychosis (Figure 12-42B; see also Chapter 4 and Figures 4-34, 4-52D, and 4-55). From what we know about the psychosis network, delusions and hallucinations seem to be regulated by a neuronal network that connects glutamate, GABA, serotonin, and dopamine neurons (compare Figures 12-42A and 12-42B). The sites of connections/synapses between these different neurons are considered to be "nodes" in this network, where their neurotransmitters act to regulate the entire interconnected brain circuit of psychosis (Figure 12-42A). In dementia, the accumulation of Aβ plaques, tau tangles, Lewy bodies, and/or strokes in the cortical node connecting GABA and glutamate, hypothetically can knock out critical regulatory neurons, especially inhibitory GABA interneurons, causing glutamate hyperactivity and consequential downstream dopamine hyperactivity and psychosis (Figure 12-42B).

Why do some dementia patients experience psychosis and not others? One hypothesis is that in patients with dementia-related psychosis, neurodegeneration has progressed in such a way as to knock out regulatory neurons, not only in the memory pathway (Figure 12-33B) but also in the psychosis pathway (Figure 12-42B). In other dementia patients without psychosis, the neurodegeneration has not (yet) knocked out the neurons regulating the psychosis network.

Although any node in the psychosis network is a theoretical site for therapeutic action, at the present time, there is no effective way to attack the psychosis network with GABA or glutamate agents. Although blocking dopamine receptors often has antipsychotic effects in patients with dementia-related psychosis, these agents increase stroke and death, so they are not approved for the treatment of dementia-related psychosis.

Then, how can we quell the hyperactivity in the psychosis network in dementia? The answer is to block the normal excitatory input of serotonin in this network at $5HT_{2A}$ receptors with the selective agent pimavanserin (Figure 12-42C; see Chapter 5 for further discussion of

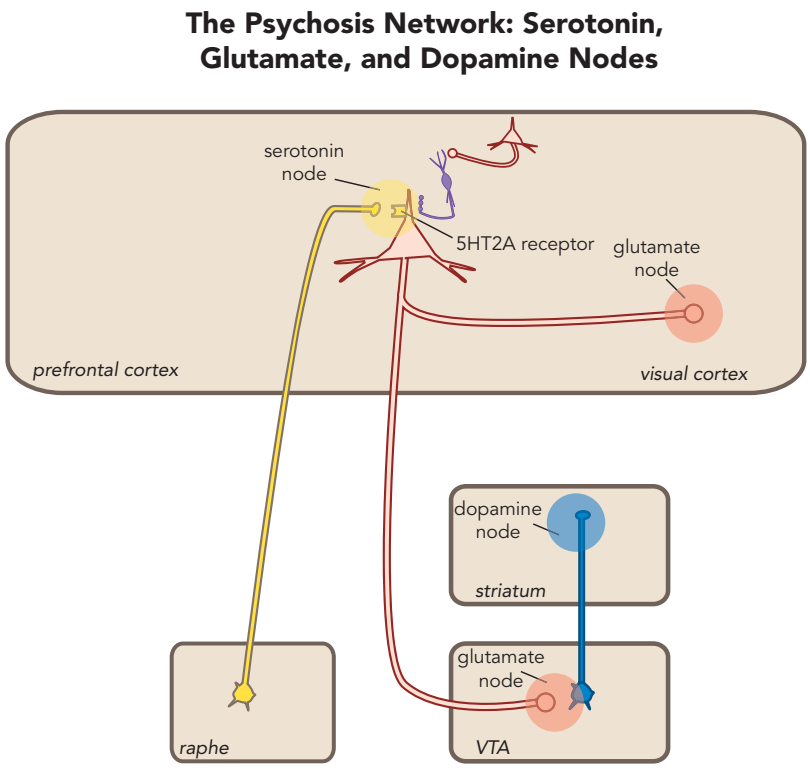


Figure 12-42A The psychosis network at baseline. The symptoms of psychosis seem to be mediated by communication at synapses (nodes) between glutamate, γ-aminobutyric acid (GABA), serotonin, and dopamine neurons. Glutamate neurons in the prefrontal cortex project to the ventral tegmental area (VTA) where they connect with dopamine neurons (glutamate node). Those dopamine neurons then project to the striatum. Serotonin neurons in the raphe nucleus project to the prefrontal cortex, where they connect with glutamate neurons (serotonin node). Glutamate neurons project from the prefrontal cortex to the visual cortex where they connect with other glutamate neurons (glutamate node).

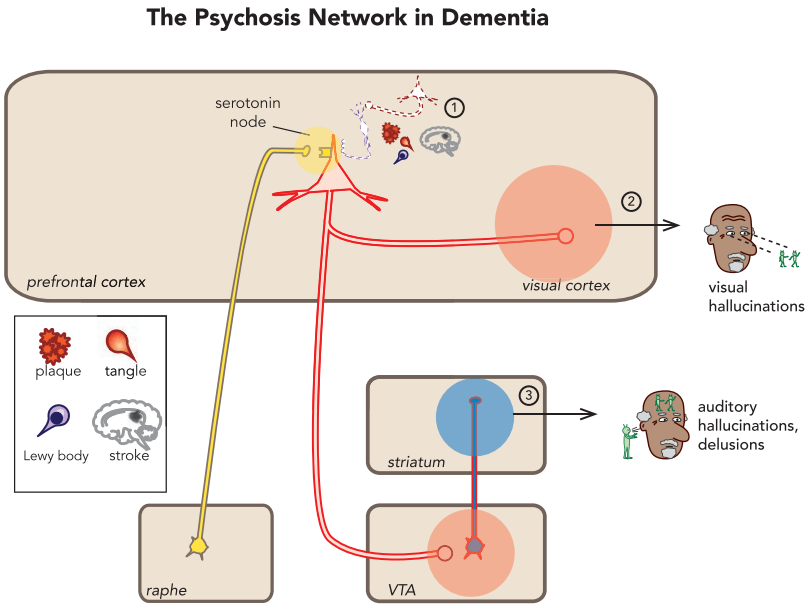


Figure 12-42B The psychosis network in dementia. (1) Accumulation of Aβ plaques, tau tangles, and/or Lewy bodies, as well as the damage caused by strokes, may destroy some glutamatergic pyramidal neurons and GABAergic interneurons while leaving others intact. The loss of GABA inhibition upsets the balance of control over glutamatergic pyramidal neurons, at least temporarily. When the effects of stimulation of excitatory $5HT_{2A}$ receptors are not countered by GABA inhibition, there is a net increase in glutamatergic neurotransmission. (2) Excessive glutamate release in the visual cortex can cause visual hallucinations. (3) Excessive glutamate release into the ventral tegmental area (VTA) causes hyperactivity of the mesolimbic dopamine pathway, resulting in delusions and auditory hallucinations.

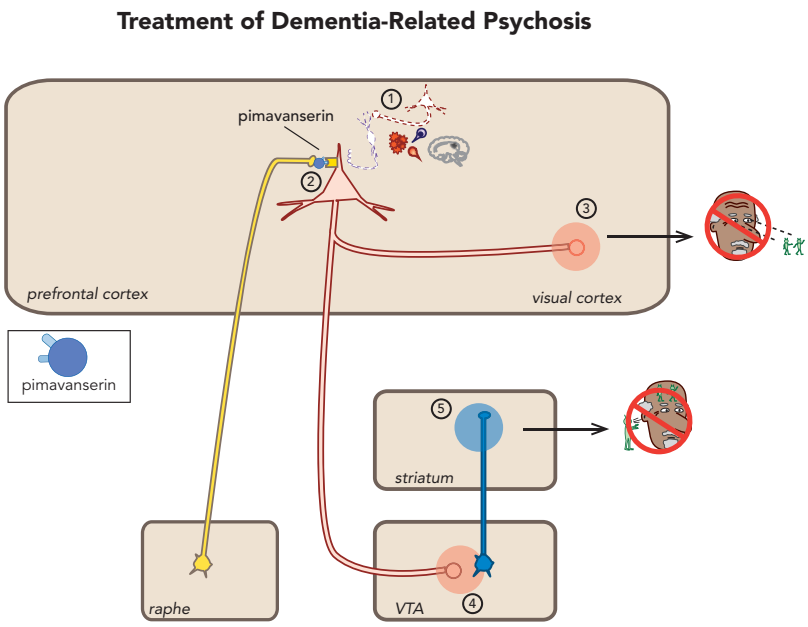


Figure 12-42C The psychosis network in dementia with treatment. (1) Accumulation of Aβ plaques, tau tangles, and/or Lewy bodies, as well as the damage caused by strokes, may destroy some glutamatergic pyramidal neurons and GABAergic interneurons while leaving others intact. The loss of GABA inhibition upsets the balance of control over glutamatergic pyramidal neurons, at least temporarily. (2) When the $5HT_{2A}$ antagonist pimavanserin binds to $5HT_{2A}$ receptors on glutamate neurons in the prefrontal cortex, this compensates for the loss of GABA inhibition due to neurodegeneration of glutamate and GABA neurons. (3) Normalization of glutamate neurotransmission downstream in the visual cortex leads to reduction in visual hallucinations. (4) Normalization of glutamate neurotransmission downstream in the ventral tegmental area (VTA) leads to (5) normalization of dopamine neurotransmission and reduction in delusions and auditory hallucinations.

pimavanserin in psychosis and Figures 5-16, 5-17, and 5-59). In dementia-related psychosis, pimavanserin hypothetically reduces overactivity in the psychosis network caused by plaques, tangles, Lewy bodies, or strokes, presumably by lowering the normal $5HT_{2A}$ stimulation to surviving glutamate neurons that have lost their GABA inhibition by neurodegeneration. This hypothetically rebalances the output of the surviving glutamate neurons so that $5HT_{2A}$ antagonism and its reduction of neuronal stimulation compensates for the loss of GABA inhibition. The $5HT_{2A}$ antagonist pimavanserin is approved for the treatment of Parkinson's disease psychosis and there are positive trials of this agent in dementia-related psychosis of all causes.

Neuronal Networks of Agitation in Alzheimer Disease

A simple model for the circuitry of agitation in AD is that there is an imbalance in "top-down" cortical inhibition with "bottom-up" limbic and emotional drives (Figures 12-43 and 12-44). Indeed, this simple model has been implicated in a wide range of related symptoms across multiple disorders, such as the psychomotor agitation of psychosis (discussed in Chapter 4), mania and mixed features (discussed in Chapter 6), disorders of impulsivity such as ADHD (discussed in Chapter 10), and many impulsive–compulsive syndromes such as obsessive–compulsive disorder (OCD), gambling, substance abuse, and even violence (discussed in Chapter 13). In AD, neurodegeneration destroys the neurons responsible for top-down inhibition and this is what is thought to allow bottom-up drives to proceed unabated and thus allow the overt manifestations of agitation.

A more sophisticated model of agitation in AD hypothesizes a deficiency in thalamic filtering of sensory input due to loss of top-down cortical inhibition that results in the *motor* and *emotional* outputs of agitation (Figures 12-45A, 12-45B, 12-46A, and 12-46B). Normal top-down cortical inhibition filters out *sensory* input so it does not generate a reflexive and thoughtless *motor* response (Figure 12-45A). Similarly, intact top-down cortical inhibition also filters out *emotional* input so that it does not generate an *emotional* response (Figure 12-46A).

In AD patients, sensory, emotional, and motor areas of the cortex tend to survive while top-down inhibitor neocortical neurons degenerate, keeping the ability to express motor and emotional output intact but not the ability to inhibit it (Figures 12-45B and 12-46B). Thus, when top-down inhibitory drive is destroyed, *sensory* input is able to break out of the thalamus and into the cortex and to provoke thoughtless reflexive *motor* agitation (Figure 12-45B). Without top-down inhibitory drive, emotional input also triggers lots of bottom-up trouble from the limbic instigator, the amygdala (Figure 12-46B). That is, when *emotional* input is unfiltered by the thalamus, it can set off the amygdala to deliver bottom-up limbic fervor (Figure 12-46B). Specifically, amygdala output to the ventral tegmental area activates dopamine release in the mesolimbic pathway, worsening the thalamic filter and sparking *emotions* (Figure 12-46B). Amygdala output to the locus coeruleus elicits norepinephrine release in the cortex mobilizing arousal and emotions (Figure 12-46B). Finally, amygdala output directly to cortex sets off emotional and affective agitation (Figure 12-46B).

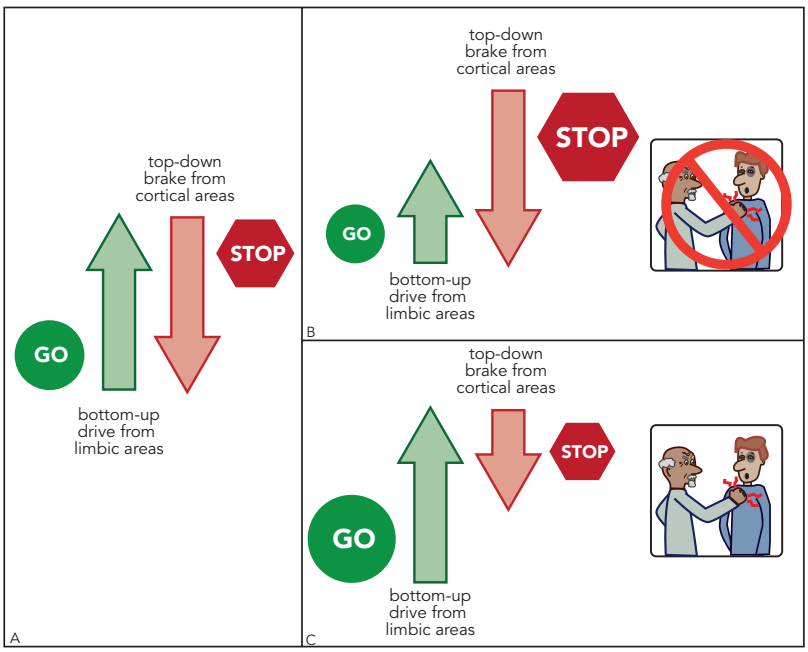


Figure 12-43 Agitation in Alzheimer disease. (A) "Top-down" cortical inhibition and "bottom-up" limbic drive is in balance. (B) Normal activation of top-down circuitry inhibits the more impulsive bottom-up drive from limbic regions, preventing inappropriate behavior symptoms. (C) In Alzheimer disease, neurodegeneration may lead to insufficient top-down inhibition of bottom-up limbic drive, with resulting behavioral symptoms.

The Agitation/Impulsivity Network: Top-Down Brakes Balance Bottom-Up Sensory and Emotional Drives

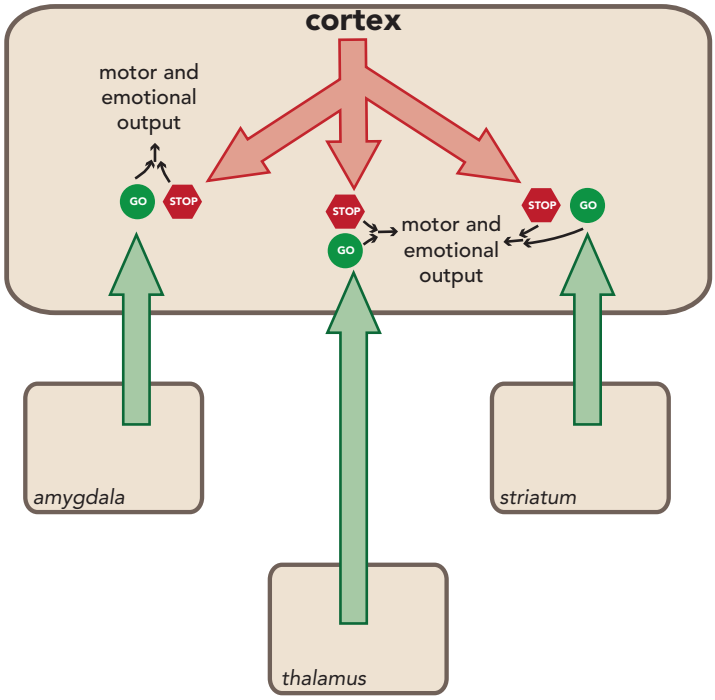


Figure 12-44 **Agitation/impulsivity network.** Bottom-up sensory and emotional input from the amygdala, thalamus, and striatum is relayed to the cortex. Top-down cortical inhibition balances the bottom-up input, resulting in appropriate motor and emotional output.

Top-Down Inhibition Prevents Overstimulation of the Agitation Network: Motor Output

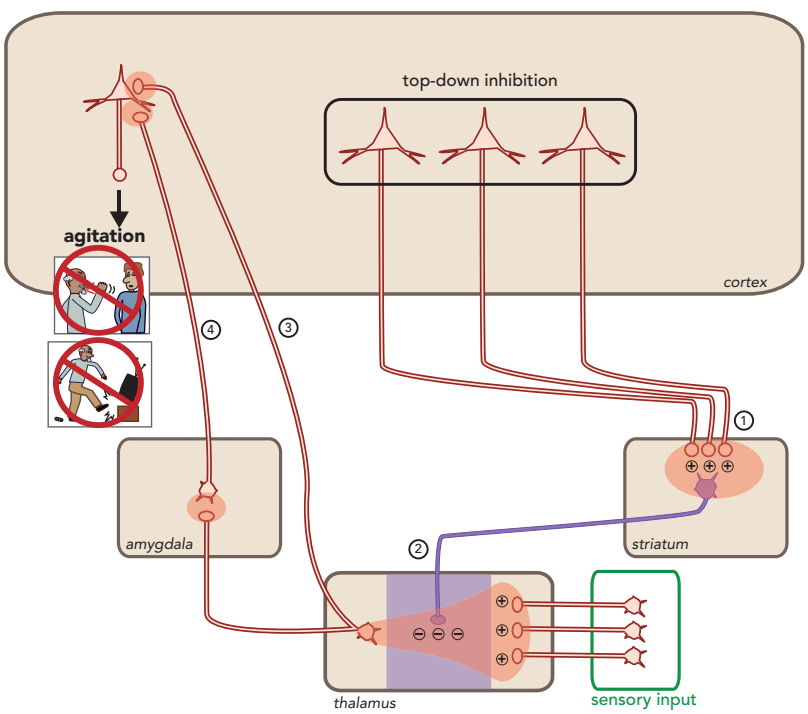


Figure 12-45A **Top-down inhibition prevents overstimulation of agitation network: motor output.** (1) Top-down cortical inhibition occurs when glutamate neurons in the cortex release glutamate in the striatum. (2) This stimulates GABA release in the thalamus, which filters out sensory input. (3) Thus, thalamic output directly to the cortex and (4) via the amygdala does not generate a reflexive motor response.

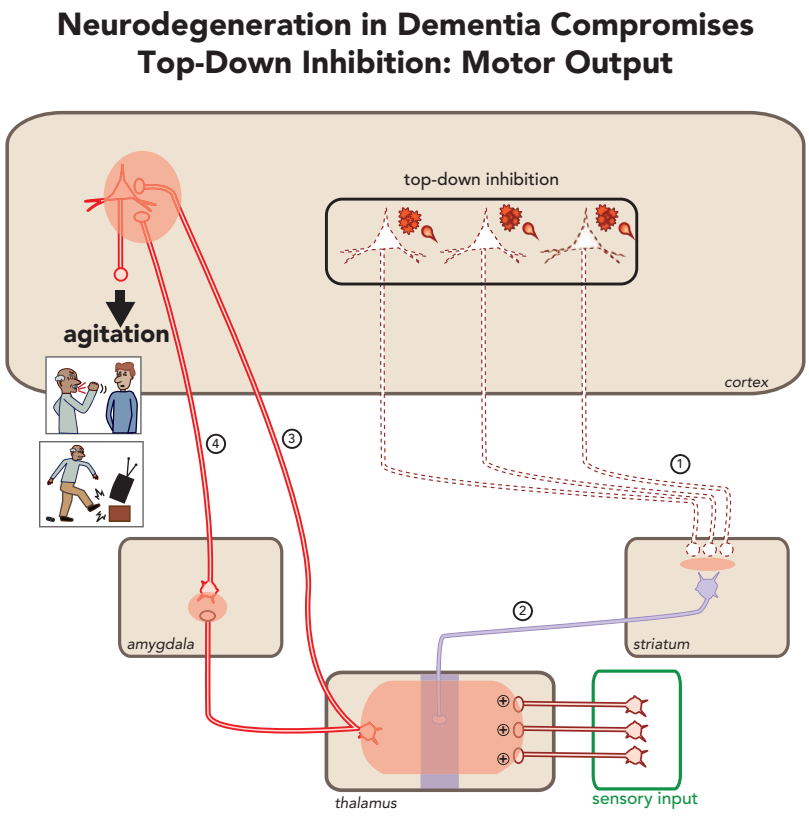


Figure 12-45B **Neurodegeneration in dementia compromises top-down inhibition: motor output.** (1) Accumulation of Aβ plaques and tau tangles destroys glutamate neurons projecting to the striatum and thus reduces top-down cortical inhibition. (2) GABA input into the thalamus is insufficient and sensory input is not adequately filtered. (3) Excessive thalamic output directly to the cortex and (4) via the amygdala generates a reflexive motor response.

Up until now, treatments of agitation in AD have not been particularly effective, including dopamine receptor blockers already mentioned. In the absence of any approved agents, first-line pharmacological treatment of agitation and aggression in dementia is actually considered by many experts to be therapy with selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs), which can help some patients. Second-line treatments that may help avoid use of dopamine receptor blocking drugs include β blockers, carbamazepine, and perhaps gabapentin and pregabalin, but not valproate, topiramate, oxcarbazepine, or benzodiazepines. Unfortunately, in addition to not causing robust efficacy, many of these agents are associated with significant side effects including sedation, unsteady gait, diarrhea, and weakness. Carbamazepine has perhaps shown the greatest efficacy amongst unapproved drugs so far in treating neuropsychiatric symptoms of dementia but has significant side-effect risks and may interact with other medications commonly prescribed to elderly patients. Cholinesterase inhibitors have little if any benefit for most of the behavioral symptoms of dementia except in patients with Lewy body dementias.

Targeting Multimodal Neurotransmitters (Norepinephrine, Serotonin, and Dopamine) for the Symptomatic Treatment of Agitation in Alzheimer Disease

Brexpiprazole is a serotonin–dopamine–norepinephrine antagonist/partial agonist discussed in Chapter 5 as one of the drugs approved to treat psychosis (Figure 5-57) and in Chapter 7 as one of the drugs to augment SSRIs/SNRI to treat unipolar major depression. This agent combines several simultaneous mechanisms to quell the excessive activity of the agitation network in AD: namely by its well-known dopamine D_2 partial agonist actions combined with $5HT_{1A}$ partial agonist and $5HT_{2A}$ antagonist actions, as well as by its relatively unique additional actions blocking both α_1- and α_2-adrenergic receptors (Figure 5-57 and Figure 12-47). Despite brexpiprazole having a warning for increased mortality in dementia-related *psychosis*, using this agent for *agitation* in AD and in doses lower than those generally used to treat psychosis in schizophrenia may provide a greater safety margin, especially since it is the hypothetical synergy of its five actions that leads to therapeutic efficacy in agitation of AD (Figure 12-47).

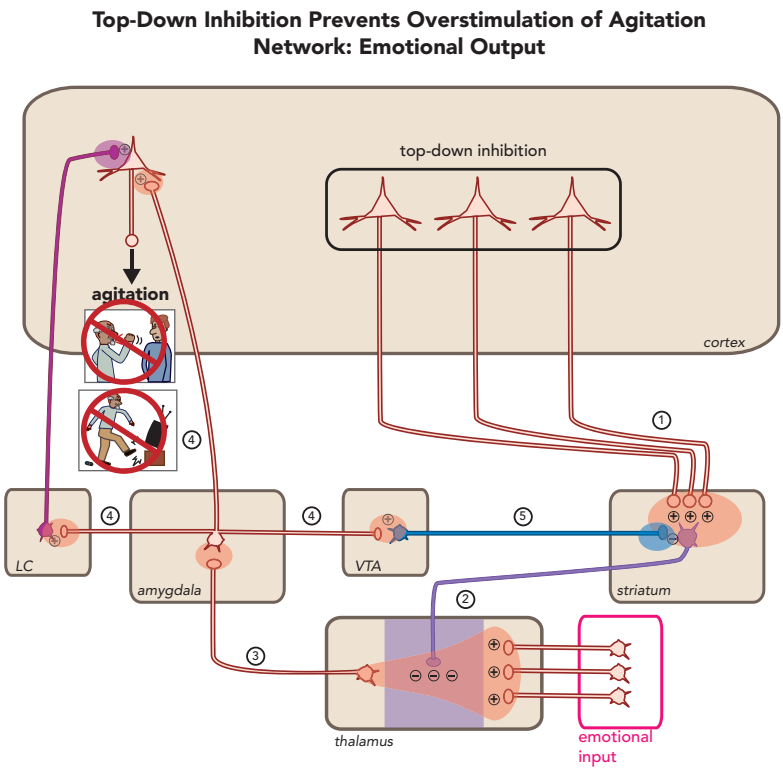


Figure 12-46A **Top-down inhibition prevents overstimulation of agitation network: emotional output.** (1) Top-down cortical inhibition occurs when glutamate neurons in the cortex release glutamate in the striatum. (2) This stimulates GABA release in the thalamus, which filters out emotional input. (3) Thus, thalamic output to the amygdala leads to (4) controlled output to the locus coeruleus (LC) and cortex and does not generate a reflexive emotional response. Controlled output to the ventral tegmental area (VTA) likewise leads to (5) controlled dopamine output from the VTA to the striatum.

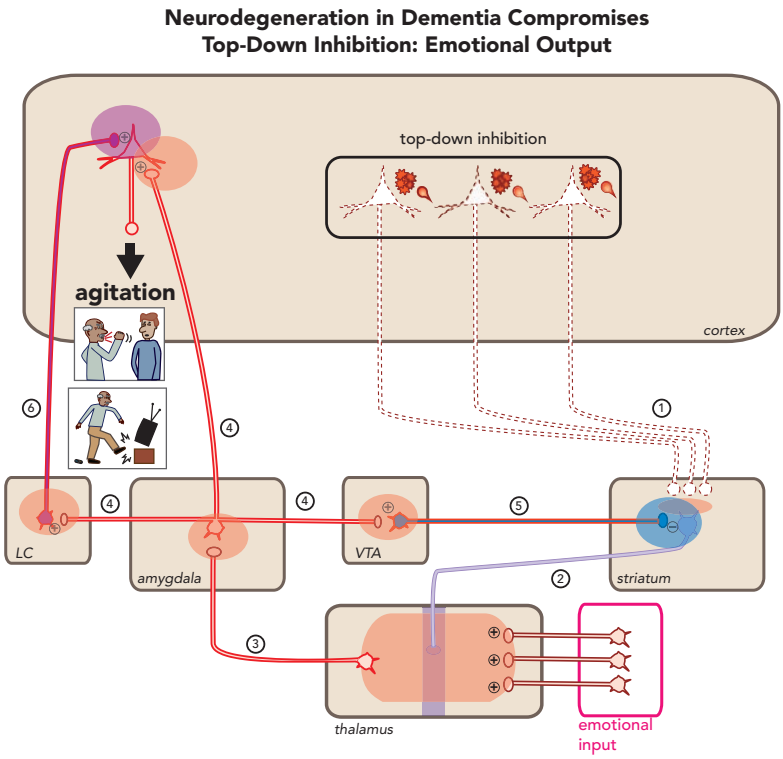


Figure 12-46B **Neurodegeneration in dementia compromises top-down inhibition: emotional output.** (1) Accumulation of Aβ plaques and tau tangles destroys glutamate neurons projecting to the striatum and thus reduces top-down cortical inhibition. (2) GABA input into the thalamus is insufficient and emotional input is not adequately filtered. (3) Excessive thalamic output to the amygdala leads to (4) excessive output to the locus coeruleus (LC), cortex, and ventral tegmental area (VTA). (5) Dopamine is released from VTA into the striatum, further reducing the thalamic filter and contributing to a reflexive emotional response. (6) Norepinephrine is released from the LC to the cortex, contributing to a reflexive emotional response.

Specifically, by reducing dopamine output from the ventral tegmental area (VTA) triggered by amygdala activation, this would lead to improving the thalamic filtering of emotional input (shown in Figure 12-46B).

Also, the multimodal actions of brexpiprazole have several points of interaction to quell excessive cortical output from surviving pyramidal neurons that drive motor and emotional agitation (Figure 12-47). Blocking

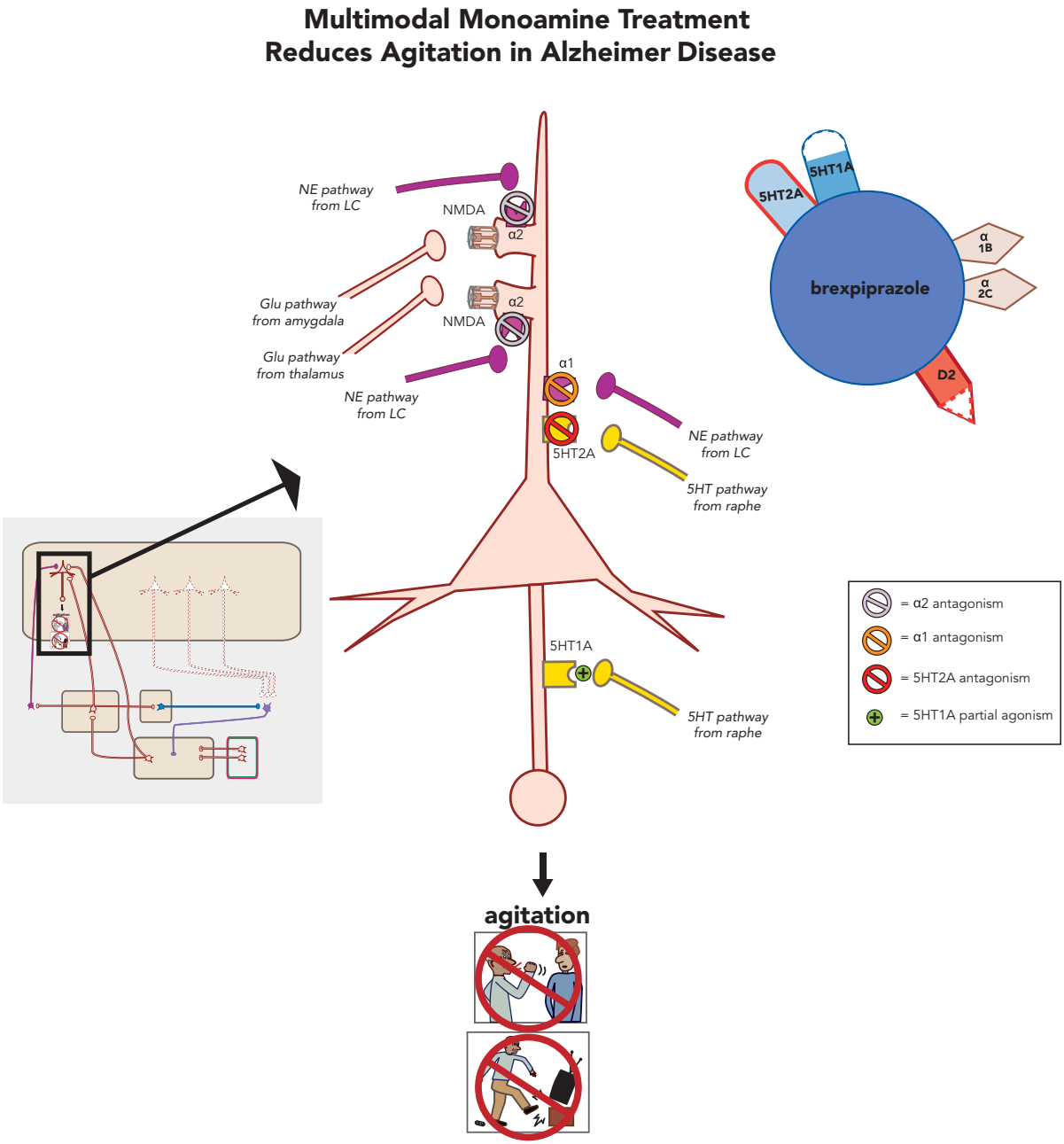


Figure 12-47 Multimodal monoamine treatment for agitation. Brexpiprazole has multiple pharmacological mechanisms that may hypothetically work synergistically to reduce agitation. Blocking activation by norepinephrine (NE) from locus coeruleus (LC) output at α_{2c} and α_1 postsynaptic receptors on dendrites of pyramidal neurons should reduce arousal and emotional responses. Blocking normal serotonin excitation by antagonist actions at $5HT_{2A}$ receptors and enhancing normal serotonin inhibition by partial agonist actions at $5HT_{1A}$ receptors should also combine to reduce limbic drives to motor and emotional outputs of agitation.

activation by norepinephrine from locus coeruleus output at α_{2c} and α_1 postsynaptic receptors on dendrites of pyramidal neurons should reduce arousal and emotional responses (Figure 12-47); blocking normal serotonin excitation by antagonist actions at $5HT_{2A}$ receptors and enhancing normal serotonin inhibition by partial agonist actions at $5HT_{1A}$ receptors should also combine to reduce limbic drives to motor and emotional outputs of agitation (Figure 12-47). Brexpiprazole is approved for use in schizophrenia and depression, and is in late-stage clinical testing for agitation in AD.

Targeting Glutamate for the Symptomatic Treatment of Agitation in Alzheimer Disease

Excessive glutamate output in memory circuits has already been discussed (Figures 12-37A, 12-37B, and 12-37C; see also Figure 4-52D and discussion in Chapter 4). Although the NMDA glutamate antagonist memantine has proven effective in symptomatic treatment of *cognition/memory* in AD, it has not been systematically tested in *agitation* of AD. Furthermore, the widespread use of memantine does not suggest any anecdotal evidence for efficacy in agitation, perhaps because it is a relatively weak blocker of NMDA receptors, with low potency.

More robust blockade of NMDA receptors is attained by dextromethorphan, discussed in Chapter 7 on drugs for depression and illustrated in Figure 7-84. As mentioned in Chapter 7 there are multiple forms of dextromethorphan in testing, including a deuterated derivative as well as combinations of dextromethorphan with one or another of two different CYP450 2D6 inhibitors, either bupropion or quinidine. The formulation of dextromethorphan with the CYP450 2D6 inhibitor and norepinephrine–dopamine reuptake inhibitor (NDRI) bupropion (also known as AXS-05; Figure 7-84) has promising results in major depressive disorder and treatment-resistant depression (discussed in Chapter 7 on treatment of mood disorders) and in agitation of AD (mentioned here and illustrated in Figure 12-48). Although there are several potential therapeutic mechanisms of dextromethorphan combinations, it is likely that NMDA antagonist action is how this drug works to quell agitation in AD. Hypothetically dextromethorphan–bupropion blocks the excessive excitatory glutamate output from the agitation network that leads to motor (Figure 12-45B) and emotional agitation (Figure 12-46B) by blocking NMDA receptors in cortex, thalamus, amygdala, ventral tegmental area, and locus coeruleus (Figure 12-48).

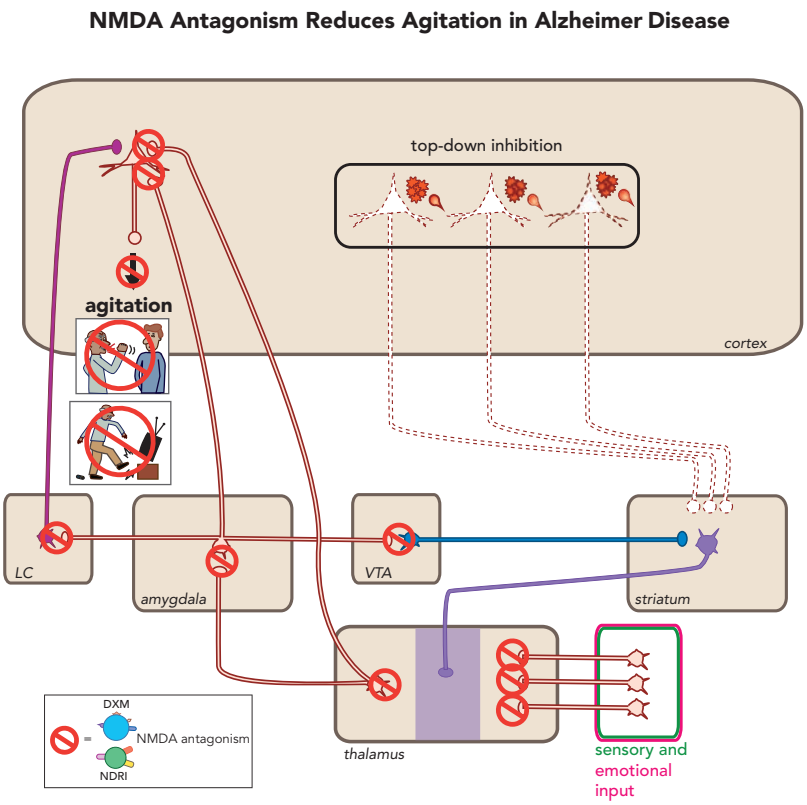


Figure 12-48 NMDA antagonist treatment for agitation. The NMDA antagonist dextromethorphan (DXM), in combination with the norepinephrine–dopamine reuptake inhibitor (NDRI) bupropion, is in testing as a treatment for agitation. Hypothetically, dextromethorphan–bupropion blocks the excessive excitatory glutamate output from the agitation network that leads to motor and emotional agitation by blocking NMDA receptors in the cortex, thalamus, amygdala, ventral tegmental area (VTA), and locus coeruleus (LC).

Dextromethorphan combined with quinidine is approved for the treatment of pseudobulbar affect, and dextromethorphan and derivates combined with either bupropion or quinidine are in late-stage testing for major depressive disorder, for treatment-resistant depression, and for agitation in AD.

Treating Depression in Dementia

A well-established association exists between depression and dementia; however, the exact nature of this intricate relationship is not fully understood (Figure 12-49). Individuals with major depressive disorder often complain of memory problems (so-called pseudodementia when it occurs in the elderly), which can sometimes be reversed with antidepressant treatment, but depression may also be an untreatable prodromal symptom of, or risk factor for, inevitable dementia (Figure 12-49). In fact, a history of major depressive disorder is associated with a twofold increase in the risk for developing dementia, particularly vascular dementia, whereas major depressive disorder with an onset in later life may signify a prodromal sign of AD. Additionally, symptoms of depression are seen in at least 50% of individuals diagnosed with dementia, and should be addressed whenever feasible.

Given that symptoms of depression can significantly impact quality of life for patients with dementia and may actually exacerbate cognitive decline, addressing depressive symptoms using non-pharmacological (Table 12-9) and/or pharmacological means (Figure 12-50) should be a priority. Psychosocial interventions are always worth trying as treatments for depression in dementia, but the usual drugs for depression discussed in Chapter 7 are often not effective in depression associated with dementia, perhaps because the neural circuits these drugs act upon may have degenerated. Further complicating the treatment of depression in dementia are the potential depression-exacerbating effects of medications for somatic ailments common in the elderly population, as well as the potential interactions of such medications with standard antidepressants. In terms of pharmacological management of major depressive disorder in patients with dementia, SSRIs including sertraline, citalopram, escitalopram, and fluoxetine have shown some limited efficacy (see Chapter 7 for discussion of these and other drugs for depression). In general, long-term antidepressant treatment has been associated with a lower risk of dementia, improved cognition, and a slower rate of decline in elderly patients with dementia. Data are somewhat

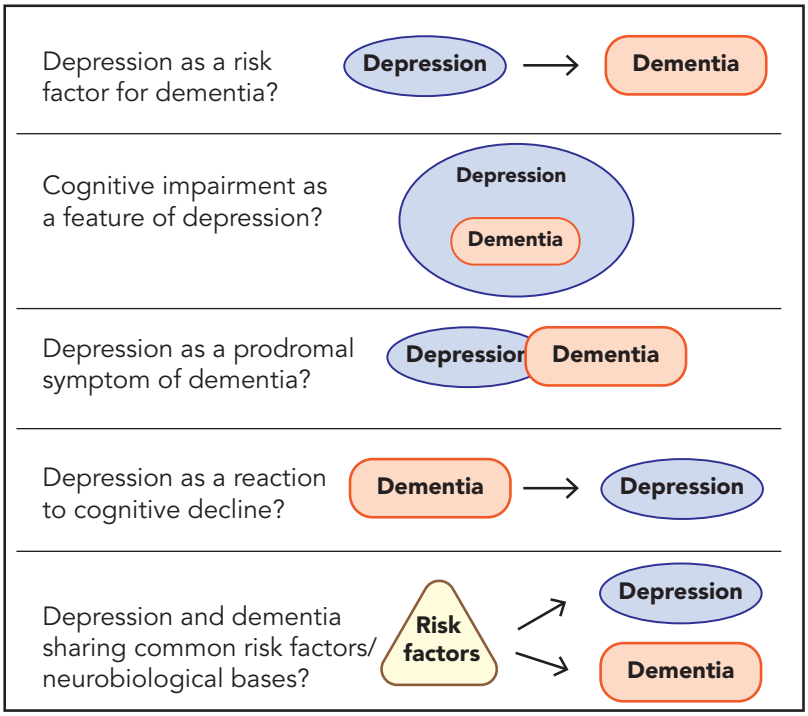


Figure 12-49 Hypothetical associations between depression and dementia. It is well established that an association exists between depression and dementia; however, the exact nature of this intricate relationship is not fully understood.

inconclusive in terms of their efficacy in treating major depressive disorder in dementia; however, SSRIs (e.g., citalopram but has QT prolongation; escitalopram may have similar efficacy without QT prolongation) may have some additional applicability towards ameliorating agitation and inappropriate behaviors in patients with dementia. Although considered relatively tolerable, SSRIs may be associated with increased falls and osteoporosis, and they may have interactions with other medications. Additionally, SSRIs may worsen some symptoms of Parkinson's disease such as restless leg syndrome, periodic limb movements, and REM sleep behavior disorders. Therefore, if a trial of an SSRI (or any other antidepressant medication) is deemed necessary, the lowest effective dose should be used and continuous monitoring should be exercised.

Another agent for treating depression in dementia is trazodone, which blocks the serotonin transporter at antidepressant doses (see Chapter 7 and Figures 7-44 and 7-45). Trazodone also has serotonin 2A and 2C, H_1 histamine and α_1-adrenergic antagonist properties (Figures 7-44 and 7-45), which can make it very sedating. At low doses, trazodone does not adequately block serotonin reuptake but retains its other properties (Figure 7-46). Because trazodone has a relatively short half-life (6–8 hours), if dosed only once daily at night, particularly at low doses, it can improve sleep without having daytime effects. The utility of trazodone in treating secondary behavioral symptoms in patients with dementia may lie more in its ability to improve sleep rather than depression. Trazodone may also improve other behavioral symptoms of dementia especially in FTD but not particularly in AD.

Vortioxetine (Chapter 7 and Figure 7-49) in particular may improve cognitive function in depression, especially processing speed (Figure 7-50) as can some SNRIs like duloxetine (Figure 7-29) in the elderly with depression. However, these pro-cognitive effects have not been demonstrated specifically in dementia patients who have depression.

Pseudobulbar Affect (Pathological Laughing and Crying)

Pseudobulbar affect (PBA) is an emotional expression disorder, characterized by uncontrolled crying or laughing that may be disproportionate or inappropriate to the social context. It is often mistaken for a mood disorder but is actually a disorder of the expression of affect, which is inconsistent or disproportionate to mood. PBA can accompany a variety of neurodegenerative diseases such as AD and various other dementias,

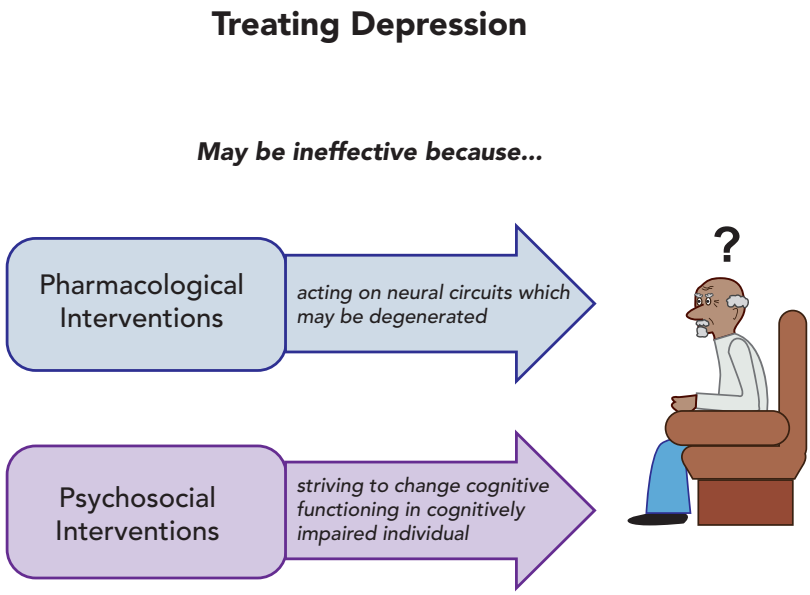


Figure 12-50 Treating depression in patients with dementia. The treatment of depression in elderly patients with dementia may be complicated by the fact that the neural circuits acted on by pharmacological interventions for depression may have degenerated. Although psychosocial interventions are an appropriate option, they may be difficult to implement for cognitively impaired individuals.

multiple sclerosis, amyotrophic lateral sclerosis, as well as traumatic brain injury, and others hypothetically due to disruption of emotional expression networks (top-down inhibition; see Figures 12-44 and 12-46B). PBA can be treated with the combination of dextromethorphan and quinidine (see Figure 7-84), presumably due to actions on NMDA glutamate and σ receptors. Dextromethorphan combined with either quinidine or bupropion is discussed as a possible treatment for resistant depression in Chapter 7 (Figures 7-84 and 7-85), and above, in this chapter, as a possible treatment for agitation in AD (Figure 12-48). Serotonergic agents such as SSRIs can also be used "off-label" for PBA symptoms in some patients.

Apathy

Apathy, characterized as diminished motivation and reduced goal-directed behavior, accompanied by decreased emotional responsiveness, affects approximately 90% of patients with dementia across the disease course. Apathy is indeed one of the most persistent and frequent secondary behavioral symptoms of dementia and has been shown to predict disease-worsening and add tremendously to caregiver burden. Given the current conceptual status of apathy as a mix of cognitive and mood symptoms, there have been challenges in defining apathy, since it is not only a symptom of dementia, but also a symptom of schizophrenia (see Chapter 4 on schizophrenia for discussion of negative symptoms), and of major depressive episodes, both unipolar and bipolar (see Chapter 6 on depression for discussion of lack of motivation and lack of interest).

The ABC (Affective/emotional, Behavioral, Cognitive) model of apathy categorizes three types of apathy, which can hypothetically be linked to deficits in different brain regions, as well as their connections to reward centers in the basal ganglia (Figure 12-51). Another subtyping is:

- lack of initiative
- lack of interest
- emotional blunting

But no matter how characterized, there is a consensus that *lack of motivation* is at the core of apathy. Lack of motivation is associated with

- lack of goal-directed behavior (either spontaneous or in reaction to the environment)
- lack of goal-directed cognitive activity, frequently manifested as loss of interest
- lack of spontaneous or reactive emotional expression, often characterized as emotional blunting

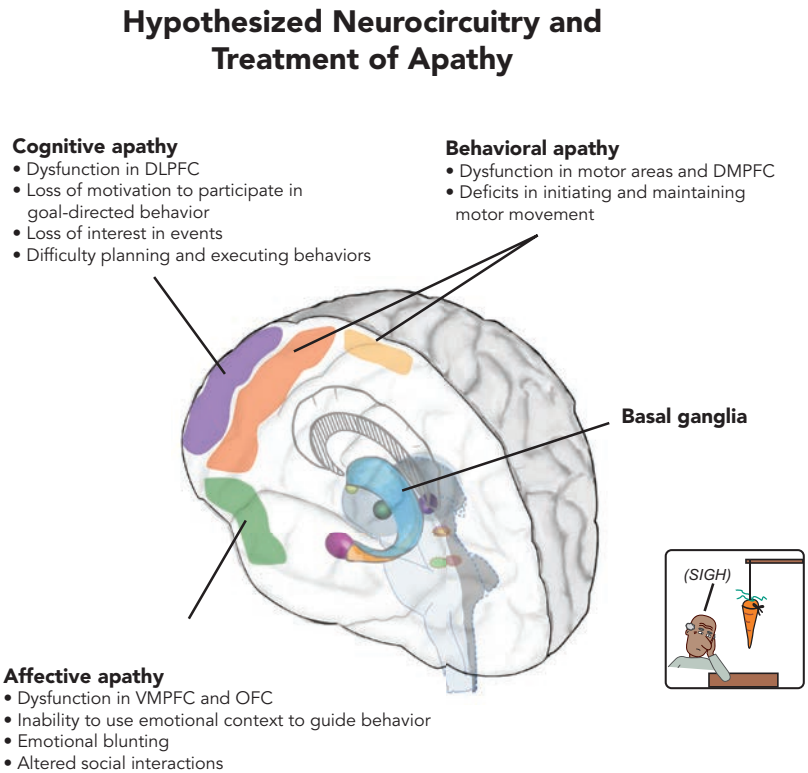


Figure 12-51 Hypothesized neurocircuitry and treatment of apathy. The ABC (Affective/emotional, Behavioral, Cognitive) model of apathy categorizes three types of apathy, which can hypothetically be linked to deficits in different brain regions, as well as their connections to reward centers in the basal ganglia. DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; VMPFC, ventromedial prefrontal cortex; OFC, orbital frontal cortex.

These various descriptions all integrate the notion of lack of spontaneous behaviors and emotions with diminished reactivity to the environment, often the opposite to what is observed in agitation (see Table 12-8).

The clinical presentation of apathy often differs among various types of dementias; for instance, affective apathy is more common in the behavioral variant of FTD compared to AD. Both dopaminergic and cholinergic neurotransmitter systems seem to be involved in the various types of apathy; potential treatments, therefore, include dopamine agonists such as bupropion, levodopa, and stimulants, as well as cholinesterase inhibitors, but none is approved for this use and none is particularly robust in efficacy.

A primary reason why drugs used for depression do not work well in apathy of dementia is that apathy is *not* depression. That is, guilt, worthlessness, and hopelessness, the symptom hallmarks of depression (see Chapter 6 and Figure 6-1), are typically *not* present in patients with apathy in dementia. When use of medications for apathy in dementia is needed, cholinesterase inhibitors may be effective in some patients and are a first-line consideration in AD, but might work better for prevention of these symptoms than for their treatment once they have emerged. Also, FTD patients may be more likely to benefit from SSRIs (e.g., citalopram or escitalopram) or SNRIs.

Other Treatments for the Behavioral Symptoms of Dementia

As mentioned earlier and shown in Table 12-9, there are several non-pharmacological options for treating neuropsychiatric symptoms in patients with dementia, and given the risks associated with many pharmacological treatments, the lack of approval of many agents, and their relative lack of efficacy, non-pharmacological interventions should always be considered first-line. This will also be the case even if pimavanserin is approved for psychosis in all-cause dementia and if brexpiprazole and dextromethorphan–bupropion are approved for agitation in AD.

It is particularly important to keep in mind that physical pain, infection, or local irritation can be the underlying cause for many secondary behavioral symptoms in patients with dementia. Just as with household pets or small children, a patient with dementia may not be able to express or describe the physical pain they are experiencing; thus it is up to astute clinicians and caregivers to identify and treat causes of pain that may be leading to neuropsychiatric symptoms, such as agitation and depression, in patients with dementia. If pain is contributing to behavioral symptoms, psychotropic medications may have little effect whereas alleviating the source of the pain may be quite effective. For instance, treatment with simple acetaminophen (paracetamol) can sometimes ameliorate agitation. Similarly, other modifiable sources of behavioral symptoms (e.g., boredom, excess stimulation, etc.) should be recognized and addressed.

SUMMARY

The most common dementia is Alzheimer disease (AD), and the leading theory for its etiology is the amyloid cascade hypothesis. Other dementias including vascular dementia, dementia with Lewy bodies, Parkinson's disease dementia, and frontotemporal dementia are also discussed as well, as are their differing pathologies, clinical presentations, and neuroimaging findings. New diagnostic criteria define three stages of AD: asymptomatic, mild cognitive impairment, and dementia. Major research efforts have recently pivoted away from attempting to find disease-modifying treatments that could halt or even reverse the course of this illness by interfering with Aβ accumulation in the brain because many such treatments have failed over the past 30 years. Leading treatments for AD today include symptomatic treatment of memory and cognition with the cholinesterase inhibitors, based upon the cholinergic hypothesis of amnesia, and memantine, an NMDA antagonist, based upon the glutamate hypothesis of cognitive decline. Novel treatments on the threshold of approval include the $5HT_{2A}$ antagonist pimavanserin for symptomatic treatment of dementia-related psychosis, and both brexpiprazole and dextromethorphan–bupropion for symptomatic treatment of agitation in AD.

13 Impulsivity, Compulsivity, and Addiction

What Are Impulsivity and Compulsivity? 538
Neurocircuitry and the Impulsive–Compulsive Disorders 539
The Dopamine Theory of Addiction: The Mesolimbic Dopamine Circuit as the Final Common Pathway of Reward 542
Substance Addictions 544
Stimulants 544
Nicotine 547
Alcohol 553
Sedative Hypnotics 556
Gamma-Hydroxybutyrate (GHB) 559
Opiates or Opioids? 559
Cannabis 563
Hallucinogens 567
Empathogens 569
Dissociatives 569
Abuse Your Way to Abstinence? 571
"Therapeutic" Dissociation, Hallucinations, and Empathy? 574
Behavioral Addictions 575
Binge Eating Disorder 575
Other Behavioral Addictions 575
Obsessive–Compulsive and Related Disorders 576
Impulse Control Disorders 577
Summary 578

Impulsivity and compulsivity are symptoms that cut across many psychiatric disorders. Some conditions with impulsivity as a prominent feature have already been discussed, including mania (Chapter 4); attention deficit hyperactivity disorder (ADHD; Chapter 11), and agitation in dementia (Chapter 12). Several other disorders in which impulsivity and/or compulsivity are core features are discussed in this chapter. Full clinical descriptions and formal criteria for how to diagnose the numerous known diagnostic entities discussed here should be obtained by consulting standard diagnostic and reference sources. Here we emphasize what is known or hypothesized about the brain circuits and neurotransmitters mediating impulsivity and compulsivity, and how engaging neurotransmitters at various nodes in impulsivity/compulsivity networks can result in successful psychopharmacological treatments.

WHAT ARE IMPULSIVITY AND COMPULSIVITY?

Impulsivity can be defined as a predisposition towards rapid, unplanned reactions to internal or external stimuli, with diminished regard for the negative consequences of these reactions. In contrast, *compulsivity* is defined as the performance of repetitive and dysfunctionally impairing behavior that has no adaptive function. Compulsive behavior is performed in a habitual or stereotypical fashion, either according to rigid rules or as a means of avoiding perceived negative consequences. These two symptom constructs can perhaps be best differentiated by *how* they both fail to control responses: impulsivity as the inability to stop *initiating* actions, and compulsivity as the inability to *terminate* ongoing actions. These constructs have thus been viewed historically as diametrically opposed, with impulsivity being associated with risk seeking and compulsivity with harm avoidance. Currently the emphasis is on the fact that both share different forms of cognitive inflexibility leading to a profound feeling of lack of control.

More precisely, *impulsivity* is action without forethought; the lack of reflection on the consequences of one's behavior; the inability to postpone reward with preference for immediate reward over more beneficial but delayed reward; a failure of motor inhibition, often choosing risky behavior; or (less scientifically) lacking the will power not to give in to temptations and provocative stimuli from the environment. On the other hand, *compulsivity* is action inappropriate to the situation but which nevertheless persists, and which often results in undesirable consequences. In fact, compulsions are characterized by the curious inability to adapt behavior after negative feedback.

Habits are a type of compulsion, and can be seen as responses triggered by environmental stimuli, regardless

of the current desirability of the consequences of that response. Whereas goal-directed behavior is mediated by knowledge of and desire for its consequences, habits are controlled by external stimuli through stimulus–response associations that are stamped into brain circuits through behavioral repetition and formed after considerable training, can be automatically triggered by stimuli, and are defined by their insensitivity to their outcomes. Given that goal-directed actions are relatively cognitively demanding, for daily routines, it can be adaptive to rely on habits that can be performed with minimal conscious awareness. However, habits can also represent severely maladaptive perseveration of behaviors as components of various impulsive–compulsive disorders (see Table 13-1).

Another way to look at addiction is as a habit much like the behavior of a Pavlovian dog! That is, drug seeking and drug taking behaviors can be viewed as *conditioned responses* to the *conditioned stimuli* of being around people or places or items associated with drugs, or having craving and withdrawal. When addicted, drug seeking and taking are automatic, thoughtless, conditioned responses that occur in an almost reflexive fashion to conditioned stimuli, just as Pavlov's dogs developed mouth-watering in response to a bell associated with food. When such stimulus–response conditioning runs amok in addiction, it does not perform an adaptive purpose of sparing cognitive efforts from doing routine tasks. Instead, the "habit" of drug addiction has become a perverse form of learning, almost as though one has learned how to have a psychiatric disorder!

NEUROCIRCUITRY AND THE IMPULSIVE–COMPULSIVE DISORDERS

Impulsivity and compulsivity are thought to be mediated by neuroanatomically and neurochemically distinct, but in many ways parallel, components of cortico-subcortical circuitry (Figures 13-1 and 13-2). When these networks are dysfunctional, they hypothetically result in "lack of control" of thoughts and behaviors. Simply put, impulsivity and compulsivity are both symptoms that result from the brain having a hard time saying "no."

Why can't impulses and compulsions be stopped in various psychiatric disorders? An over-simplified explanation was discussed in Chapter 12 and illustrated in Figures 12-43 and 12-44, showing either too much "bottom-up" limbic emotional drive or too little "top-down" cortical inhibition of these drives. In Alzheimer disease, for example, impulsivity resulting in agitation is thought to be due principally to neurodegeneration of top-down controls (see Chapter 12 and Figures 12-45B and 12-46B). In ADHD, impulsivity, especially motor impulsivity, is thought to be due to neurodevelopmentally delayed or absent top-down

Table 13-1 Impulsive–compulsive disorders

Substance addictions
Cannabis
Nicotine
Alcohol
Opioids
Stimulants
Hallucinogens
Empathogens
Dissociatives
Behavioral addictions
Binge eating disorder
Gambling disorder
Internet gaming disorder
Obsessive–compulsive related disorders
Obsessive–compulsive disorder
Body dysmorphic disorder
Trichotillomania
Skin picking
Hoarding
Shopping
Hypochondriasis
Somatization
Impulse control disorders
Agitation in Alzheimer disease
Motor and behavioral impulsivity in ADHD
Mood disorders
Provocative behaviors in mania
Disruptive mood dysregulation disorder
Pyromania
Kleptomania
Paraphilias
Hypersexual disorder
Autism spectrum disorders
Tourette syndrome and tic disorders
Stereotyped movement disorders
Borderline personality disorder
Self harm and parasuicidal behaviors
Conduct disorder
Antisocial personality disorder
Oppositional defiant disorder
Intermittent explosive disorder
Aggression and violence:
impulsive
psychotic
psychopathic

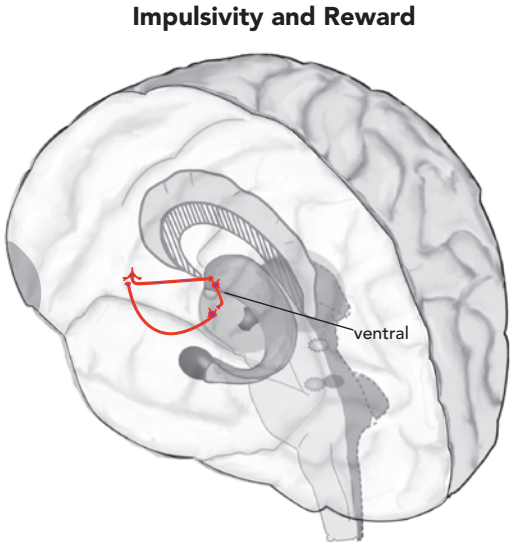


Figure 13-1 Circuitry of impulsivity and reward. The "bottom-up" circuit that drives impulsivity is a loop with projections from the ventral striatum to the thalamus, from the thalamus to the ventromedial prefrontal cortex (VMPFC) and the anterior cingulate cortex (ACC), and from the VMPFC/ACC back to the ventral striatum. This circuit is usually modulated "top-down" from the prefrontal cortex. If this top-down response inhibition system is inadequate or is overcome by activity from the ventral striatum, impulsive behaviors may result.

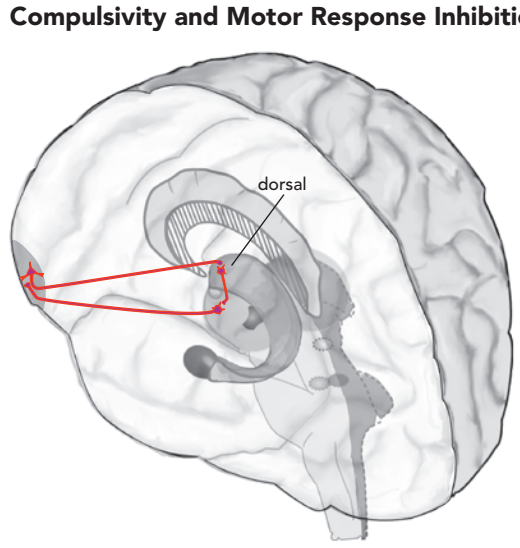


Figure 13-2 Circuitry of compulsivity and motor response inhibition. The "bottom-up" circuit that drives compulsivity is a loop with projections from the dorsal striatum to the thalamus, from the thalamus to the orbitofrontal cortex (OFC), and from the OFC back to the dorsal striatum. This habit circuit can be modulated "top-down" from the OFC. If this top-down response inhibition system is inadequate or is overcome by activity from the dorsal striatum, compulsive behaviors may result.

cortical controls (see Chapter 11 and Figures 11-17 through 11-21). In a wide variety of other disorders discussed below, the problem may lie anywhere within two parallel cortico-striatal circuits, namely at two striatal nodes (one impulsive and the other compulsive), which drive these behaviors, or at two corresponding prefrontal cortical nodes, which restrain them (Figures 13-1 and 13-2). Overlap between these two parallel networks exists such that a problem in the impulsive circuit can end up as a problem in the compulsive circuit and vice versa, leading to the concept of "impulsive–compulsive disorders," all of which have this symptom domain as one of their core features. Such psychiatric conditions incorporate a wide range of disorders, from obsessive–compulsive disorder (OCD) to addictions, and far beyond (Table 13-1). Although there are many other important symptom domains in these various conditions that distinguish one from another, all can be associated with disordered impulsivity and/or compulsivity, and this is the shared domain of their psychopathology that is discussed here.

Neuroanatomically, impulsivity is thus seen as regulated by an action–outcome ventrally dependent learning system (Figure 13-1) whereas compulsivity is hypothesized to be controlled by a habit system that is dorsal (Figure 13-2). That is, many behaviors start out as impulses mediated by the ventral loop, which reacts to reward and motivation (Figure 13-1). Over time, however, the locus of control for these behaviors migrates dorsally (Figure 13-2) due to a cascade of neuroadaptations and neuroplasticity that engage a dorsal "habit system" by means of which an impulsive act eventually becomes compulsive (Figures 13-2 and 13-3). This naturally occurring process can have adaptive value in everyday life, freeing the brain to spend its efforts on novel, cognitively demanding activities. However, when it runs hypothetically amok in a myriad of psychiatric disorders (Table 13-1), the goal is to stop or reverse this spiral of information from the impulsive neuronal loop to the compulsive "habit" loop. Unfortunately, there are relatively few highly effective treatments for impulsive–compulsive disorders today. We have discussed effective treatments for ADHD in Chapter 11 and for agitation in Alzheimer disease in Chapter 12. Here we review the hypothetically shared neurobiology of many other impulsive–compulsive disorders and discuss what treatments are available for some of these conditions.

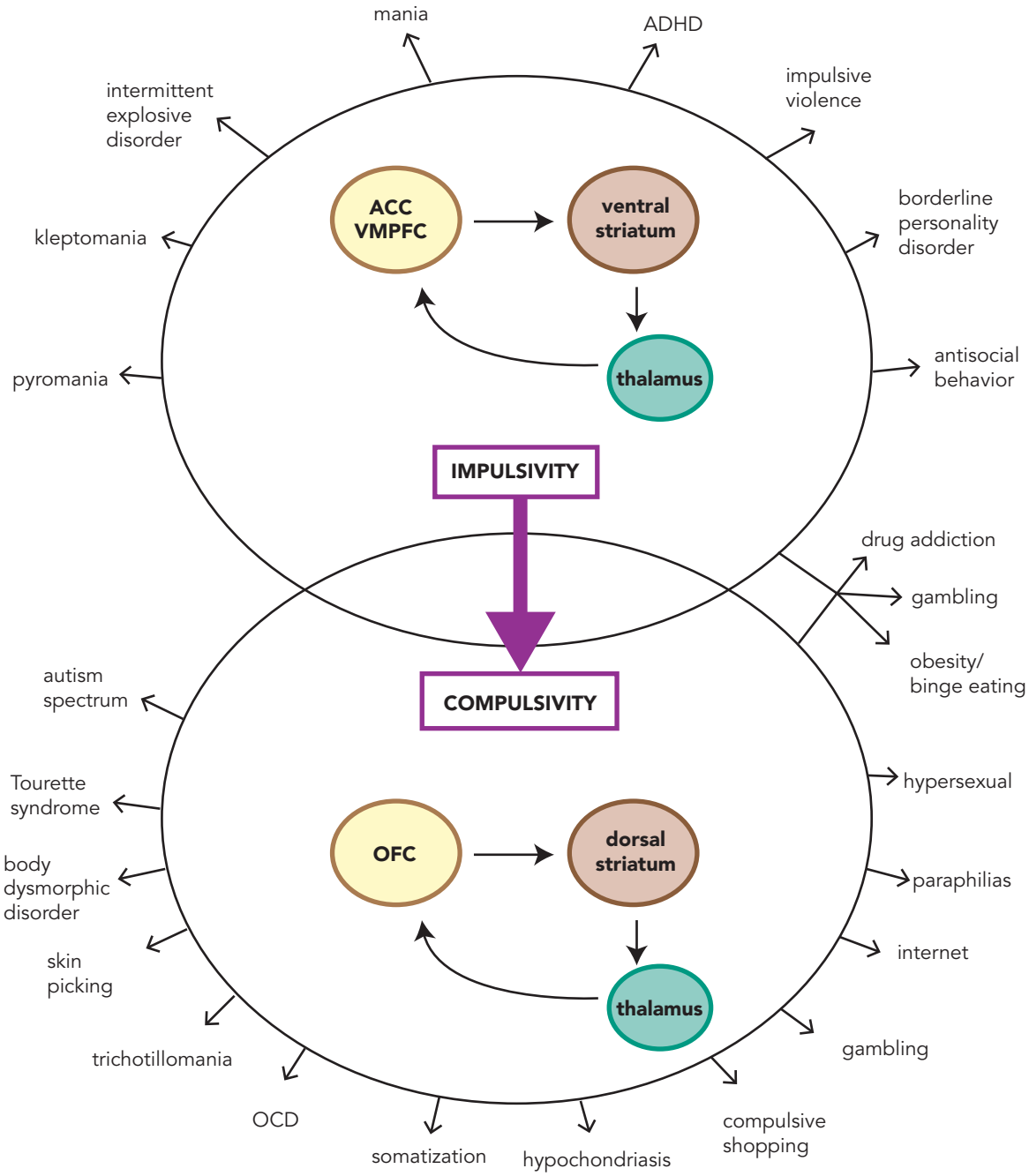


Figure 13-3 Impulsive–compulsive disorder construct. Impulsivity and compulsivity are seen in a wide variety of psychiatric disorders. Impulsivity can be thought of as the inability to stop the initiation of actions and involves a brain circuit centered on the ventral striatum and linked to the thalamus, to the ventromedial prefrontal cortex (VMPFC), and to the anterior cingulate cortex (ACC). Compulsivity can be thought of as the inability to terminate ongoing actions and hypothetically involves a brain circuit centered on the dorsal striatum and linked to the thalamus and orbitofrontal cortex (OFC). Impulsive acts such as drug use, gambling, and over-eating can eventually become compulsive due to neuroplastic changes that engage the dorsal habit system and theoretically cause impulses in the ventral loop to migrate to the dorsal loop.

The Dopamine Theory of Addiction: The Mesolimbic Dopamine Circuit as the Final Common Pathway of Reward

A leading theory of addiction for over 40 years has been the dopamine theory, proposing that the final common pathway of reinforcement and reward in the brain for anything pleasurable is the mesolimbic dopamine pathway (Figure 13-4). This theory is a bit of an oversimplification and perhaps most applicable to drugs that cause the greatest effects upon dopamine release, especially stimulants and nicotine, but less so for marijuana and opioids. The mesolimbic dopamine pathway is familiar to readers as it is the same brain circuit discussed in Chapter 4 on psychosis and hypothesized to be overly active in psychosis, mediating the positive symptoms of schizophrenia and also motivation and reward (see Figures 4-14 through 4-16). Some even consider the mesolimbic dopamine pathway to be the "pathway of hedonic pleasure" of the brain and dopamine to be the "neurotransmitter of hedonic pleasure." According to this notion, there are many natural ways to trigger your mesolimbic dopamine neurons to release dopamine, ranging from intellectual accomplishments, to athletic victories, to enjoying a good symphony, to experiencing an orgasm. These are sometimes called "natural highs" (Figure 13-4).

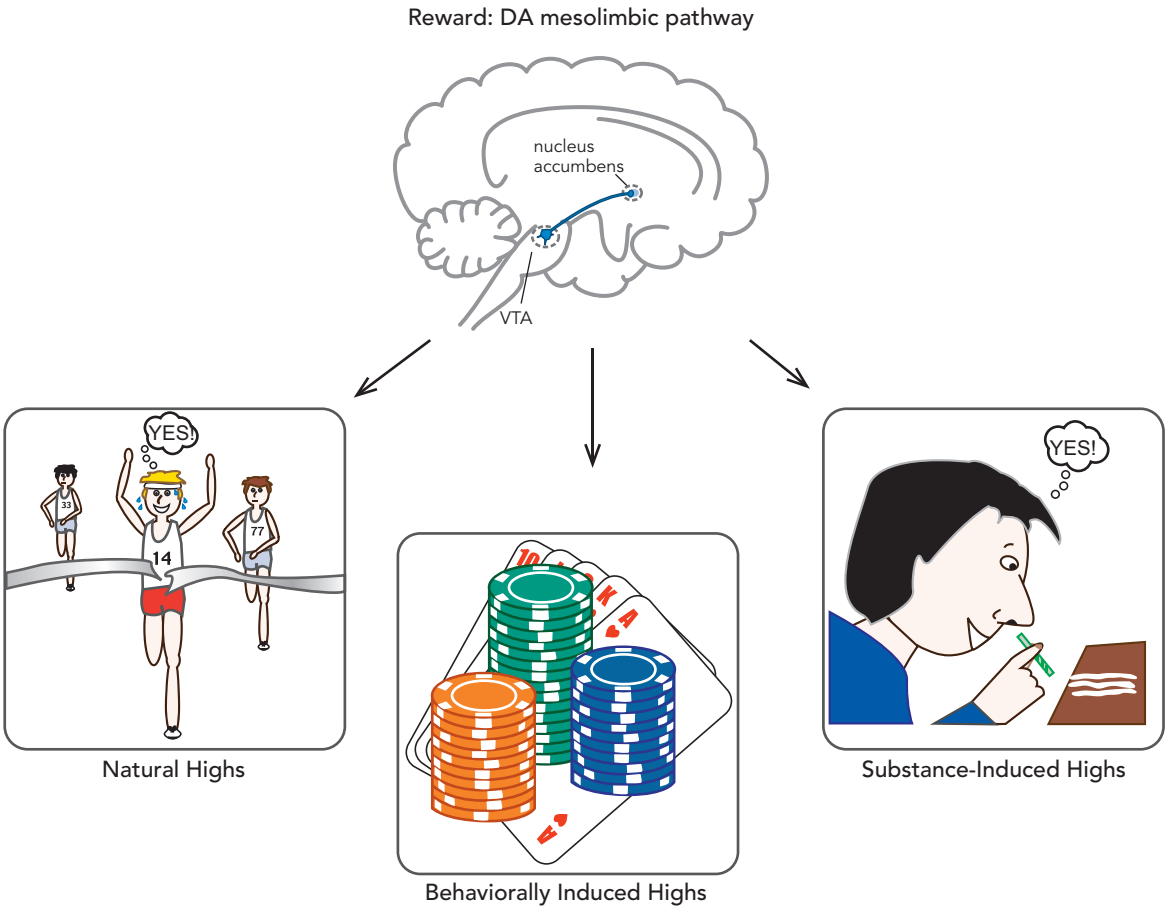


Figure 13-4 Dopamine is central to reward. Dopamine (DA), and specifically the mesolimbic pathway from the ventral tegmental area (VTA) to the nucleus accumbens, has long been recognized as a major player in the regulation of reinforcement and reward. Naturally rewarding activities, such as achieving major accomplishments, can cause fast and robust increases in DA in the mesolimbic pathway. Drugs of abuse also cause DA release in the mesolimbic pathway, and can often increase DA in a manner that is more explosive and pleasurable than that which occurs naturally.

The inputs to the mesolimbic pathway that mediate these natural highs include a most incredible "pharmacy" of naturally occurring substances, ranging from the brain's own morphine/heroin (endorphins), to the brain's own marijuana (anandamide), to the brain's own nicotine (acetylcholine), to the brain's own cocaine and amphetamine (dopamine itself) (Figure 13-5). Thus, the idea formed that all drugs of abuse – as well as many maladaptive behaviors such as gambling, binge eating, using the internet – have a final common pathway of causing pleasure. This happens by provoking dopamine release in the mesolimbic pathway in a manner often

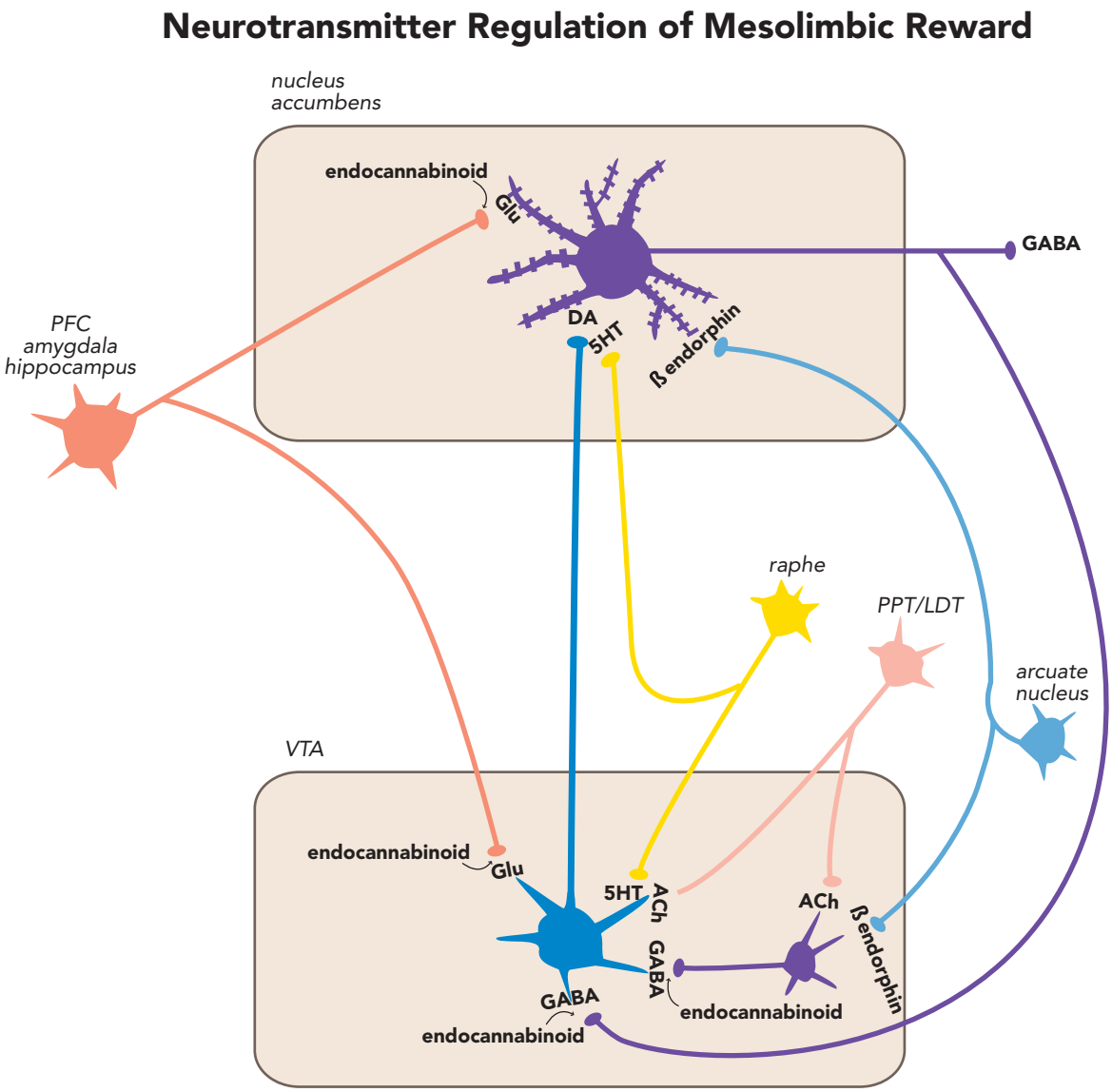


Figure 13-5 Neurotransmitter regulation of mesolimbic reward. The mesolimbic dopamine pathway is modulated by many naturally occurring substances in the brain in order to deliver normal reinforcement to adaptive behaviors (such as eating, drinking, sex) and thus to produce "natural highs," such as feelings of joy or accomplishment. These neurotransmitter inputs to the reward system include the brain's own morphine/heroin (endorphins), the brain's own cannabis/marijuana (endocannabinoids such as anandamide), the brain's own nicotine (acetylcholine [ACh]), and the brain's own cocaine/amphetamine (dopamine [DA] itself), among others. The numerous psychotropic drugs of abuse that occur in nature bypass the brain's own neurotransmitters and directly stimulate the brain's receptors in the reward system, causing dopamine release and a consequent "artificial high." Thus, alcohol, opioids, stimulants, marijuana, benzodiazepines, sedative hypnotics, hallucinogens, and nicotine all affect this mesolimbic dopaminergic system.

more explosive and pleasurable than that which occurs naturally. In this formulation, drugs bypass the brain's own neurotransmitters and directly stimulate the brain's own receptors for these same drugs, causing dopamine to be released. Since the brain already uses neurotransmitters that resemble drugs of abuse, it is not necessary to earn your reward naturally since you can get a much more intense reward in the short run and upon demand from a drug of abuse than you can from a natural high with the brain's natural system. However, unlike a natural high, a drug-induced reward can start the diabolical cascade of neuroadaptation into habit formation.

SUBSTANCE ADDICTIONS

Addiction is a horrible disease. What starts out as fun and increased dopamine release in the ventral striatum with enhanced anterior cingulate cortex (ACC) activity and reward ends up with the locus of control in the habit circuit as a mindless, automatic, and powerful compulsive drive to obtain drugs that is basically irresistible. Since it is not presently known what treatment mechanisms might suppress the wicked habit circuit that has commandeered behavioral control in the addict, treatments for addiction are few and far between and often not very effective. What is needed are treatments capable of wresting control back from the habit circuit and returning it to voluntary control, perhaps by neuroplasticity reverse-migrating control from dorsal back to ventral, where things began before addiction was present.

Once addicted, the brain is no longer rewarded principally by the drug itself, but as well by *anticipation* of the drug and its reward. This generates compulsive drug-seeking behaviors which are themselves rewarding. That is, some studies suggest that dopamine neurons terminating in the ventral striatum (Figure 13-1) actually stop responding to the primary reinforcer (i.e., taking the drug, eating the food, doing the gambling) and instead dopamine neurons terminating in the dorsal striatum (Figure 13-2) begin to respond to the *conditioned stimuli* (i.e., handling the heroin syringe, feeling the crack pipe in your hand, entering the casino) before the drug is even taken! Since drug seeking and drug taking become the main motivational drives when addicted, this explains why the addicted subject is aroused and motivated when seeking to procure drugs, but is withdrawn and apathetic when exposed to non-drug-related activities. When drug abuse reaches this stage of compulsivity, it is clearly a maladaptive perseveration of behavior – a habit and a Pavlovian conditioned response, and not any longer being simply naughty or giving in to temptation.

Stimulants

Stimulants as therapeutic agents have been discussed in Chapter 11 covering the treatment of ADHD. For optimized treatment of ADHD, stimulant dosing is carefully controlled to deliver constant drug levels within a defined therapeutic range (see Chapter 11 and Figure 11-34). Theoretically, this amplifies tonic release of dopamine (Figure 11-33) to optimize pro-cognitive ADHD therapeutic effects. On the other hand, these very same stimulants can also be used as drugs of abuse by changing the dose and the route of administration to amplify phasic dopamine stimulation and thus their reinforcing effects (Figure 11-35). Although *therapeutic* actions of stimulants are thought to be directed at the prefrontal cortex to enhance both norepinephrine and dopamine neurotransmission there, at moderate levels of dopamine transporter (DAT) and norepinephrine transporter (NET) occupancy (Figure 11-26), the *reinforcing effects* and *abuse* of stimulants occur when DATs in the mesolimbic reward circuit are suddenly blasted and massively blocked (Figure 13-6).

The speed with which a stimulant enters the brain dictates the degree of the subjective "high" (Figure 13-7). This was also discussed in Chapter 11 as one of the properties of the "mysterious DAT." This sensitivity of the DAT to the way in which it is engaged likely explains why stimulants when abused are often not ingested orally but instead are smoked, inhaled, snorted, or injected so they can enter the brain in a sudden explosive manner, to maximize their reinforcing nature. Oral absorption reduces reinforcing properties of stimulants because speed of entry to the brain is considerably slowed by the process of gastrointestinal absorption. Cocaine is not even active orally so users have learned over the years to take it intranasally so that drug rapidly enters the brain directly, bypassing the liver, and thus can have a more rapid onset than even with intravenous administration. The most rapid and robust way to deliver drugs to the brain is to smoke those that are compatible with this route of administration, as this avoids first-pass metabolism through the liver and is somewhat akin to giving the drug by intra-arterial/intra-carotid bolus via immediate absorption across the massive surface area of the lung. The faster the drug's entry into brain, the stronger are its reinforcing effects (Figure 13-7), probably because this

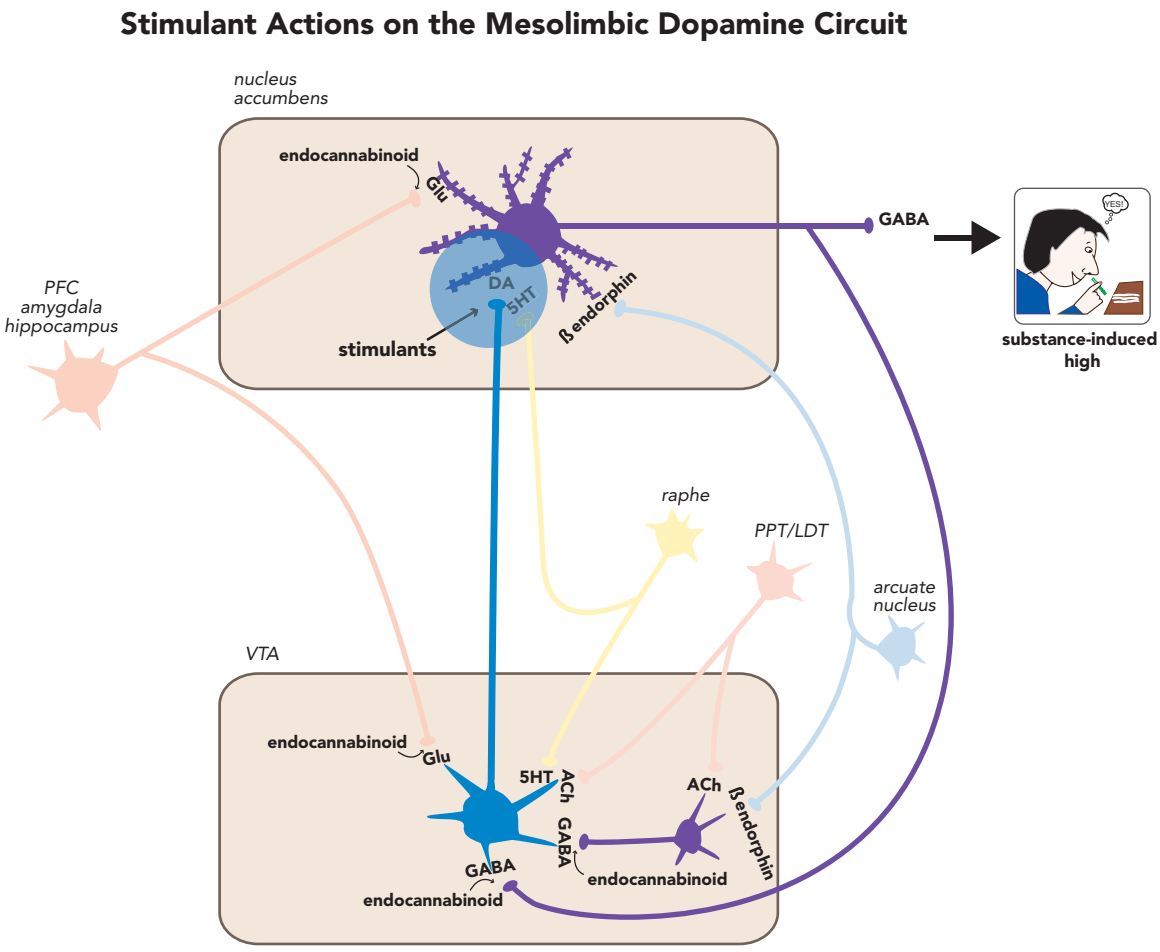


Figure 13-6 **Stimulant actions on the mesolimbic dopamine circuit.** The reinforcing effects and abuse potential of stimulants occurs when dopamine transporters (DATs) in the mesolimbic reward circuit are blocked, causing a phasic increase in dopamine (DA) in the nucleus accumbens.

form of drug delivery triggers phasic dopamine firing, the type associated with reward (see Chapter 11 for discussion and Figure 11-35).

Amphetamine, methamphetamine, and cocaine are all inhibitors of the DAT and the NET. Cocaine also inhibits the serotonin transporter (SERT) and is also a local anesthetic, which Freud himself exploited to help dull the pain of his tongue cancer. He may have also exploited the second property of the drug, which is to produce euphoria, reduce fatigue, and create a sense of mental acuity due to inhibition of dopamine reuptake at the DAT, at least for a while, until drug-induced reward is replaced by drug-induced compulsivity.

High doses of stimulants can cause tremor, emotional lability, restlessness, irritability, panic, and repetitive, stereotyped behavior. At even higher repetitive doses, stimulants can induce paranoia and hallucinations resembling schizophrenia (see Chapter 4 and Figures 4-14 through 4-16) as well as hypertension, tachycardia, ventricular irritability, hyperthermia, and respiratory depression. In overdose, stimulants can cause acute heart failure, stroke, and seizures. Over time, stimulant abuse can be progressive (Figure 13-8). Initial doses of stimulants that cause pleasurable phasic dopamine firing (Figure 13-8A) give leave to *reward conditioning* and addiction with chronic use, causing craving between stimulant doses and residual tonic dopamine firing with a lack of pleasurable phasic dopamine firing (Figure 13-8B). Now addicted, higher and higher doses of stimulants are needed in order to achieve the pleasurable highs of

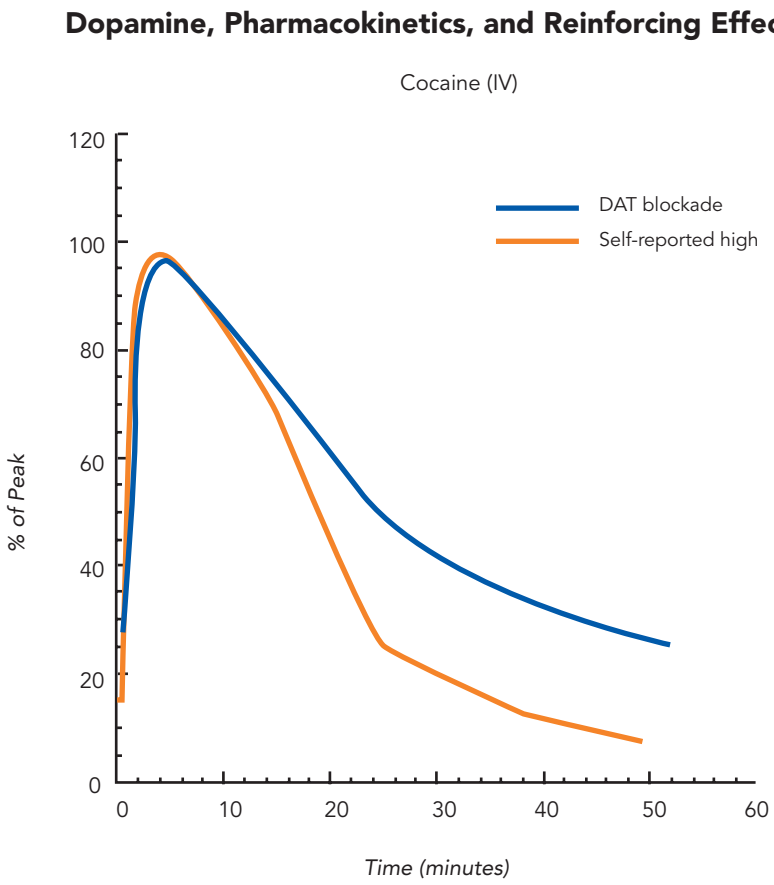


Figure 13-7 Dopamine, pharmacokinetics, and reinforcing effects. Acute drug use causes dopamine release in the striatum. However, the reinforcing effects of the drug are largely determined not only by the presence of dopamine, but also by the rate at which dopamine increases in the brain, which in turn is dictated by the speed at which the drug enters and leaves the brain. This is likely because abrupt and large increases in dopamine (such as those caused by drugs of abuse) mimic the phasic dopamine firing associated with conveying information about reward and saliency. As shown here, the self-reported high associated with intravenous (IV) cocaine use correlates with both the rate and extent of dopamine transporter (DAT) blockade. The rate of drug uptake is subject to the route of administration, with intravenous administration and inhalation producing the fastest drug uptake, followed by snorting. In addition, different drugs of abuse have different "reward values" (i.e., different rates at which they increase dopamine) based on their individual mechanisms of action.

phasic dopamine firing (Figure 13-8C). Unfortunately, the higher the high, the lower the low, and between stimulant doses, the individual experiences not only the absence of a high, but also withdrawal symptoms such as sleepiness and anhedonia (Figure 13-8D). The effort to combat withdrawal coupled with habit formation leads to compulsive use and ultimately dangerous behavior in order to secure drug supplies (Figure 13-8E). Finally, there may be enduring if not irreversible changes in dopamine neurons, including long-lasting depletions of dopamine levels and axonal degeneration, a state that clinically and pathologically is appropriately called "burn-out" (Figure 13-8F).

Atypical Stimulants

"Bath salts" are a form of stimulant. Their name derives from efforts to disguise these abusable stimulants as common Epsom salts used in baths, with similar packaging as white or colorful powders, granules, or crystal forms but quite different chemically! Bath salts are often labelled "not for human consumption" in a further attempt to be mistaken for Epsom salts and thus circumventing drug prohibition laws.

Bath salts, however, are not for bathing, but are synthetic stimulants that commonly include the active ingredient methylenedioxypyrovalerone (MDPV) and may also contain mephedrone or methylone. They are

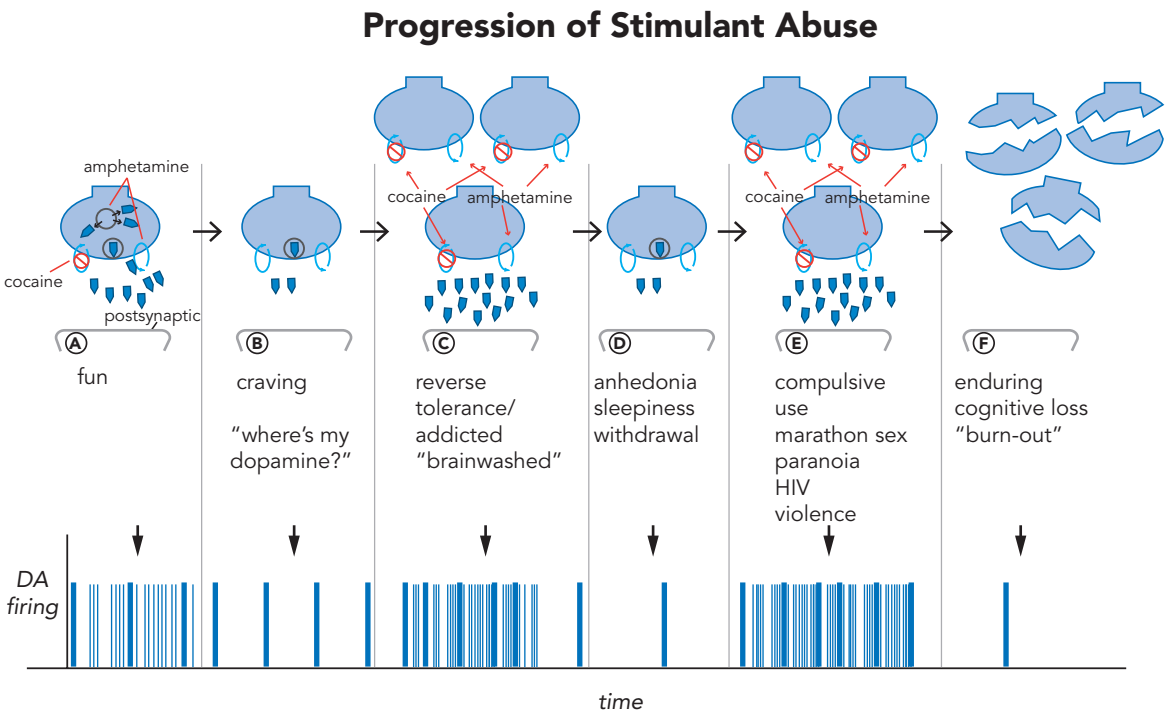


Figure 13-8 Progression of stimulant abuse. (A) Initial doses of stimulants such as methamphetamine and cocaine cause pleasurable phasic dopamine firing. (B) With chronic use, reward conditioning causes craving between stimulant doses and residual tonic dopamine firing with a lack of pleasurable phasic dopamine firing. (C) In this addicted state, higher and higher doses of stimulants are needed in order to achieve the pleasurable highs of phasic dopamine firing. (D) Unfortunately, the higher the high, the lower the low, and between stimulant doses, the individual experiences not only the absence of a high, but also withdrawal symptoms such as sleepiness and anhedonia. (E) The effort to combat withdrawal can lead to compulsive use and impulsive, dangerous behavior in order to secure the stimulant. (F) Finally, there may be enduring if not irreversible changes in dopamine neurons, including long-lasting depletions of dopamine levels and axonal degeneration, a state that clinically and pathologically is appropriately called "burn-out."

also called "plant food" and like other stimulants can have reinforcing effects but also cause agitation, paranoia, hallucinations, suicidality, and chest pain.

Some would consider *inhalants* as atypical types of stimulants since they are thought to be direct releasers of dopamine in the nucleus accumbens. Inhaling fumes – called "huffing" – of substances such as toluene found in paint thinner, felt-tip markers, glue, various aerosol sprays, and even freon found in air conditioners, can cause a feeling similar to alcohol intoxication, with dizziness, lightheadedness, and disinhibition; it can also cause impaired judgment and possibly hallucinations. Long-term huffing can cause depression, weight loss, and brain damage. Huffing can also be dangerous in the short term, as it can cause sudden death due to cardiac arrest, aspiration, or suffocation. Freon in particular can cause these effects and can also freeze the lungs, making it extremely dangerous. Substances that are huffed do not show up on drug tests.

Treatment of Stimulant Addiction

Unfortunately, there are currently no approved drug treatments for stimulant addicts, as many dopamine-linked and serotonin-linked therapeutics have failed. In the future, there may be a cocaine vaccine that removes the drug before it reaches the brain so there are no more reinforcing effects that accompany drug ingestion.

Nicotine

How common is smoking in clinical psychopharmacology practices? Some estimates are that more than half of all cigarettes are consumed by patients with a concurrent psychiatric disorder, and that smoking is the most common comorbidity among seriously mentally ill patients. Other estimates are that about 16–20% of the general population (in the US) smoke, about 25% of people who regularly see general physicians smoke, but that 40–50% of patients in a psychopharmacology practice smoke, including 60–85% of patients

with ADHD, schizophrenia, and bipolar disorder. Unfortunately, histories of current smoking are often not carefully taken or recorded as one of the diagnoses for smokers in mental health practices and only about 10% of smokers report being offered treatment pro-actively by psychopharmacologists and other clinicians even though somewhat effective treatments are available.

Nicotine acts directly upon nicotinic cholinergic receptors in mesolimbic reward circuits to release dopamine (Figure 13-9). Cholinergic neurons and the neurotransmitter acetylcholine (ACh) are discussed in Chapter 12 and illustrated in Figures 12-24 through 12-32. Nicotinic receptors are specifically illustrated in Figure 12-28. There are several subtypes of nicotinic receptors present in brain. The α_7 nicotinic receptor on postsynaptic prefrontal cortex neurons may be linked to the pro-cognitive and mentally alerting actions of nicotine, but not to addictive actions. It is the $\alpha_4\beta_2$ subtype discussed here and illustrated in Figure 13-9 that is thought to be most relevant to smoking and nicotine addiction. That is, nicotine's actions at $\alpha_4\beta_2$ nicotinic postsynaptic receptors directly on dopamine neurons in the ventral tegmental area (VTA) are those that are theoretically linked to addiction (Figure 13-9). Nicotine also indirectly activates dopamine release from the VTA by activating nicotinic presynaptic receptors on glutamate neurons, causing glutamate release, which in turn causes dopamine release (Figure 13-9). Nicotine also appears to desensitize $\alpha_4\beta_2$ postsynaptic receptors on inhibitory GABAergic interneurons in the VTA, indirectly leading to dopamine release in the nucleus accumbens by disinhibiting dopaminergic mesolimbic neurons (Figure 13-9).

The $\alpha_4\beta_2$ nicotinic receptors adapt to the chronic intermittent pulsatile delivery of nicotine in a way that leads to addiction (Figure 13-10). Initially these receptors in the resting state are opened by delivery of nicotine, which in turns leads to dopamine release and reinforcement, pleasure, and reward (Figure 13-10A). By the time the cigarette is finished, these receptors become desensitized, so that they cannot function temporarily, and thus cannot react either to acetylcholine or nicotine (Figure 13-10A). In terms of obtaining any further reward, you might as well stop smoking at this point. An interesting question to ask is: how long does it take for the nicotinic receptors to desensitize? The answer seems to be: about as long as it takes to inhale all the puffs of a standard cigarette and burn it down to a butt. Thus, it is probably not an accident that cigarettes are the length that they are. Shorter does not maximize the pleasure. Longer is a waste since by then the receptors are all desensitized anyway (Figure 13-10A).

The problem for the smoker is that when the receptors resensitize to their resting state, this initiates craving and withdrawal due to the lack of release of further dopamine (Figure 13-10A). Another interesting question is: how long does it take to resensitize nicotinic receptors? The answer seems to be: about the length of time that smokers take between cigarettes. For the average one-pack-per-day smoker, awake for 16 hours, that would be about 45 minutes, possibly explaining why there are 20 cigarettes in a pack (i.e., enough for an average smoker to keep his or her nicotinic receptors completely desensitized all day long).

Putting nicotinic receptors out of business by desensitizing them causes neurons to attempt to overcome this lack of functioning receptors by upregulating the number of receptors (Figure 13-10B). That, however, is futile, since nicotine just desensitizes all of them the next time a cigarette is smoked (Figure 13-10C). Furthermore, this upregulation is self-defeating because it serves to amplify the craving that occurs when the extra receptors are resensitizing to their resting state (Figure 13-10C).

From a receptor point of view, at first the goal of smoking is to desensitize all nicotinic $\alpha_4\beta_2$ receptors and get the maximum dopamine release. Eventually, however, the goal is mostly to prevent craving. Positron emission tomography (PET) scans of $\alpha_4\beta_2$ nicotinic receptors in human smokers confirm that nicotinic receptors are exposed to just about enough nicotine for just about long enough from each cigarette to accomplish this. Craving seems to be initiated at the first sign of nicotinic receptor resensitization. Thus, the bad thing about receptor resensitization is craving. The good thing from an addicted smoker's point of view is that as the receptors resensitize, they are available to release more dopamine and cause pleasure or suppress craving and withdrawal again.

Treatment of Nicotine Addiction

Treating nicotine dependence is not easy. There is evidence that nicotine addiction begins with the first cigarette, with the first dose showing signs of lasting a month in experimental animals (e.g., activation of the anterior cingulate cortex for this long after a single dose). Craving begins within a month of repeated administration. Perhaps even more troublesome is the finding that the "diabolical learning" of dorsal to ventral

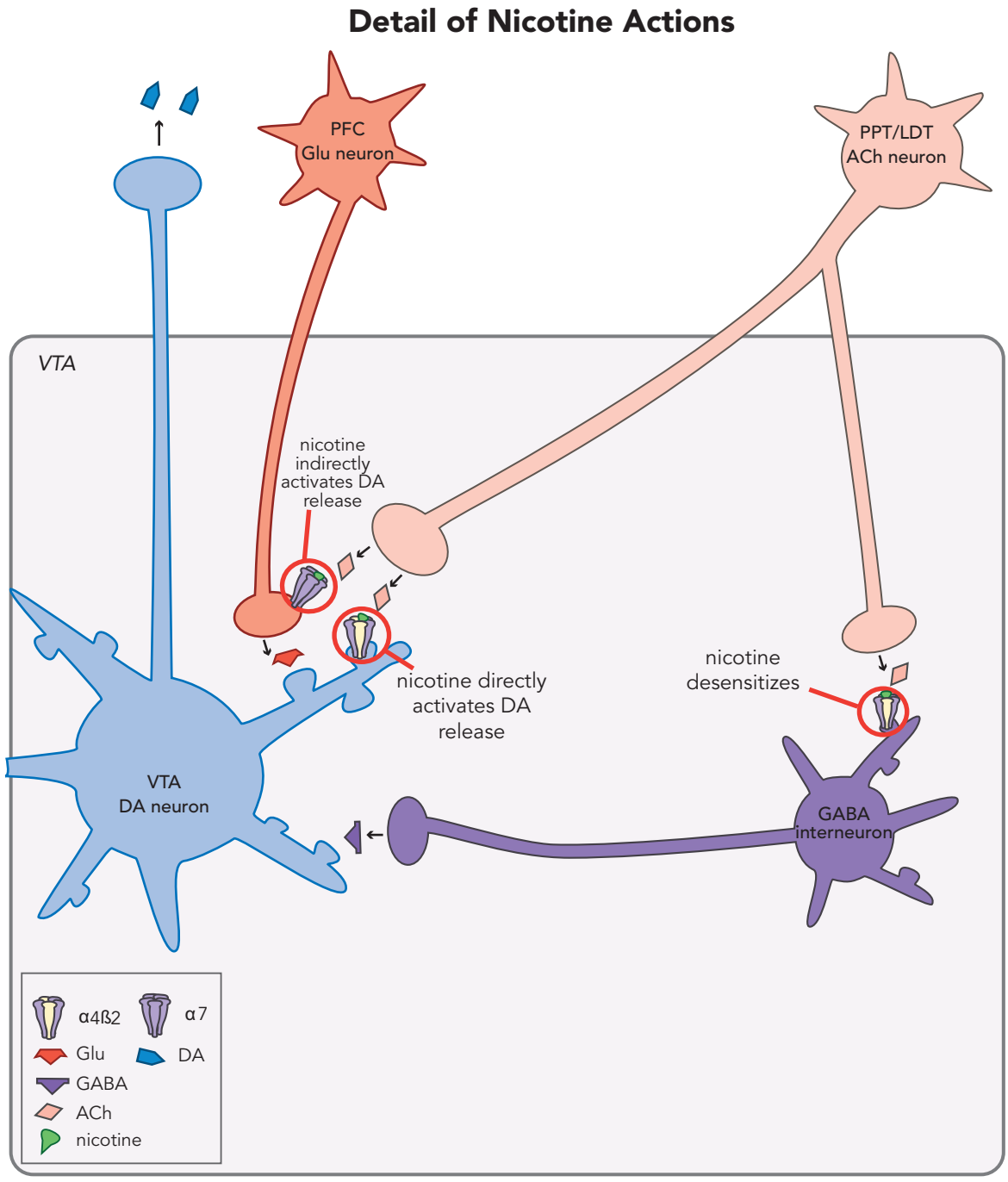


Figure 13-9 **Actions of nicotine.** Nicotine directly causes dopamine (DA) release in the nucleus accumbens by binding to $\alpha_4\beta_2$ nicotinic postsynaptic receptors on dopamine neurons in the ventral tegmental area (VTA). In addition, nicotine binds to α_7 nicotinic presynaptic receptors on glutamate (Glu) neurons in the VTA, stimulating glutamate release that in turn leads to dopamine release in the nucleus accumbens. Nicotine also seems to desensitize $\alpha_4\beta_2$ postsynaptic receptors on GABA interneurons in the VTA; the reduction of GABA neurotransmission disinhibits mesolimbic dopamine neurons and thus is a third mechanism for enhancing dopamine release in the nucleus accumbens.

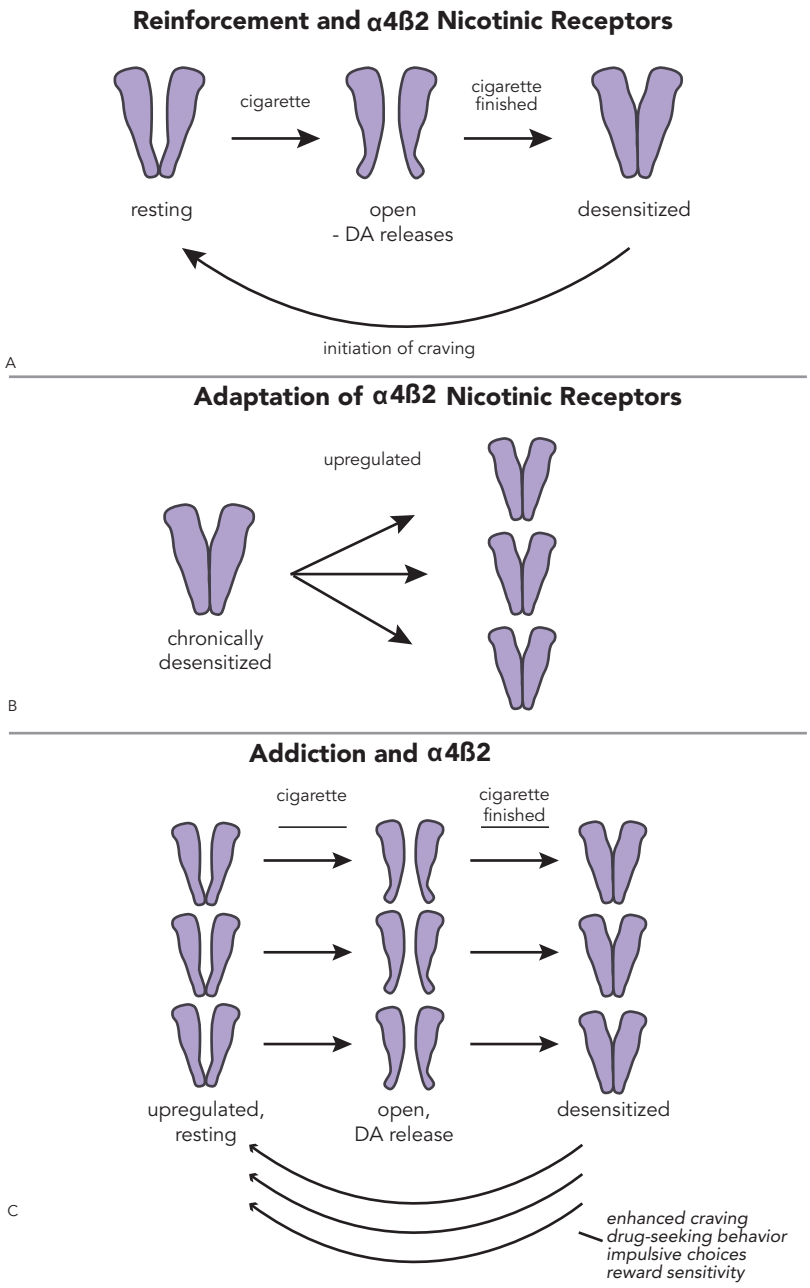


Figure 13-10 Reinforcement and $\alpha_4\beta_2$ nicotinic receptors. (A) In the resting state $\alpha_4\beta_2$ nicotinic receptors are closed (left). Nicotine administration, as by smoking a cigarette, causes the receptor to open, which in turn leads to dopamine release (middle). Long-term stimulation of these receptors leads to their desensitization, such that they temporarily can no longer react to nicotine (or to acetylcholine); this occurs in approximately the same length of time it takes to finish a single cigarette (right). As the receptors resensitize (return to resting state), they initiate craving and withdrawal due to the lack of release of further dopamine. (B) With chronic desensitization, $\alpha_4\beta_2$ receptors upregulate to compensate. (C) If one continues smoking, however, the repeated administration of nicotine continues to lead to desensitization of all of these $\alpha_4\beta_2$ receptors and thus the upregulation does no good. In fact, the upregulation can lead to amplified craving as the extra receptors resensitize to their resting state.

migration of control from impulsive to compulsive circuits may be very, very long-lasting once exposure to nicotine is stopped. Some evidence even suggests that these changes last a lifetime, with a form of "molecular memory" to nicotine, even in long-term abstinent former smokers. One of the first successful agents proven to be effective for treating nicotine addiction is nicotine itself, but in a route of administration other than smoking: gums, lozenges, nasal sprays, inhalers, and transdermal patches. Delivering nicotine by these other routes does not attain the high levels nor the pulsatile blasts that are delivered to the brain by smoking, so they are not very reinforcing, just as discussed for delivery of stimulants above and illustrated in Figure 13-7. However, these alternative forms of nicotine delivery can help to reduce craving due to a steady amount of nicotine that is delivered and presumably desensitizing an important number of resensitizing and craving nicotinic receptors.

Another treatment for nicotine dependence is varenicline, a selective $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist (Figures 13-11 and 13-12). Figure 13-11 contrasts the effects of nicotinic partial agonists (NPAs) with nicotinic full agonists and with nicotinic antagonists on the cation channel associated with nicotinic cholinergic receptors. Nicotinic full agonists include acetylcholine, which is very short-acting, and nicotine, which is very long-acting. They open the channel fully and frequently (Figure 13-11, left). By contrast, nicotinic antagonists stabilize the channel in the closed state, but do not desensitize these receptors (Figure 13-11, right). NPAs stabilize nicotinic receptors in an intermediate state that is not desensitized and where the channel opens less frequently than with a full agonist, but more frequently than with an antagonist (Figure 13-11, middle).

How addicting is tobacco and how well do NPAs work to achieve cessation of smoking? About two-thirds of smokers want to quit, one-third try, but only 2–3% succeed long term. Of all the substances of abuse, some surveys show that tobacco has the highest probability of making you dependent when you have tried a substance at least once. It could be argued, therefore, that nicotine might be the most addicting substance known. The good news is that the NPA varenicline triples or quadruples the 1-month, 6-month, and 1-year quit rates compared to placebo; the bad news is that this means only about 10% of smokers who have taken varenicline are still abstinent a year later. Many of these patients are prescribed varenicline for only 12 weeks, which might be far too short a period of time for maximal effectiveness.

Another approach to the treatment of smoking cessation is to try to reduce the craving that occurs during abstinence by boosting dopamine with the norepinephrine–dopamine reuptake inhibitor (NDRI) bupropion (see Chapter 7 and Figures 7-34 through 7-36). The idea is to give back some of the dopamine downstream to the craving postsynaptic D_2 receptors in the nucleus accumbens while they are readjusting to the lack of getting their dopamine "fix" from the recent withdrawal of nicotine (Figure 13-13). Thus, while smoking, dopamine is happily released in the nucleus accumbens because of the actions of nicotine on $\alpha_4\beta_2$

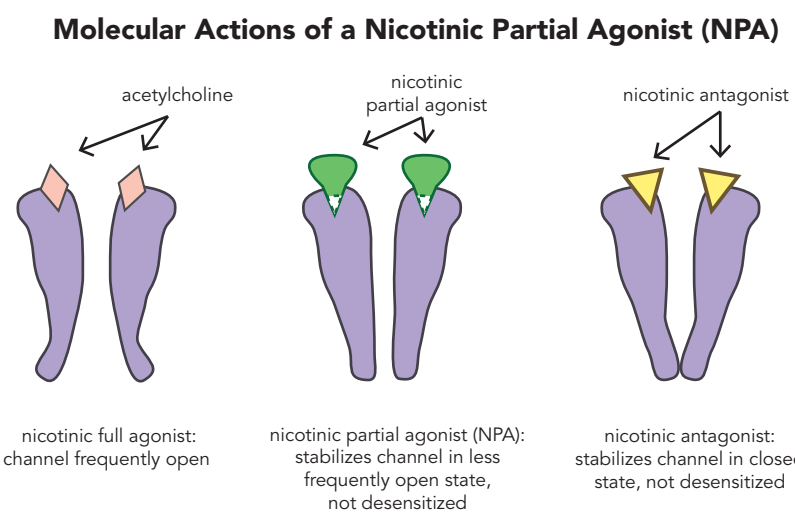


Figure 13-11 Molecular actions of a nicotinic partial agonist (NPA). Full agonists at $\alpha_4\beta_2$ receptors, such as acetylcholine and nicotine, cause the channels to open frequently (left). In contrast, antagonists at these receptors stabilize them in a closed state, such that they do not become desensitized (right). Nicotinic partial agonists (NPAs) stabilize the channels in an intermediate state, causing them to open less frequently than a full agonist but more frequently than an antagonist (middle).

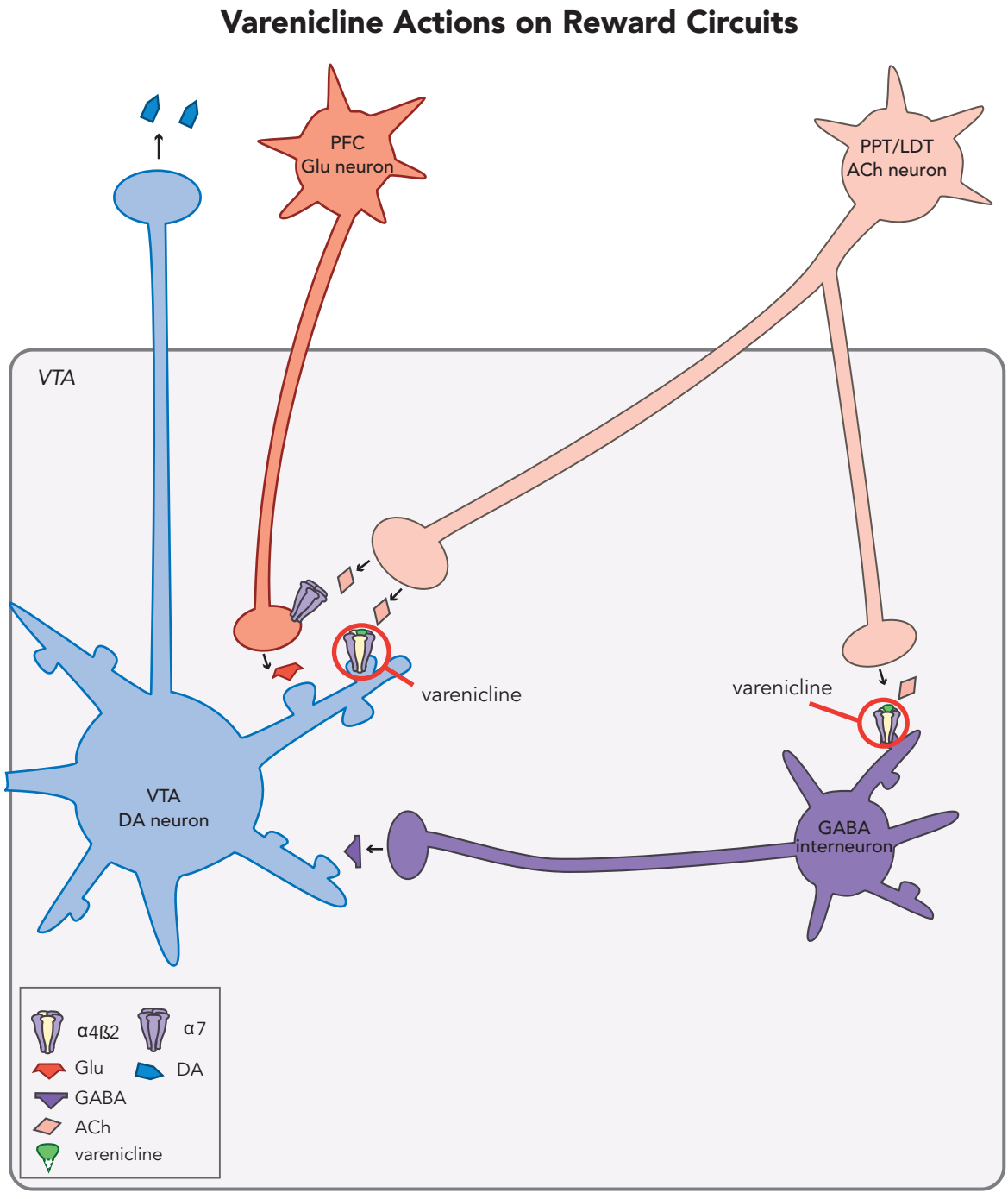


Figure 13-12 **Varenicline actions on reward circuits.** Varenicline is a nicotinic partial agonist (NPA) selective for the $\alpha_4\beta_2$ receptor subtype. When varenicline binds to $\alpha_4\beta_2$ nicotinic receptors – located on dopamine (DA) neurons, glutamate (Glu) neurons, and GABA interneurons in the ventral tegmental area (VTA) – it stabilizes the channels in an intermediate state, with less frequent opening than would occur if nicotine were bound, but more frequent than if a nicotinic antagonist were bound. Thus, it can reduce the dopaminergic reward that would occur if a patient did smoke (by competing with nicotine) but also reduce withdrawal symptoms by stimulating at least some neurotransmission.

receptors on the VTA dopamine neuron (shown in Figure 13-13A). During smoking cessation, resensitized nicotinic receptors no longer receiving nicotine are craving due to an absence of dopamine release in the nucleus accumbens (where is my dopamine?) (Figure 13-13B). When the NDRI bupropion is administered, theoretically a bit of dopamine is now released in the nucleus accumbens, making the craving less but usually not eliminating it (Figure 13-13C). How effective is bupropion in smoking cessation? Quit rates for bupropion are about half that of the NPA varenicline. Quit rates for nicotine in alternative routes of administration such as transdermal patches are similar to those of bupropion. Novel approaches to treating nicotine addiction include the investigation of nicotine vaccines and other direct-acting nicotinic cholinergic agents.

Alcohol

The famous artist Vincent van Gogh reportedly drank ruinously, some speculating that he self-medicated his bipolar disorder this way, a notion reinforced by his explanation, "If the storm within gets too loud, I take a glass too much to stun myself." Alcohol may stun but it does not treat psychiatric disorders adaptively long term. Unfortunately, many alcoholics who have comorbid psychiatric disorders continue to self-medicate with alcohol rather than seeking treatment with a more appropriate psychopharmacological agent. In addition to frequent comorbidity with psychiatric disorders, it is estimated that 85% of alcoholics also smoke. Many alcoholics abuse additional drugs as well, including benzodiazepines, marijuana, opioids, and others.

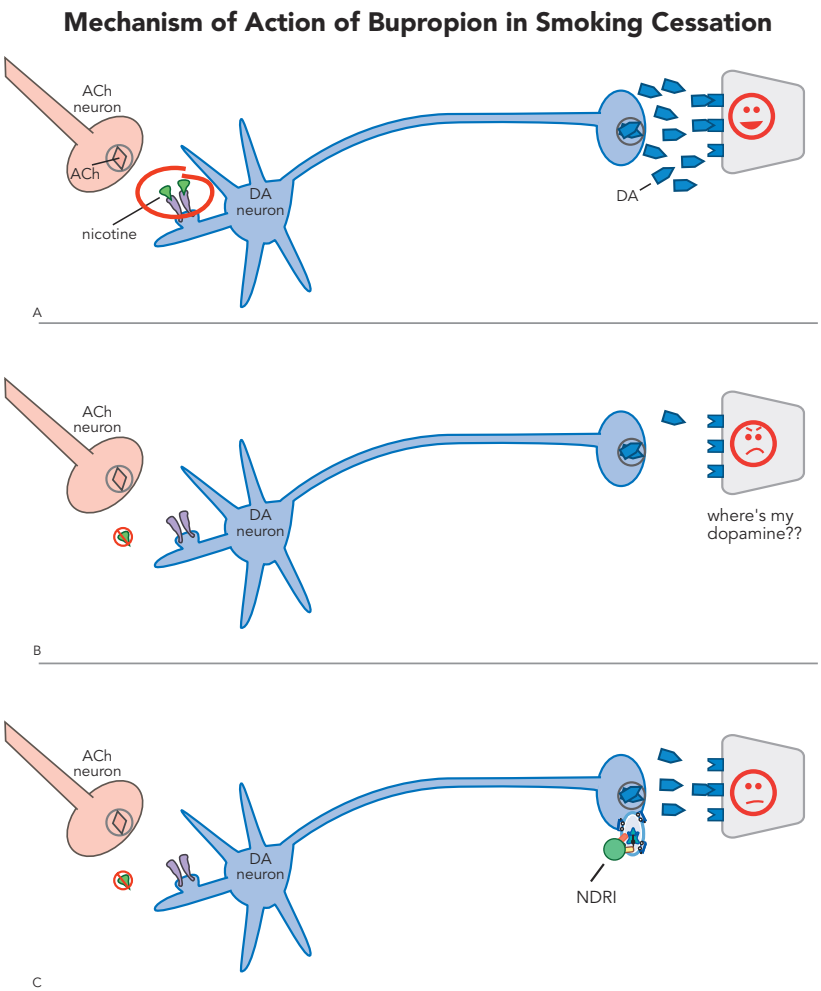


Figure 13-13 Mechanism of action of bupropion in smoking cessation. (A) A regular smoker delivers reliable nicotine (circle), releasing dopamine (DA) in the limbic area at frequent intervals, which is rewarding to the limbic dopamine D_2 receptors on the right. (B) However, during attempts at smoking cessation, dopamine will be cut off when nicotine no longer releases it from the mesolimbic neurons. This upsets the postsynaptic D_2 limbic receptors and leads to craving and what some call a "nicotine fit." (C) A therapeutic approach to diminishing craving during the early stages of smoking cessation is to deliver a bit of dopamine itself by blocking dopamine reuptake directly at the nerve terminal with bupropion. Although not as powerful as nicotine, it does take the edge off and can make abstinence more tolerable.

Although we are still struggling to understand how alcohol actually exerts its psychotropic actions, an overly simplified view of alcohol's mechanism of action is that it enhances inhibition at GABA (γ-aminobutyric acid) synapses and reduces excitation at glutamate synapses. Alcohol actions at GABA synapses hypothetically enhance GABA release via blocking presynaptic $GABA_B$ receptors and also by positively allosterically modulating postsynaptic $GABA_A$ receptors, especially those containing δ subunits that are responsive to neuroactive steroids but not to benzodiazepines (Figures 13-14 and 13-15). Non-benzodiazepine-sensitive $GABA_A$ receptors containing δ subunits are discussed in Chapter 7 and illustrated in Figure 7-56. Alcohol also hypothetically acts at presynaptic metabotropic glutamate receptors (mGluRs) and presynaptic voltage-sensitive calcium channels (VSCCs) to inhibit glutamate release (Figure 13-15). mGluRs are introduced in Chapter 4 and illustrated in Figures 4-23 and 4-24. VSCCs and their role in glutamate release are introduced in Chapter 3 and illustrated in Figures 3-22 through 3-24. Alcohol may also reduce the actions of glutamate at postsynaptic NMDA

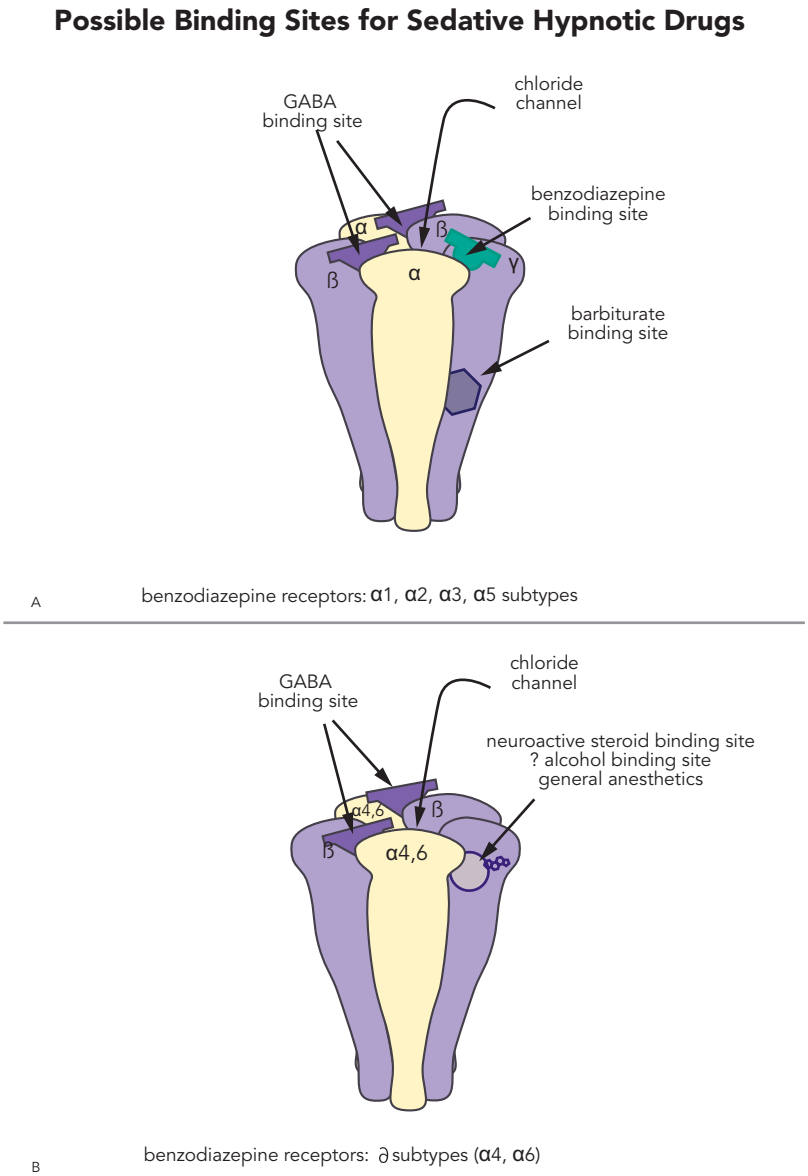


Figure 13-14 Binding sites for sedative hypnotic drugs. (A) Benzodiazepines and barbiturates both act as positive allosteric modulators at $GABA_A$ receptors, but at different binding sites from each other. Benzodiazepines do not act at *all* $GABA_A$ receptors; rather, they are selective for the α_1, α_2, α_3, and α_5 subtypes of receptors that also contain γ but not δ subunits. (B) General anesthetics, alcohol, and neuroactive steroids may bind to other types of $GABA_A$ receptors, particularly those containing δ subunits.

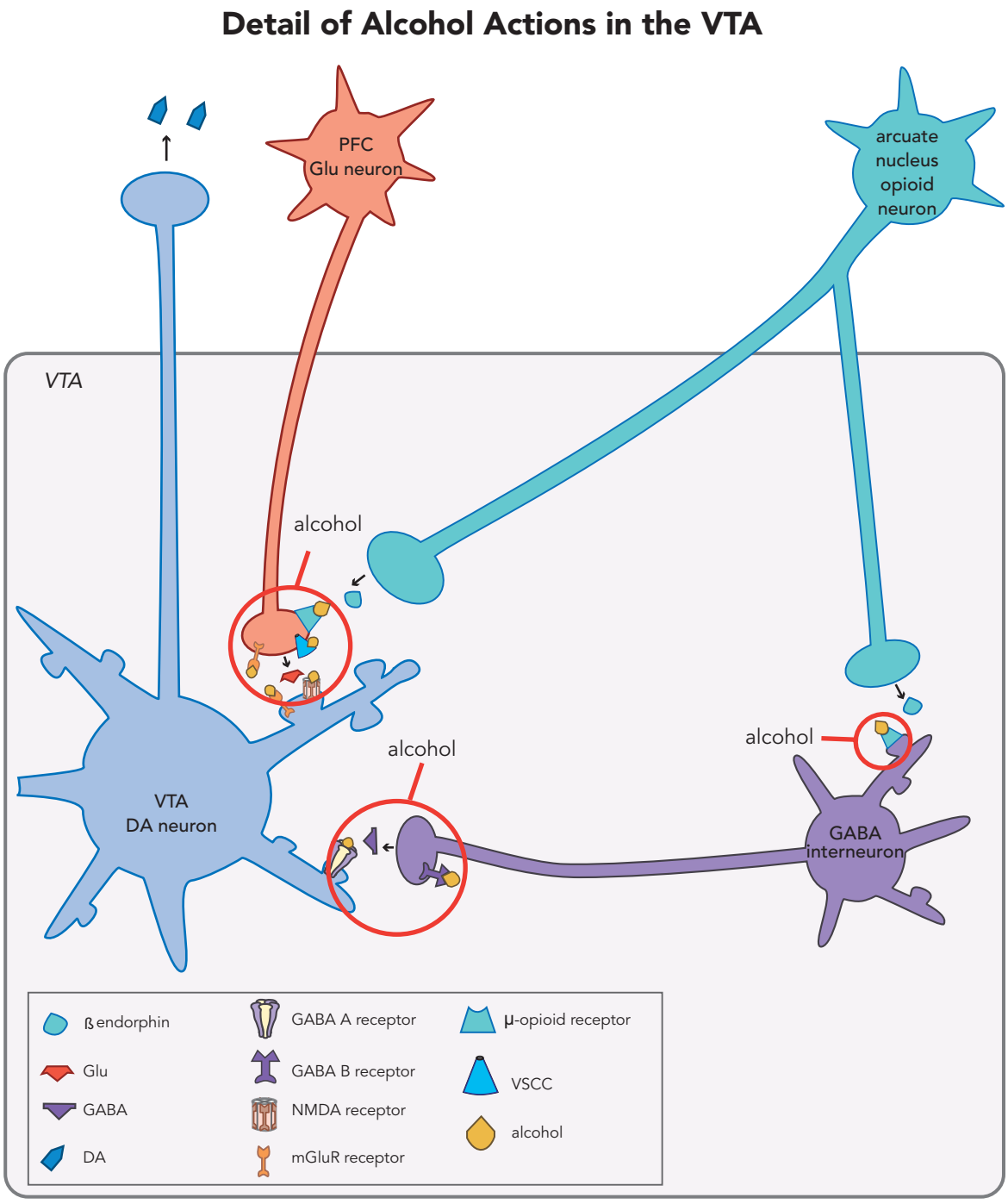


Figure 13-15 Actions of alcohol in the ventral tegmental area (VTA). Alcohol hypothetically enhances inhibition at GABA synapses by binding at both $GABA_A$ and $GABA_B$ receptors, and hypothetically reduces excitation at glutamate synapses by acting at postsynaptic metabotropic glutamate (mGluR) receptors and presynaptic voltage-sensitive calcium channels (VSCCs). Alcohol may also reduce the actions of glutamate at postsynaptic NMDA receptors and postsynaptic mGluR receptors. In addition, alcohol's reinforcing effects may be mediated by actions at opioid synapses within the VTA. Stimulation of μ-opioid receptors there causes dopamine release in the nucleus accumbens. Alcohol may either directly act upon μ receptors or cause release of endogenous opioids such as enkephalin.

(*N*-methyl-D-aspartate) receptors and at postsynaptic mGluR receptors (Figure 13-15).

Alcohol's reinforcing effects are theoretically mediated not only by its effects at GABA and glutamate synapses, causing downstream dopamine release in the mesolimbic pathway, but also by actions at opioid synapses within mesolimbic reward circuitry (Figure 13-15). Opioid neurons arise in the arcuate nucleus and project to the VTA, synapsing on both glutamate and GABA neurons. The net result of alcohol actions on opioid synapses is thought to be the release of dopamine in the nucleus acccumbens (Figure 13-15). Alcohol may do this by either directly acting upon μ-opioid receptors or by releasing endogenous opioids such as β-endorphin.

Treatment of Alcoholism

The actions of alcohol on opioid synapses create the rationale for blocking μ-opioid receptors with antagonists such as naltrexone or nalmefene (Figure 13-16). Naltrexone and nalmefene (approved outside the US) are μ-opioid antagonists that hypothetically block the euphoria and "high" of heavy drinking. This theory is supported by clinical trials that show that naltrexone given either orally or by a 30-day-long acting injection reduces days of heavy drinking (defined as five or more drinks per day for a man and four or more for a woman) and also increases the chances of attaining complete abstinence from alcohol. If you drink when you take an opioid antagonist, the opioids released by alcohol do not lead to pleasure, so why bother drinking? Some patients may also say, why bother taking the opioid antagonist, of course, and relapse back into drinking alcohol. Thus, a long-acting injection may be preferable but, unfortunately, hardly any of this is prescribed.

Acamprosate is a derivative of the amino acid taurine and interacts with both the glutamate system to inhibit it, and with the GABA system to enhance it, a bit like a form of "artificial alcohol" (compare Figure 13-15 with Figure 13-17). Thus, when alcohol is taken chronically and then withdrawn, the adaptive changes that it hypothetically causes in both the glutamate system and the GABA system create a state of glutamate overexcitement and even excitotoxicity as well as GABA deficiency. To the extent that acamprosate can substitute for alcohol in patients during withdrawal, the actions of acamprosate mitigate the glutamate hyperactivity and the GABA deficiency (Figure 13-17). This occurs because acamprosate appears to have direct blocking actions on certain glutamate receptors, particularly mGluR receptors (specifically mGlu5 and perhaps mGlu2). One way or another, acamprosate apparently reduces the glutamate release associated with alcohol withdrawal (Figure 13-17). Actions, if any, at NMDA receptors may be indirect, as are actions at GABA systems, both of which may be secondary downstream effects from acamprosate's actions on mGluR receptors (Figure 13-17). Although approved, acamprosate is not prescribed very often.

Disulfiram is the classic drug for treating alcoholism. It is an irreversible inhibitor of the liver enzyme aldehyde dehydrogenase that normally metabolizes alcohol. When alcohol is ingested in the presence of disulfiram, alcohol's metabolism is inhibited and the result is the build-up of toxic levels of acetaldehyde. This creates an aversive experience with flushing, nausea, vomiting, and hypotension, hopefully conditioning the patient to a negative rather than positive response to drinking. Obviously, compliance is a problem with this agent, and its aversive reactions are occasionally dangerous. Use of disulfiram was greater in the past and is not prescribed very often today.

Unapproved agents that may be effective in treating alcoholism include the anticonvulsant topiramate and the $5HT_3$ antagonist ondansetron. Several other agents are used "off-label," especially in Europe. The subject of how to treat alcohol abuse and dependence is obviously complex, and any psychopharmacological treatment for alcoholism is more effective when integrated with appropriate psychopharmacological treatment of comorbid psychiatric disorders, as well as with structured therapies such as 12-step programs, a topic which is beyond the scope of this text.

Sedative Hypnotics

Sedative hypnotics include barbiturates and related agents such as ethchlorvynol and ethinamate, chloral hydrate and derivatives, and piperidinedione derivatives such as glutethimide and methyprylon. Experts often include alcohol, benzodiazepines, (discussed in Chapter 8), and Z-drug hypnotics (discussed in Chapter 10) in this class as well. The mechanism of action of sedative hypnotics is basically thought to be the same as those described in Chapter 7 (on drugs for depression), Chapter 8 (on drugs for anxiety), and Chapter 10 (on drugs for insomnia) and illustrated in Figure 13-14, namely as positive allosteric modulators (PAMs) of either benzodiazepine-sensitive (Figure 13-14A) or benzodiazepine-insensitive (Figure 13-14B) $GABA_A$ receptors, or both. Barbiturates are much less safe in overdose than benzodiazepines, cause

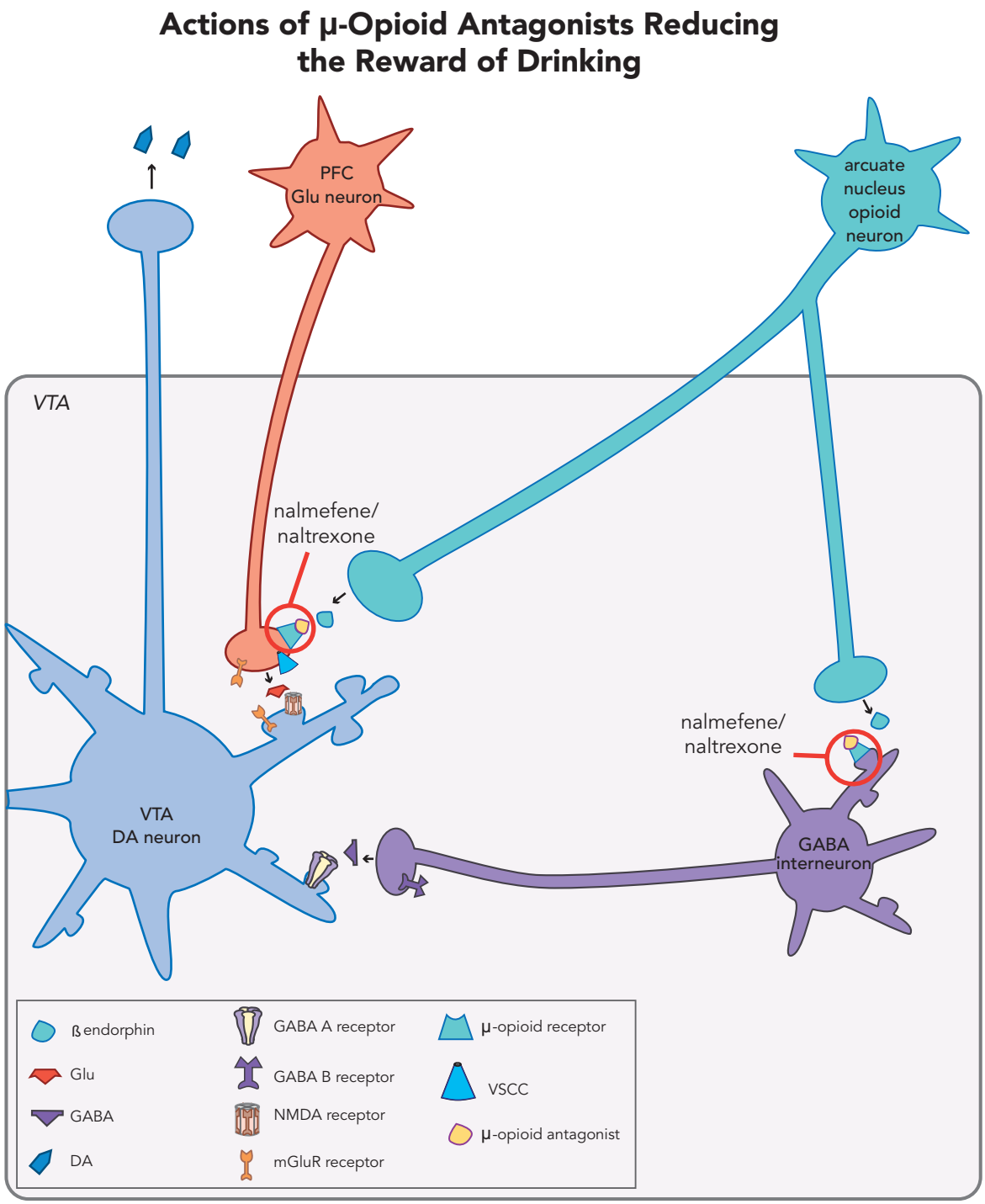


Figure 13-16 Actions of μ-opioid antagonists in the ventral tegmental area (VTA). Opioid neurons form synapses in the VTA with GABAergic interneurons and with presynaptic nerve terminals of glutamate (Glu) neurons. Alcohol either acts directly upon μ-opioid receptors or causes release of endogenous opioids such as enkephalin; in either case, the result is increased dopamine (DA) release to the nucleus accumbens. Mu-opioid receptor antagonists such as naltrexone or nalmefene block the pleasurable effects of alcohol mediated by μ-opioid receptors.

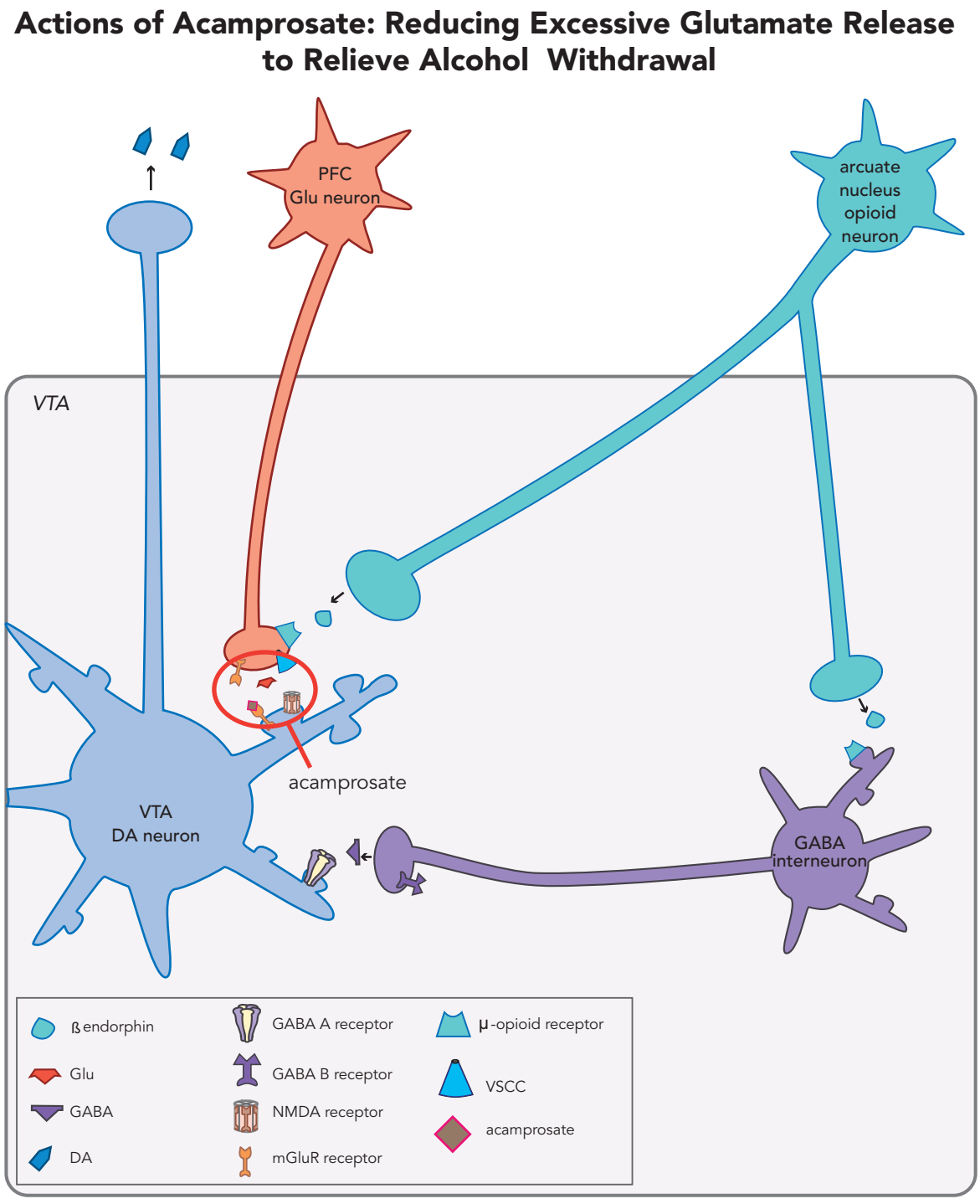


Figure 13-17 **Actions of acamprosate in the ventral tegmental area (VTA).** When alcohol is taken chronically and then withdrawn, the adaptive changes that it causes in both the glutamate system and the GABA system create a state of glutamate overexcitation as well as GABA deficiency. Acamprosate seems to reduce the glutamate release associated with alcohol withdrawal, presumably by blocking metabotropic glutamate receptors (mGluRs).

dependence more frequently, are abused more frequently, and produce much more dangerous withdrawal reactions. Because of this they are rarely prescribed today as sedative hypnotics or anxiolytics.

Gamma-Hydroxybutyrate (GHB)

This agent is discussed in Chapter 10 as a treatment for narcolepsy/cataplexy. It is sometimes also abused by individuals wanting to get high or by predators to intoxicate their dates (GHB is one of the "date rape" drugs; see further discussion in Chapter 10). The mechanism of action of GHB is as an agonist at its own GHB receptors and at $GABA_B$ receptors (illustrated in Figure 10-68).

Opiates or Opioids?

While subtle, the distinction between opioids and opiates is significant. An *opiate* is a drug naturally derived from the flowering opium poppy plant. Examples of opiates include heroin and its derivatives morphine and codeine. On the other hand, the term *opioid* is a broader term that includes opiates and refers to any substance, natural or synthetic, that binds to the brain's opioid receptors – the parts of the brain responsible for controlling pain, reward, and addictive behaviors. Some examples of synthetic opioids include the prescription painkillers hydrocodone (Vicodin) and oxycodone (OxyContin), as well as fentanyl and methadone.

Endogenous Opioid Neurotransmitter System

There are three parallel opioid systems, each with its own neurotransmitter and receptor. Neurons that release β-endorphin – sometimes referred to as the "brain's own morphine" – synapse with postsynaptic sites containing μ-opioid receptors; neurons that release enkephalin synapse with postsynaptic δ-opioid receptors; neurons that release dynorphin synapse with postsynaptic κ-opioid receptors (Figure 13-18). All three opioid peptides are derived from precursor proteins called pro-opiomelanocortin (POMC), proenkephalin, and prodynorphin, respectively (Figure 13-18). Parts of these precursor proteins are cleaved off to form endorphins or enkephalins or dynorphins, then stored in opioid neurons, to be released during neurotransmission to mediate endogenous opioid actions.

Opioid Addiction

Although illicit opioids derived from poppies have been known for their addictive properties for centuries, it has taken a recent sobering epidemic of opioid abuse with devastating effects on contemporary lives and society for us to recognize the powerful destructive potential of oral opioids prescribed legally for pain relief. Recent surveys suggest that the US consumes 85% of the world's legal and illegal supply of opioids. In the US every year, over 60 million people fill at least one prescription for an opioid, 20% of them use their opioids in a manner that was not prescribed, another 20% report sharing pills, and over 2 million become iatrogenically addicted. As the need for higher and higher dosing exceeds the pills that can be obtained from prescribers or from the street, many patients resort to the more affordable street heroin inhaled or injected to "chase the dragon" of opioid addiction. Street supplies of heroin are increasingly laced with fentanyl which is 100 times more potent than morphine. Fentanyl derivatives like the elephant

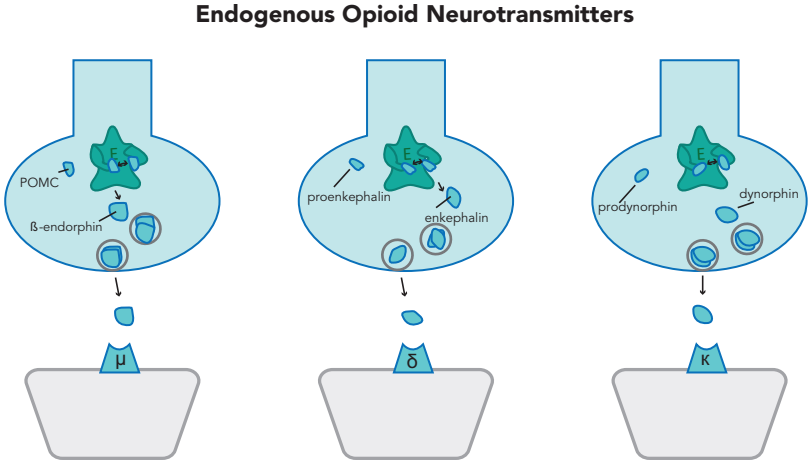


Figure 13-18 Endogenous opioid neurotransmitters. Endogenous opioids are peptides derived from precursor proteins called POMC (pro-opiomelanocortin), proenkephalin, and prodynorphin. Parts of these precursor proteins are cleaved off to form endorphins, enkephalins, or dynorphin, which are then stored in opioid neurons and released during neurotransmission to mediate reinforcement and pleasure. Neurons that release endorphin synapse with sites containing μ-opioid receptors, those that release enkephalin synapse with sites containing δ-opioid receptors, and those that release dynorphin synapse with sites containing κ-opioid receptors.

tranquilizer carfentanil are 10,000 times more potent than morphine. In fact, fentanyl and derivatives are so powerful that they are unable to be reversed by opioid antagonists such as naloxone, and thus an estimated one-third of 60,000 annual US overdose deaths from opioids are caused by fentanyl and derivatives. A very sad outcome from what may have started as legitimate treatment of acute pain.

This recent epidemic of opioid addiction has also dashed the fallacy that oral controlled-release formulations reduce addiction liability. The ongoing and sweeping contagion triggered by oral pain-relieving opioids of all types has taught us, somewhat surprisingly, that opioids may not be highly effective analgesics in the long run, but only in the short run, losing their analgesic effectiveness within days to weeks as tolerance, dependence, and addiction take hold. Thus, prescription opioids are being increasingly limited in amount and in time, both to reduce dependence in patients with pain and to prevent diversion of their opioids to others.

At and above pain-relieving doses, opioids induce euphoria, a powerful reinforcing property. There is less dopamine release with opioids than with stimulants in the mesolimbic pleasure center, but certainly not less pleasure, so it is not entirely clear how the "high" of opioids is fully mediated. Likely, the impulsive ventral circuit begins its pleasurable reinforcing work early in the use of an opioid. Opioids induce a very intense but brief euphoria, sometimes called a "rush," followed by a profound sense of tranquility, which may last several hours, followed in turn by drowsiness ("nodding"), mood swings, mental clouding, apathy, and slowed motor movements. In overdose, these same opioids act as depressants of respiration, and can also induce coma. The acute actions of opioids other than fentanyl and derivatives can be reversed by synthetic opioid antagonists, such as naloxone, which compete as antagonists at μ-opioid receptors if given soon enough and in sufficient dosage. The opioid antagonists can also precipitate a withdrawal syndrome in opioid-dependent persons.

When taken chronically, opioids readily cause both tolerance and dependence because adaptation of opioid receptors occurs quite readily. This adaptation hypothetically correlates with the migration of behavioral control from ventral circuits to dorsal habit circuits. The first sign of this is the need of the patient to take a higher and higher dose of opioid in order to relieve pain or to induce the desired euphoria. Eventually, there may be little room between the dose that causes euphoria and that which produces toxic effects of an overdose. Another sign that dependence has occurred and that opioid receptors have adapted is the development of a withdrawal syndrome once the chronically administered opioid wears off. The opioid withdrawal syndrome is characterized by the patient feeling dysphoria, craving another dose of opioid, being irritable, and having signs of autonomic hyperactivity such as tachycardia, tremor, and sweating. Pilo-erection ("goose-bumps") is often associated with opioid withdrawal, especially when the drug is stopped suddenly ("cold turkey"). This is so subjectively horrible that the opioid abuser will often stop at nothing in order to get another dose of opioid to relieve symptoms of withdrawal. Thus, what may have begun as a quest for pain relief or euphoria may end up as a quest to avoid withdrawal.

Treatment of Opioid Addiction

Treatment of opioid addiction begins with managing withdrawal. Running out of money and drug supply as well as being incarcerated can be forms of forced withdrawal, but a gentler version is to reduce or even avoid withdrawal symptoms. One way to do this is to substitute a prescribed opioid at known dose and avoid intravenous administration. There are two options: methadone or buprenorphine. Methadone is a full agonist at μ-opioid receptors and can suppress withdrawal symptoms completely given orally and usually administered daily at a clinic. Buprenorphine is a μ-opioid partial agonist that has less powerful agonist effects, yet can suppress withdrawal symptoms especially when mild withdrawal has already begun after stopping abused opioids. Buprenorphine is administered sublingually as it is not well absorbed if swallowed. It can also be prescribed in a several-day supply and taken as an outpatient instead of returning daily to a clinic. Buprenorphine is usually combined with naloxone. Naloxone is not absorbed orally or sublingually, yet prevents intravenous abuse, since naloxone is active by injection. The injection of the combination of buprenorphine and naloxone results in no high and may even precipitate withdrawal, so prevents diversion for intravenous abuse of the sublingual preparation. Buprenorphine can also be administered as an implantable 6-month formulation or as a 1-month depot injection.

Although tapering off methadone or buprenorphine directly to a state of opioid abstinence is theoretically

possible, it is rarely successful long term. Of those opioid addicts who enter residential rehabilitation and treatment for 30–90 days off all drugs, some analyses suggest relapse back into opioid abuse as high as 60–80% within a month and 90–95% by 3 months. The drive to reinstitute street opioids coming from the addict's habit circuit – especially if re-exposed to the environmental cues linked to previous opioid abuse such as the people, places, and paraphernalia associated with prior opioid abuse – is akin to putting oneself in the situation where bells for Pavlov's dogs are ringing loud and clear. Involuntary, mindless, and powerful habit drives then take over reflexively, bypassing voluntary will power, no longer able to suppress drug seeking and drug taking. This outcome results whether the opioid addict is trying to stop methadone, buprenorphine, or street opioids.

How can this dismal outcome be avoided? First of all, it is important to recognize that the intensity and duration of withdrawal from most drugs including opioids are linked to drug half-life, with short-half-life full agonists such as morphine or heroin producing much more intense and short-lasting withdrawal symptoms than either long-acting methadone, which has a less intense but much longer duration withdrawal, or buprenorphine, the withdrawal of which is both less intense and shorter (Figure 13-19). Second of all, the intensity but not the duration of withdrawal of both methadone (Figure 13-20) and buprenorphine (Figure 13-21) can be reduced by the addition of an α_{2A} agonist. Both clonidine and lofexidine are α_2-adrenergic agonists that reduce signs of autonomic hyperactivity during withdrawal and aid in the detoxification process. And finally, in an attempt to enhance successful long-term abstinence, opioid addicts may be transitioned not to abstinence but to maintenance on a long-acting injectable opioid antagonist like naltrexone. In the short run, naltrexone shortens the withdrawal time of an α_2 agonist administered either with methadone (Figure 13-20) or with buprenorphine (Figure 13-21). The advantages of giving naltrexone long term are having the drug present at therapeutic levels all day long, in contrast to administering naltrexone orally (Figure 13-22). Furthermore, with naltrexone monthly injections the opioid-abstinent person now only has to make a decision to take medication once every 30 days instead of 30 times in 30 days. Even better, an impulsive patient cannot readily stop his/her injectable naltrexone in order to relapse.

Agonist substitution treatments like methadone or buprenorphine – often called medication-assisted therapy (MAT) – are most successful in the setting of a structured maintenance treatment program that includes random urine drug screening and intensive

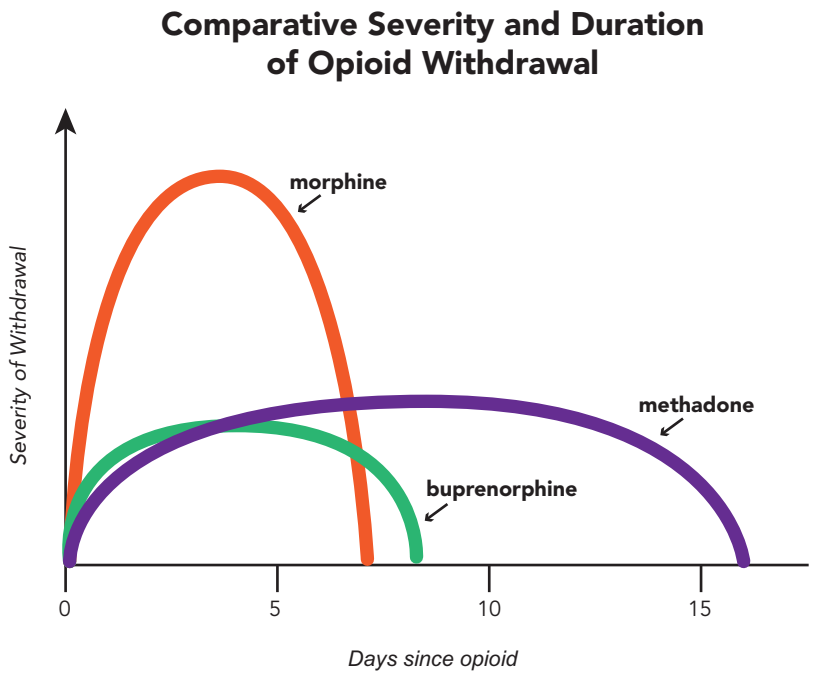


Figure 13-19 Comparative severity and duration of opioid withdrawal. Following abrupt discontinuation, the time to onset of peak withdrawal symptoms and the duration of symptoms are dependent on the half-life of the drug involved. With morphine (and heroin) withdrawal, symptoms peak within 36–72 hours and last for 7–10 days. With methadone withdrawal, symptoms are less severe and peak at 72–96 hours, but can last for 14 days or more. With buprenorphine withdrawal, symptoms peak after a few days and are less severe than with morphine/heroin; the duration of symptoms is similar to morphine/heroin.

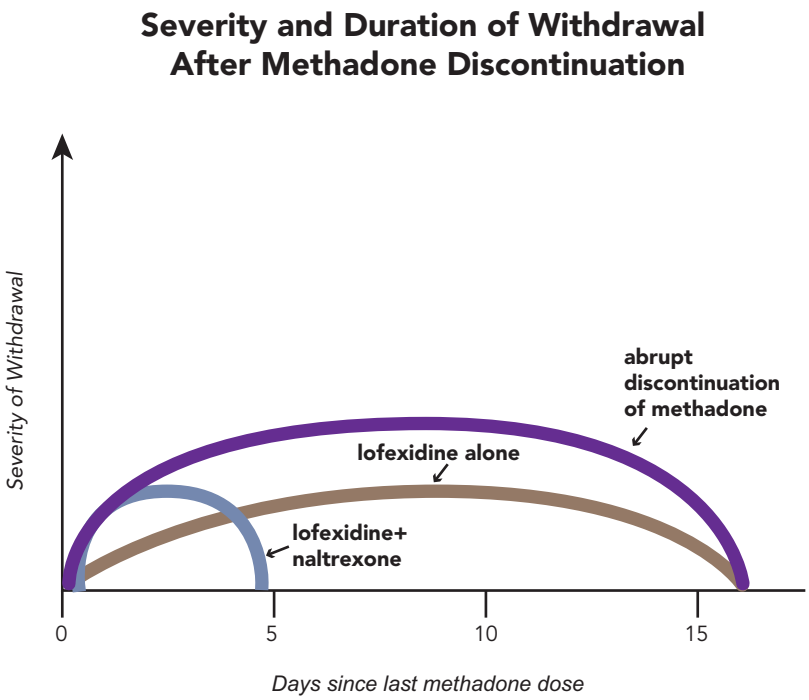


Figure 13-20 **Severity and duration of withdrawal after methadone discontinuation.** With abrupt discontinuation of methadone, withdrawal symptoms peak at 72–96 hours but can last for 14 days or more. The intensity, but not the duration, of withdrawal symptoms can be reduced by adding an α_2-adrenergic agonist such as lofexidine or clonidine. Specifically, these agents can relieve autonomic symptoms. Adding both an α_2-adrenergic agonist and a μ-opioid receptor antagonist such as naltrexone can reduce the severity as well as the duration of withdrawal symptoms.

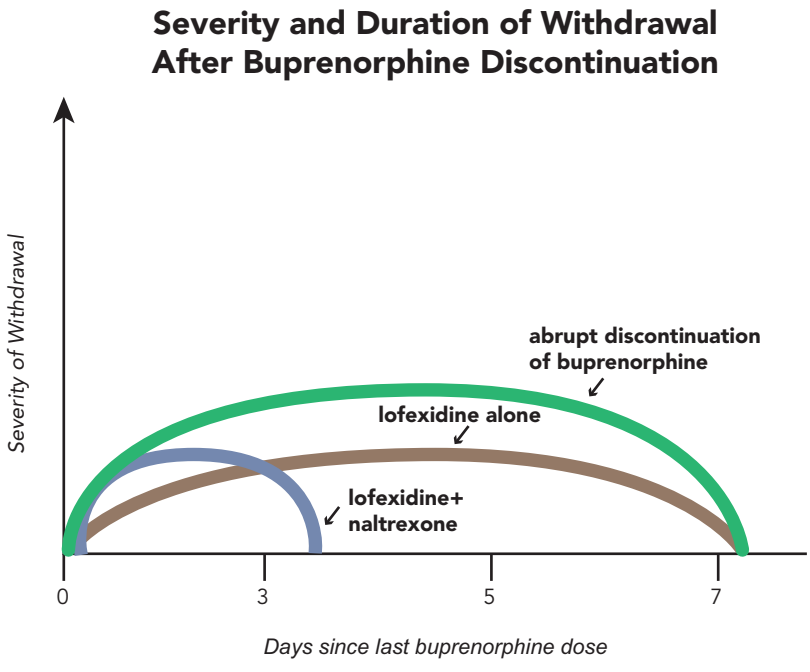


Figure 13-21 **Severity and duration of withdrawal after buprenorphine discontinuation.** With abrupt discontinuation of buprenorphine, withdrawal symptoms peak at around 72 hours and last for about a week. The intensity, but not the duration, of withdrawal symptoms can be reduced by adding an α_2-adrenergic agonist such as lofexidine or clonidine. Specifically, these agents can relieve autonomic symptoms. Adding both an α_2-adrenergic agonist and a μ-opioid receptor antagonist such as naltrexone can reduce the severity as well as the duration of withdrawal symptoms.

psychological, medical, and vocational services. The same is true for those on long-acting naltrexone injections. Unfortunately, only a minority of opioid addicts enter treatment, only a minority of those in treatment receive MAT, and almost none of them receive injectable naltrexone. Whether this is because of philosophical differences of various treatment facilities, economic incentives, or therapeutic nihilism is unknown but it seems that the currently available best treatments are insufficiently prescribed.

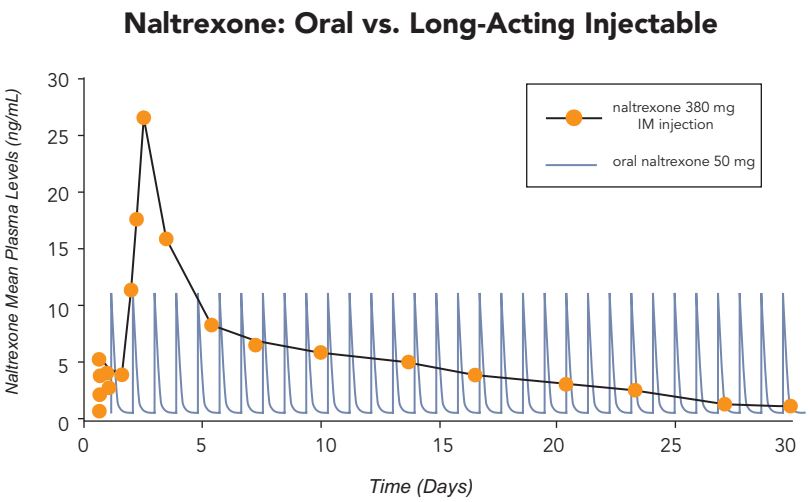


Figure 13-22 **Naltrexone formulations.** The μ-opioid receptor antagonist naltrexone is available in both an oral formulation and as a once-monthly intramuscular (IM) injection. With oral naltrexone, one experiences fluctuating, dose-dependent plasma concentrations. In addition, one must decide daily whether or not to continue treatment. With the monthly injection, one experiences increased and consistent plasma concentrations and only has to make the decision to take medication once every 30 days.

Cannabis

You can indeed get stoned without inhaling (see endocannabinoids released in Figure 13-5)! The brain makes its own cannabis-like neurotransmitters – anandamide and 2-arachidonoylglycerol (2-AG) (Figures 13-23 and 13-24). So does the body. These neurotransmitters and their receptors cannabinoid 1 and 2 (CB1 and CB2) make up the "endocannabinoid" system – the endogenous cannabinoid system (Figure 13-23). In the brain, release of classic neurotransmitters can stimulate the synthesis of endocannabinoids from precursors stored in postsynaptic lipid membranes (Figure 13-24A). Upon release of these endocannabinoids into the synapse, they travel retrograde to presynaptic CB1 receptors and "talk back" to the presynaptic neuron where they can inhibit the release of the classic neurotransmitter (Figure 13-24B). Retrograde neurotransmission was introduced in Chapter 1 and illustrated in Figure 1-5. Both CB1 receptors and CB2 receptors are localized in brain, with CB1 receptors present in greater density. Both receptors bind both endocannabinoids, 2-AG with high efficacy and anandamide with low efficacy (Figure 13-23). CB2 receptors are also in the periphery, mostly on immune cells, and also bind the same two endocannabinoids (Figure 13-23).

Cannabis is a mixture of hundreds of chemicals and over 100 alkaloid cannabinoids. The most important of these are tetrahydrocannabinol (THC) and cannabidiol (CBD) (Figure 13-25). THC interacts with CB1 and CB2 receptors and has psychoactive properties. CBD is an isomer of THC and relatively inactive at CB1 and CB2 receptors (Figure 13-25). CBD does not have psychoactive properties and its mechanism of action is really unknown (Figure 13-25). Cannabis comes in various mixtures of THC and CBD (Figure 13-26). Higher CBD content has a lower risk of hallucinations, delusions, and memory impairment (Figure 13-26). Pure CBD might even be antipsychotic and anxiolytic (Figure 13-26). Over time, cannabis has become more potent in terms of more THC and less CBD, with resultant higher risk of hallucinations, delusions, anxiety, and memory impairment (Figure 13-26). It is not currently possible to identify in advance those vulnerable to psychosis or to the precipitation of schizophrenia by cannabis. Nevertheless, an influential recent study concluded that if nobody smoked high-potency cannabis, 12% of all cases of first-episode psychosis across Europe would be prevented, rising to 32% in London and 50% in Amsterdam. Cannabis can also exacerbate psychosis in patients who already have a psychotic illness.

In usual intoxicating doses for most persons without risk for psychosis, cannabis produces a sense of well-being, relaxation, a sense of friendliness, a loss of temporal awareness, including confusing the past with the present, slowing of thought processes, impairment of short-term memory, and a feeling of achieving special insights. At high doses, cannabis can induce panic, toxic delirium as well as psychosis, especially in the vulnerable. One complication of long-term cannabis use is the "amotivational syndrome" in frequent users. This syndrome is seen predominantly in heavy daily cannabis users and is characterized

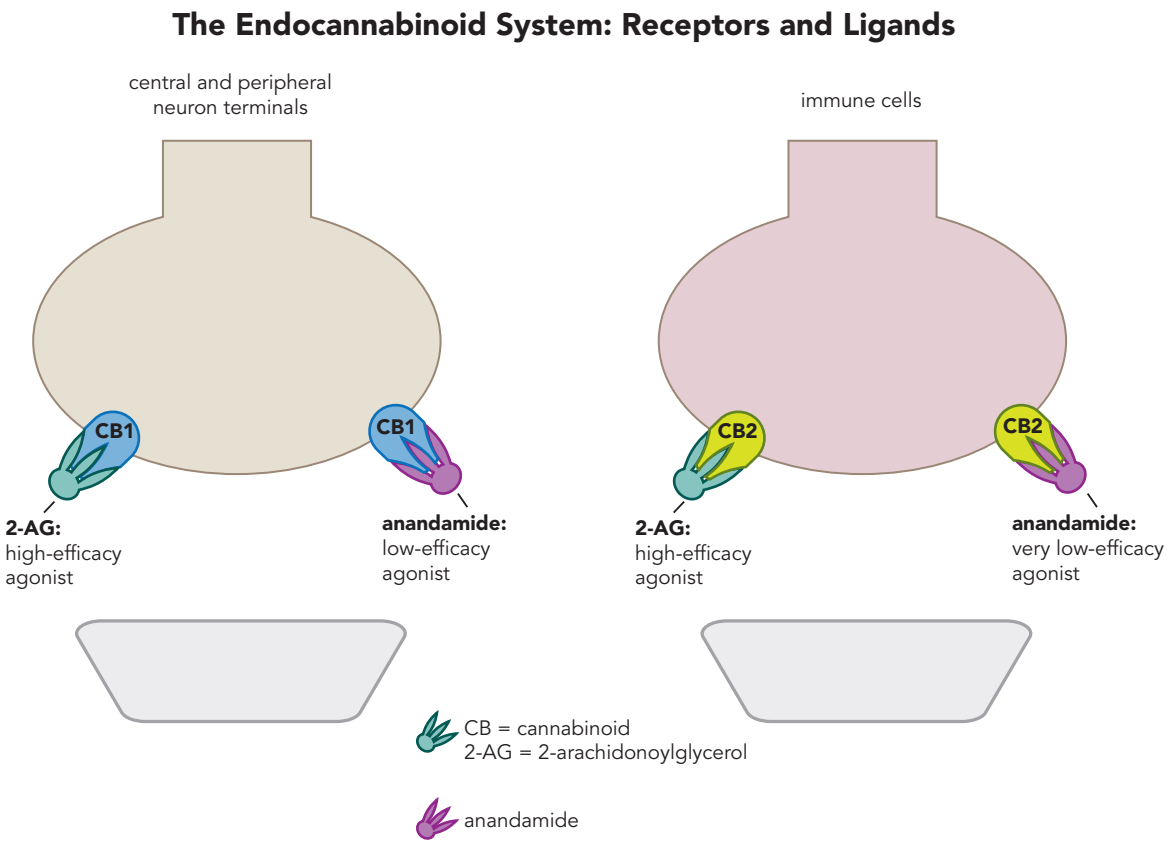


Figure 13-23 **The endocannabinoid system: receptors and ligands.** There are two main types of cannabinoid (CB) receptors. CB1 receptors are the most abundant and are present at neuron terminals throughout the central and peripheral nervous systems. CB2 receptors are not expressed as widely in the brain, although they are present in glial cells and in the brainstem. Instead, CB2 receptors are primarily found in immune cells, where they modulate cell migration and cytokine release. Of the multiple endogenous cannabinoids, the best understood are anandamide and 2-arachidonoylglycerol (2-AG). Anandamide is a low-efficacy agonist at CB1 receptors and a very low-efficacy agonist at CB2 receptors. 2-AG is a high-efficacy agonist at both CB1 and CB2 receptors.

by the emergence of decreased drive and ambition, thus "amotivational." It is also associated with other socially and occupationally impairing symptoms, including a shortened attention span, poor judgment, easy distractibility, impaired communication skills, introversion, and diminished effectiveness in interpersonal situations. Personal habits may deteriorate, and there may be a loss of insight, and even feelings of depersonalization.

Recent years have led to a search for potential therapeutic uses of cannabis in general and for THC and CBD in particular. The problem with "medical marijuana" is that it is not a prescription option that can be developed according to the standards of prescription medication. Those standards require consistent, pure, well-defined chemical formulation of the therapeutic agent whereas medical marijuana is an unprocessed plant containing 500 chemicals with 100+ cannabinoids. Prescription drugs require a consistent, well-defined pharmacokinetic profile, and safety and efficacy data from double-blind, placebo-controlled, randomized clinical trials, as well as warnings for all potential side effects. However, medical marijuana contains compounds that vary from plant to plant, with residual impurities such as pesticides and fungal contaminants, and dosing which is not well regulated. Even so, there have been a myriad of studies of medical marijuana, and these have been recently reviewed by a panel of experts who report various benefits and risks for which there is a range of evidence, from substantial evidence, to moderate evidence, to limited evidence (Table 13-2), to insufficient evidence (Table 13-3).

The Endocannabinoid System: Retrograde Neurotransmission

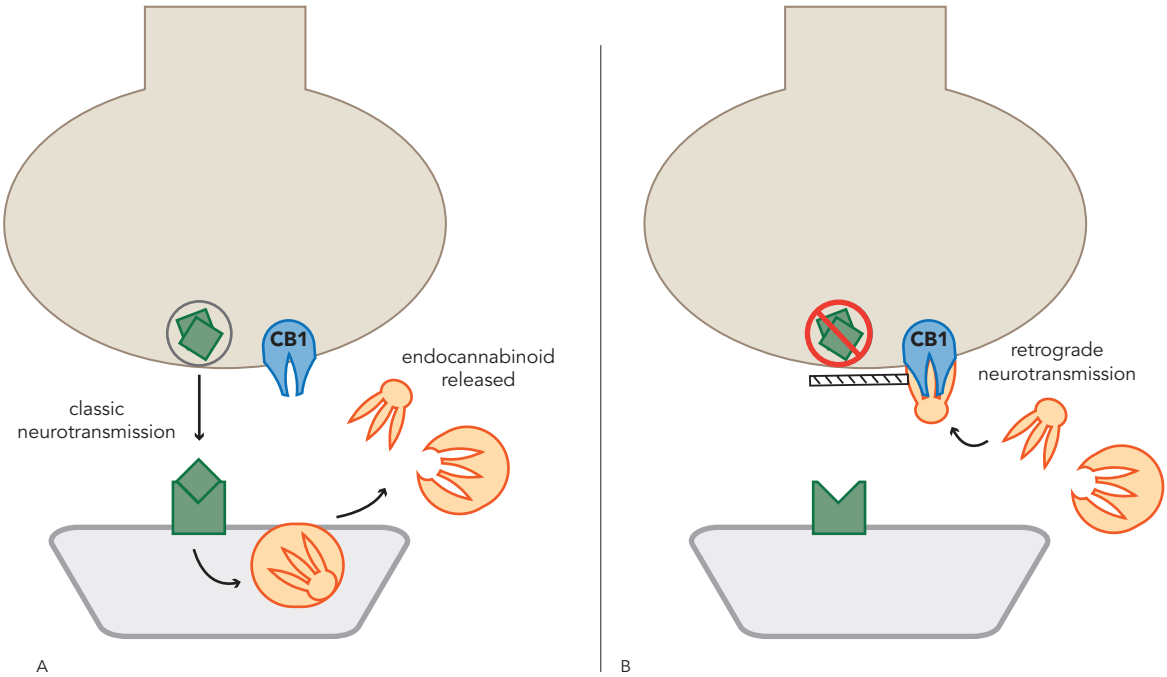
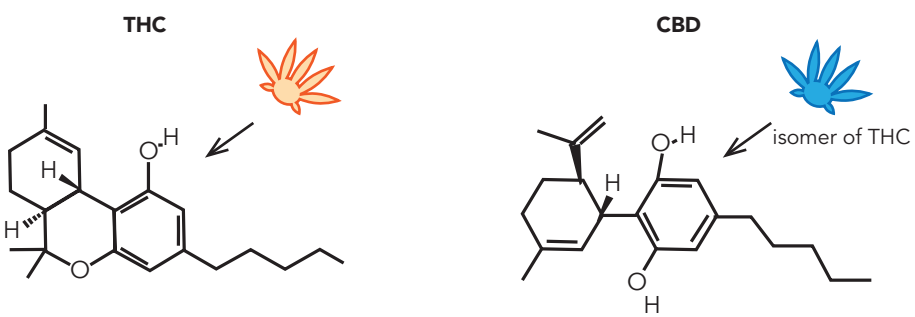


Figure 13-24 The endocannabinoid system: retrograde neurotransmission. (A) Precursors to the endocannabinoids are stored in the lipid membrane of the postsynaptic neuron. When that neuron is activated, either via depolarization or the presence of a neurotransmitter binding to a G-protein-coupled receptor, this triggers an enzymatic reaction to form and release the endocannabinoid. (B) The endocannabinoid then binds to a presynaptic cannabinoid receptor, causing the inhibition of neurotransmitter release. This form of neurotransmission is known as retrograde neurotransmission.

Tetrahydrocannabinol (THC) vs. Cannabidiol (CBD)



psychoactive
anxiogenic

Potential Therapeutic Properties?
- Anti-inflammatory
- Euphoria
- "Opiate type pain relief"

NOT psychoactive
anxiolytic
anticonvulsant

Potential Therapeutic Properties?
- Neuropathic pain relief
- Anti-inflammatory
- Patient-specific

Figure 13-25 Tetrahydrocannabinol (THC) vs. cannabidiol (CBD). There are two well-known and relatively well-studied exogenous cannabinoids: (1) tetrahydrocannabinol (THC), which is considered psychoactive and binds as a partial agonist at CB1 and CB2 receptors, causing inhibition of neurotransmitter release; and (2) cannabidiol (CBD), which is not considered psychoactive and for which the binding at CB receptors is not entirely clear, although it does seem to interact with other neurotransmitter systems, such as the serotonin system.

Table 13-2 Areas where there is a range of benefits and risks of cannabis

	Associated with benefits to:	Associated with risk of:
Substantial evidence	Chronic pain Chemotherapy-induced nausea Spasticity in multiple sclerosis (patient-reported)	Respiratory symptoms Motor vehicle crashes Lower birth weight Psychosis
Moderate evidence	Sleep in obstructive sleep apnea, fibromyalgia, chronic pain, and multiple sclerosis Airway dynamics Forced vital capacity Cognition in psychosis	Overdose injuries in pediatric population Impaired learning, memory, and attention Increased (hypo)mania in bipolar disorder Depressive disorders Suicidality and suicide completion Social anxiety disorder Development of substance use disorder for other substances
Limited evidence	Increasing appetite/decreasing weight loss in HIV/AIDS Spasticity in multiple sclerosis (clinician-reported) Tourette syndrome Anxiety PTSD	Testicular cancer Acute myocardial infarction Ischemic stroke of subarachnoid hemorrhage Prediabetes Chronic obstructive pulmonary disease Pregnancy complications Infant admission to neonatal intensive care Impaired academic achievement Increased unemployment Impaired social functioning Increased positive symptoms in schizophrenia Bipolar disorder Anxiety disorders (other than social anxiety disorder) Increased severity of PTSD symptoms

THC vs. CBD: Psychiatric Effects

	 Cannabis with Low CBD Content	 Cannabis with High CBD Content	 CBD Alone
Psychosis symptoms	Higher risk of hallucinations and delusions	Lower risk of hallucinations and delusions	Possible antipsychotic effects
Psychotic disorder	Earlier age of onset	Later age of onset	
Cognition	Higher risk of acute memory impairment	Lower risk of acute memory impairment	
Anxiety	Anxiogenic Increased amygdalar activity		Anxiolytic Reduced amygdalar activity

Figure 13-26 **THC vs. CBD: psychiatric effects.** Each strain of cannabis may contain a different combination of the 60–100 known cannabinoids. Cannabis with THC and low CBD content may carry higher risk of psychotic symptoms, memory impairment, and anxiety. Cannabis with THC and high CBD content may have lower risk of psychotic symptoms, memory impairment, and anxiety. Pure CBD has been studied for its potential use as an antipsychotic agent or anxiolytic.

Table 13-3 Areas where there is insufficient evidence for benefits or risks of cannabis

	Associated with benefits to:	Associated with risk of:
Insufficient evidence	Dementia Intraocular pressure associated with glaucoma Depression in chronic pain or multiple sclerosis Cancer Anorexia nervosa Irritable bowel syndrome Epilepsy Spasticity in spinal cord injury Amyotrophic lateral sclerosis Huntington's disease Parkinson's disease Dystonia Addiction Psychosis	Lung, head, and neck cancers Esophageal cancer Prostate and cervical cancer Certain leukemias Asthma Liver fibrosis or hepatic disease in individuals with Hepatitis C Adverse immune cell response Adverse effects on immune status in HIV Oral human papilloma virus All-cause mortality Occupational accidents/injuries Death from overdose Later outcomes to offspring (e.g., sudden infant death syndrome, academic achievement, later substance abuse) Worsening of negative symptoms in schizophrenia

Table 13-4 Approved uses for THC and CBD

	Active ingredient	Formulation	Approval(s)	Schedule
Dronabinol	Synthetic THC	Oral capsule or solution	Chemo-induced nausea and vomiting (US) Appetite boost in AIDS wasting syndrome (US)	III
Nabilone	Synthetic THC analogue	Oral capsule	Chemo-induced nausea and vomiting (US)	II (due to its potency)
Nabiximols	Purified ~1:1 THC and CBD	Spray	Spasticity caused by multiple sclerosis (UK, Canada, Europe, Australia, New Zealand, Israel) Pain in multiple sclerosis and in cancer (Canada, Israel)	N/A
Epidiolex	CBD purified from marijuana	Oral solution	Seizures associated with two rare and severe forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome, in patients 2 years of age and older (US)	Not a controlled substance

However, both pure THC and pure CBD have been FDA approved according to traditional drug standards for various indications (Table 13-4). Whether some of those areas where some degree of benefit and safety has been described for cannabis (see Table 13-2) will eventually lead to formal FDA approval of pure compounds for any of those indications is currently under investigation.

Hallucinogens

It can be a challenge to categorize the various substances that cause not only occasional hallucinations, but more commonly, non-ordinary psychological states and altered states of consciousness. The terminology for these substances is ever evolving and more descriptive than scientific. Here we will use the category hallucinogen to imply three classes of

agents that act, at least in part, as agonists at $5HT_{2A}$ receptors (Figure 13-27). These are:

- tryptamines (such as psilocybin)
- ergolines (such as lysergic acid diethylamide [LSD])
- phenethylamines (such as mescaline)

Hallucinogens are not selective for $5HT_{2A}$ receptors alone, and their actions at other serotonin receptor subtypes may contribute to their mind-altering states (see Chapter 7 and Figure 7-88). Psilocybin (4-diphosphoryloxy-*N*,*N*-dimethyltryptamine) is a prototypical hallucinogen that is derived from hallucinogenic mushrooms. It is both an active drug and a prodrug for another hallucinogen called psilocin (*N*,*N*-dimethyltryptamine or DMT). Together, psilocybin, psilocin, and the other tryptamines, ergolines, and phenethylamines in this category act not only at $5HT_{2A}$ receptors, but also at $5HT_{2B}$, $5HT_{7}$, $5HT_{1D}$, $5HT_{1E}$, $5HT_{2C}$, $5HT_{6}$, and even more serotonin receptor subtypes (see Figure 7-88). Some evidence suggests that $5HT_{2A}$ antagonists, but not D_2 dopamine antagonists, can reverse the action of hallucinogens in humans, supporting the predominant mechanism of action of hallucinogens as being agonists at $5HT_{2A}$ receptors (Figure 13-27).

Hallucinogens can produce incredible tolerance, sometimes after a single dose. Desensitization of $5HT_{2A}$ receptors is hypothesized to underlie this rapid clinical and pharmacological tolerance. Another unique dimension of hallucinogen use is the production of "flashbacks," namely the spontaneous recurrence of some of the symptoms of intoxication that lasts from a few seconds to several hours but in the absence of recent administration of the hallucinogen, mostly reported with LSD. This occurs days to months after the last drug experience, and can apparently be precipitated by a number of environmental stimuli. The psychopharmacological mechanism underlying flashbacks is unknown but its phenomenology suggests the possibility of a neurochemical adaptation of the serotonin system and its receptors, related to reverse tolerance that is incredibly long-lasting. Alternatively, flashbacks could be a form of emotional conditioning embedded in the amygdala and then triggered when a later emotional experience that one has when one is not taking a hallucinogen nevertheless reminds one of experiences that occurred when intoxicated with a hallucinogen. This could precipitate a whole cascade of feelings that occurred while intoxicated with a hallucinogen. This is analogous to the types of re-experiencing flashbacks that occur without drugs in patients with posttraumatic stress disorder

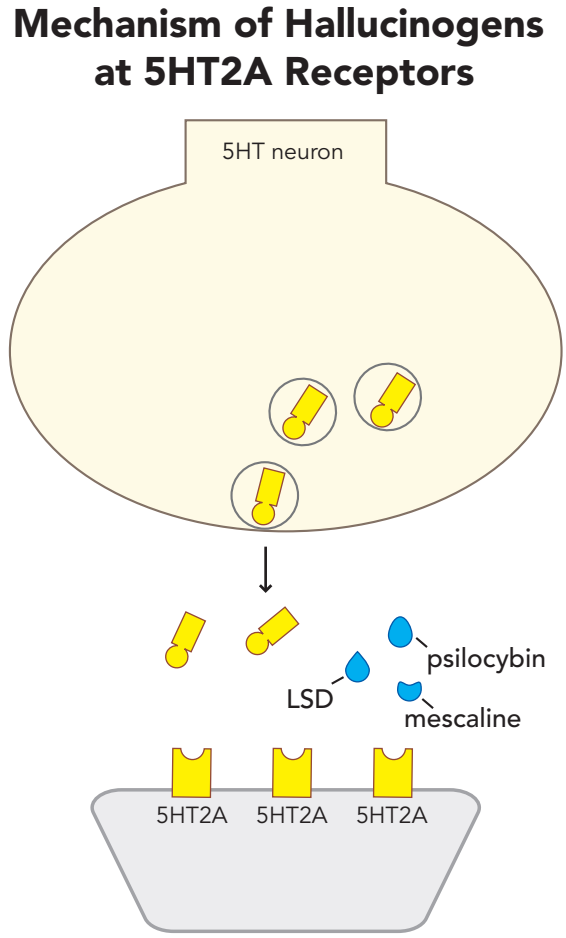


Figure 13-27 Mechanism of hallucinogens at $5HT_{2A}$ receptors. The primary action of hallucinogenic drugs such as psilocybin, lysergic acid diethylamide (LSD), and mescaline is agonism at $5HT_{2A}$ receptors. These hallucinogens may have additional actions at other serotonin receptors.

(PTSD) and is why hallucinogenic and empathogenic drugs are now being cautiously used for therapeutic purposes in PTSD (see below).

The state of hallucinogenic intoxication, sometimes called a "trip," is associated with changes in sensory experiences, including visual illusions and sometimes hallucinations. Actually, hallucinogens often don't cause *hallucinations* (the apparent perception of something that is not actually present), but are much more likely to cause *illusions* (distortions of sensory experiences that are present). These experiences are produced with a clear level of consciousness and a lack of confusion and may be both psychedelic and psychotomimetic. *Psychedelic* is the term for the subjective experience that,

due to heightened sensory awareness, one's mind is being expanded or that one is in union with mankind or the universe and having some sort of a religious experience. *Psychotomimetic* means that the experience mimics a state of psychosis, but the resemblance between a trip and psychosis is superficial at best. The stimulants cocaine and amphetamine (see discussion in Chapter 4 and also the discussion above for stimulants in this chapter) and the club drug phencyclidine (PCP; discussed in Chapter 4 and also below) much more genuinely mimic psychosis than do hallucinogens. Instead, hallucinogen intoxication includes visual illusions; visual "trails," where the image smears into streaks of its image as it moves across a visual trail; macropsia and micropsia; emotional and mood lability; subjective slowing of time; the sense that colors are heard and sounds are seen; intensification of sound perception; depersonalization and derealization; yet retaining a state of full wakefulness and alertness. Other changes may include impaired judgment, fear of losing one's mind, anxiety, nausea, tachycardia, increased blood pressure, and increased body temperature. Not surprisingly, hallucinogen intoxication can cause what is perceived as a panic attack, often called a "bad trip." As intoxication escalates, one can experience an acute confusional state called delirium, where the abuser is disoriented and agitated. This can evolve further uncommonly into frank psychosis with delusions and paranoia.

Empathogens

Another category of psychoactive drug is called an empathogen or an entactogen. Empathogens produce an altered state of consciousness described as experiences of emotional communion, oneness, relatedness, emotional openness – that is, empathy or sympathy. The prototype empathogen is MDMA (3,4-methylenedioxymethamphetamine). MDMA is a synthetic amphetamine derivative that acts more selectively on serotonin transporters (SERTs) than upon dopamine transporters (DATs) and norepinephrine transporters (NETs), whereas amphetamine itself acts more selectively on DATs and NETs than on SERTs. Amphetamine's primary actions on both dopamine and norepinephrine synapses are explained in Chapter 11 and illustrated in Figure 11-32.

For its more important serotonin actions, MDMA targets the SERT as a *competitive* inhibitor and pseudosubstrate (Figure 13-28, upper left), binding at the *same* site where serotonin binds to this transporter, thus inhibiting serotonin reuptake (Figure 13-28, upper left). At psychoactive doses, following competitive inhibition of the SERT (Figure 13-28, upper left), MDMA is actually transported as a hitch-hiker into the presynaptic serotonin terminal. Once there in sufficient quantities, MDMA is also a competitive inhibitor of the vesicular monoamine transporter (VMAT) for serotonin (Figure 12-28, upper right). Once MDMA hitch-hikes another ride into synaptic vesicles, it displaces the serotonin there, causing serotonin release from synaptic vesicles into the cytoplasm presynaptically (Figure 12-28, lower left) and then from the presynaptic cytoplasm into the synapse to act at serotonin receptors (Figure 12-28, lower right). Once in the synapse, the serotonin can play upon any serotonin receptors that are there, but the evidence suggests that this is mostly upon $5HT_{2A}$ receptors, just like the hallucinogens. However, given that the clinical state after MDMA differs somewhat from the clinical state after hallucinogens, the pattern of action at serotonin receptors likely differs somewhat. Both human and animal studies show that MDMA actions can be blocked by selective serotonin reuptake inhibitors (SSRIs), supporting the notion that MDMA gets into the presynaptic neuron to release serotonin aboard the SERT.

Although there is certainly overlap between the experiences of the so-called hallucinogen psilocybin and the so-called empathogen MDMA, some of the differences are more culturally bound than scientific. The subjective effects of MDMA emphasized by users include a sense of well-being, elevated mood, euphoria, a feeling of closeness with others, and increased sociability. MDMA can produce a complex subjective state, sometimes referred to as "Ecstasy," which is also what users call MDMA itself. It is also called "Molly," presumably slang for "molecular." MDMA was initially popular in the nightclub scene and at all-night dance parties ("raves") where dehydration and overheating from too much dancing in enclosed spaces led to some deaths from hyperthermia. Some MDMA users report experiencing visual hallucinations, pseudo-hallucinations/illusions, synesthesia, facilitated recollections or imagination, and altered perception of time and space. Others who take MDMA can have unpleasant mania-like experiences, anxious derealization, thought disorders, or fears of loss of thought and body control.

Dissociatives

Dissociatives are the NMDA (*N*-methyl-D-aspartate) receptor antagonists phencyclidine (PCP) and ketamine.

Mechanism of MDMA at Serotonin Synapses

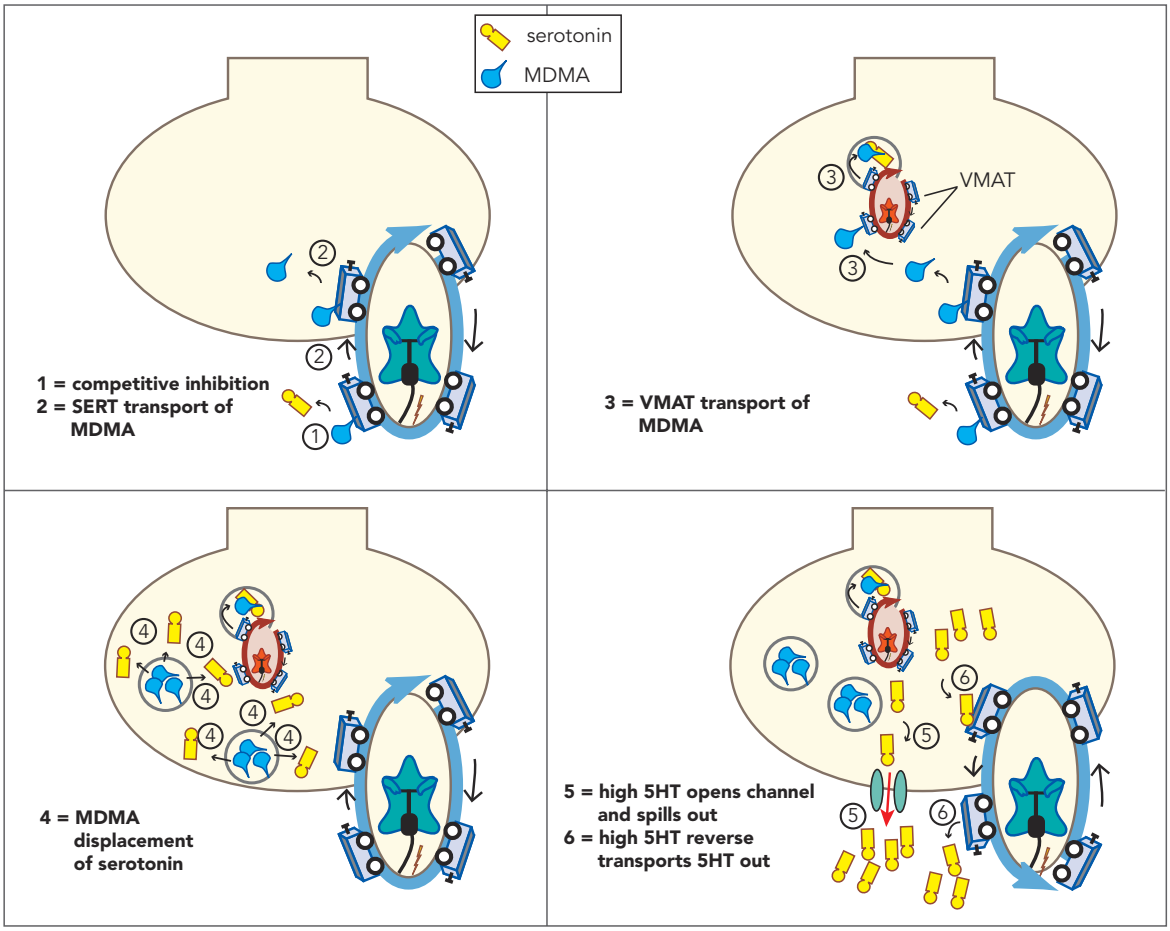


Figure 13-28 Mechanism of MDMA at serotonin synapses. MDMA is a synthetic amphetamine derivative that acts more selectively on the serotonin transporter (SERT) than on the dopamine transporter (DAT). MDMA is a competitive inhibitor and pseudosubstrate at SERTs, thus both blocking serotonin from binding (1) and itself being taken up into the serotonin terminal via SERTs (2). MDMA is also a competitive inhibitor of vesicular monoamine transporters (VMATs) and can be packaged into vesicles (3). At high levels, MDMA will lead to the displacement of serotonin from the vesicles into the terminal (4). Furthermore, once a critical threshold of serotonin has been reached, serotonin will be expelled from the terminal via two mechanisms: the opening of channels to allow for a massive dumping of serotonin into the synapse (5) and the reversal of SERTs (6).

Both act at the same site on NMDA receptors (discussed in Chapter 4 and illustrated in Figures 4-1, 4-29B, 4-30 through 4-33, and Table 4-1). These agents were both originally developed as anesthetics because they cause a dissociative state characterized by catalepsy, amnesia, and analgesia. In this state patients experience distorted perceptions of sight and sound, and feelings of detachment – dissociation – from their environment. Signals from the brain to the conscious mind and to the body seem to be blocked. If deep enough for surgery or painful procedures, this is considered a form of anesthesia called *dissociative anesthesia* in which the patient does not necessarily lose consciousness. The patient, however, does experience a sense of conscious dissociation in which they are disconnected from the environment and from their body and they experience a lack of continuity between thoughts, memories, surroundings, actions, and identity. This dissociative state can be associated with hallucinations, feelings of sensory deprivation, and a dream-like state or trance.

At higher doses, PCP and ketamine have general depressant effects and produce sedation, respiratory depression, analgesia, anesthesia, and ataxia, as well as cognitive and memory impairment and amnesia. PCP proved to be totally unacceptable for use as an anesthetic because it induces a powerful and unique psychotomimetic/hallucinatory experience very similar to schizophrenia, often when emerging from a state of anesthesia (see Chapter 4 and Figures 4-1, 4-30 through 4-33, and Table 4-1).

The NMDA receptor hypoactivity that is caused by PCP has thus become a model for the same neurotransmitter abnormalities postulated to underlie schizophrenia. PCP also causes intense analgesia, amnesia, delirium, stimulant as well as depressant actions, staggering gait, slurred speech, and a unique form of nystagmus (i.e., vertical nystagmus). Higher degrees of intoxication of PCP can cause catatonia (excitement alternating with stupor and catalepsy), hallucinations, delusions, paranoia, disorientation, and lack of judgment. Overdose can include coma, extremely high temperature, seizures, and muscle breakdown (rhabdomyolysis).

PCP's structurally related and mechanism-related analogue ketamine is still used as a dissociative anesthetic, especially in children, and causes far less of the psychotomimetic/hallucinatory experience than that seen after PCP administration. It is also used in veterinary medicine as an animal tranquilizer. Some people abuse ketamine, one of the "club drugs" that is sometimes called "special K." At subanesthetic doses, dissociatives alter many of the same cognitive and perceptual processes affected by other hallucinogenic drugs such as mescaline, LSD, and psilocybin; hence they are also considered hallucinogenic and psychedelic.

However, hallucinations are far less common with ketamine at the subanesthetic doses used to treat depression, and at these doses the most significant subjective differences between dissociatives and the hallucinogens (such as LSD, psilocybin, and mescaline) are the dissociative effects of ketamine, including: depersonalization, the feeling of being unreal, disconnected from one's self, or unable to control one's actions; and derealization, the feeling that the outside world is unreal or that one is dreaming.

Given as a subanesthetic infusion or as a nasal spray, ketamine and its enantiomer esketamine are discussed as breakthrough rapid-onset novel therapies for treatment-resistant depression in Chapter 7 and illustrated in Figures 7-59 to 7-63. These agents are also in trials for rapidly eliminating suicidal thoughts and some studies pairing ketamine/esketamine with psychotherapy sessions for various conditions have also begun to appear. The feelings of dissociation can hypothetically be used to shape psychotherapeutic outcomes as discussed below.

Abuse Your Way to Abstinence?

Essentially all of our current treatments for substance addiction target the "liking" and "wanting" of drugs, i.e., the first phase of addiction driven by *impulsively* seeking reward (Figure 13-29A). They all do this by blocking acute receptor actions (i.e., of nicotine, alcohol, or opioids; there are no approved treatments for stimulants). However, none of the currently approved treatments for substance abuse are able to block the migration of control from ventral to dorsal (Figures 13-1 and 13-2) and from impulsivity to compulsivity (Figure 13-29A). This is because we do not know the mechanism of this neuronal adaptation, so we cannot (yet) block it.

Even more importantly, addicted patients are not often treated during the *impulsivity* phase when they are still developing addiction and when receptor blocking actions of drugs might be most useful to prevent *stimulus-response conditioning*. Instead, those with substance addiction almost always seek treatment during the *compulsivity* phase of their illness, once stimulus-response conditioning has already occurred and the *habit* circuit is firmly in control. Unfortunately, we are currently unable to reverse this phenomenon pharmacologically, but only by long-term abstinence, hoping for reversal of stimulus-response conditioning over time. Staying abstinent long enough for this to occur while in the grips of addiction is the problem for any effective treatment, of course.

On the other hand, there are anecdotal reports that combining psychopharmacological treatments that can block the drug of abuse with extinction of the reward by further abusing that drug can facilitate reversal of the drug habit. What?? How can further abuse of a drug lead to non-abuse of the drug? This novel concept comes from observations that when addicted patients are becoming abstinent, they often have "slips" and "cheat" along the way. They "fall off the wagon" – or any number of other expressions for re-using again – because the nature of recovery is to relapse. If you are a horseback rider you are likely familiar with the expression "you are not a rider until you have fallen off a horse seven times." That is because the nature of riding – unfortunately – is to fall,

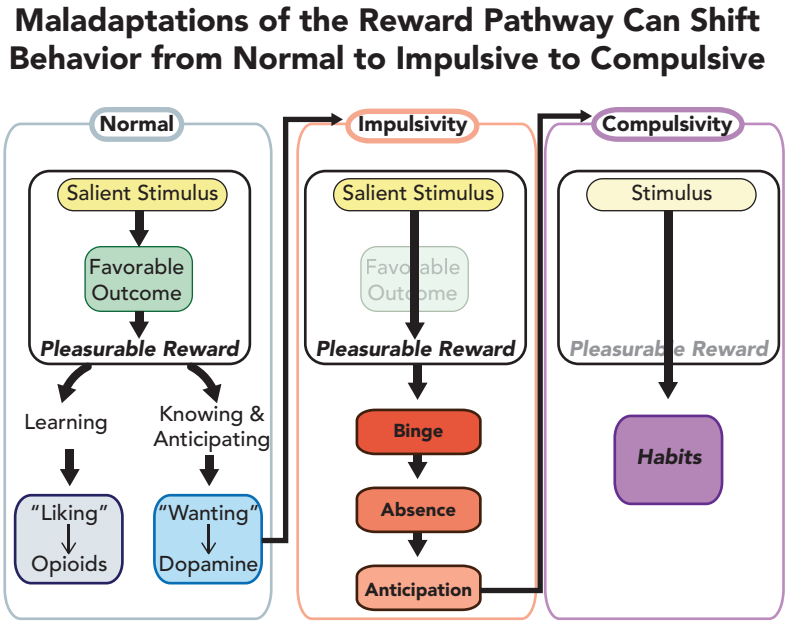


Figure 13-29A Maladaptations of the reward pathway. Left: Under normal conditions, if a salient stimulus causes a favorable outcome this behavior will be encoded as a pleasurable reward. The learning of this pleasurable reward is called "liking" and is an opioid-dependent process. The knowledge and anticipation of this pleasurable reward is called "wanting" and is a dopamine-dependent process. Center: An increase in "wanting" is thought to underlie impulsivity, such that the drive for the pleasurable reward outweighs the outcome and the behavior is repeated without forethought. Repetition of the impulsive behavior doesn't happen all the time, and the absence of the behavior can lead to a stronger desire, or anticipation, for the reward. It is this cycle of binge–abstinence–anticipation that can lead to compulsivity. Right: When a behavior becomes compulsive, the reward no longer matters and the behavior is strictly driven by the stimulus. It is through this mechanism that habits develop.

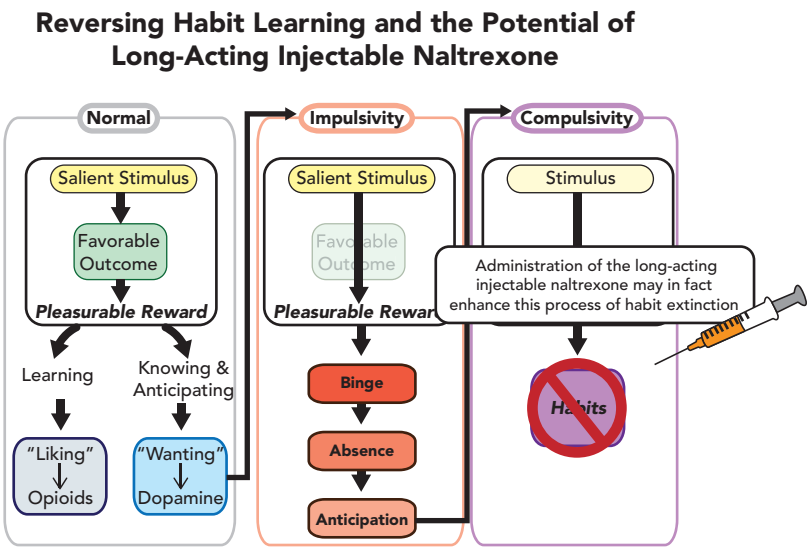


Figure 13-29B Reversing habit learning. Since drug abuse is a form of learned behavior, it is theoretically possible to induce pharmacological extinction. In the case of alcohol or opioid dependence, this can theoretically be achieved by administering a μ-opioid antagonist at the same time that alcohol or opioid use occurs (rather than during abstinence). This prevents any enjoyment or euphoria associated with taking the substance. If this approach is successful short term and repeated over and again, it begins the process of extinction or habit reversal. Eventually, the conditioned response of consuming alcohol or taking an opioid in response to conditioned stimuli (withdrawal and environmental cues) becomes extinguished. Theoretically, the brain is "relearning" to disassociate alcohol or opioid use from past triggers and control returns to circuits of voluntary actions and away from involuntary habit circuits.

especially when you are learning. Similarly, the nature of recovery is to relapse, and indeed maybe seven times or more before becoming truly abstinent. The novel concept explained here takes advantage of this inevitability of multiple relapses to reverse the habit circuit by learning that relapse is no longer rewarding.

Drink Your Way to Sobriety

This idea uses the brain's own mechanisms of neuroplasticity, learning, and migration of control in the impulsive–compulsive circuitry to induce *pharmacological extinction*. Since drug abuse is a form of learned behavior, patients with alcoholism experience enhanced reinforcement (via the opioid system) when they drink (discussed above and illustrated in Figures 13-15 and 13-16). Contrary to earlier beliefs, detoxification and alcohol deprivation do not stop alcohol craving, but instead *increase* subsequent alcohol drinking. Recovered alcoholics will often mention that many years following their last drink they still get a burst of craving just driving past their favorite bar, a vestige of their incompletely extinguished alcohol habit.

So, the idea is to give alcohol to an active alcoholic and have the patient experience the lack of enjoyment, the lack of euphoria, and the loss of craving that drinking normally produces and that heavy drinking in particular produces. The program involves taking an oral opioid antagonist (e.g., naltrexone or nalmefene) approximately 1 hour prior to consuming alcohol. When the alcohol no longer produces the desired effects because of the opioid antagonist, the alcohol is no longer reinforcing. If this approach is successful short term, and repeated over and again, it begins the process of *extinction*. The patient slowly learns that they cannot "drink over" their opioid antagonist and drinking is no longer rewarding. Or at least the reward is greatly blunted and the habit of alcohol consumption eventually becomes at least partially extinguished, making eventual abstinence easier to attain, at least in theory. Blocking the reinforcing properties of alcohol weakens the mindless automatic responses to cues in the environment to drink. The theory goes that if drinking is not reinforcing, drinking will abate. Rather like the conditioned Pavlovian dog whose mouth waters at the sound of the bell, but when food is no longer associated with the bell, sooner or later the involuntary mouth-watering is extinguished and the bell now causes no mouth-watering.

Sometimes called the Sinclair method and championed at first in Scandinavia, this therapeutic intervention for alcoholism has been tested in many clinical studies with good reported success. Interesting here is the observation that opioid antagonists are particularly *effective* when *paired with drinking*, but relatively *ineffective* when given during *abstinence*. This fits with the notion that to reverse the "habit" of drinking, extinction learning must take place where the reward of abusing alcohol is unpaired with taking alcohol (Figure 13-29B). This can also be done when attempting (and failing) to "drink over" a long-acting injection of naltrexone. Unfortunately, very little opioid antagonist therapy is prescribed for alcohol use disorder. One reason for this might be that opioid antagonist treatment is most effective in reducing heavy drinking, and not necessarily as effective in promoting complete abstinence.

Inject Your Way to Heroin Abstinence

Scandinavian and other investigators have also noted that individuals with opioid use disorder act similarly to those with alcohol use disorder in response to opioid antagonist treatment. That is, individuals dependent on opioids who attempt to "inject over" long-acting naltrexone with an illicit street opioid find that the opioid is no longer reinforcing. The more times one tries but fails to get high, the faster they develop extinction of their habit, learning that injections are associated with reward (Figure 13-29B). The learned behavior of reinforcement from opioids is now slowly reversed as the act of injecting an opioid is not rewarding. Eventually, the conditioned response of taking an opioid in response to conditioned stimuli (withdrawal and environmental cues) becomes extinguished (Figure 13-29B). Theoretically, the brain is "relearning" to disassociate opioid use from past triggers and control returns to circuits of voluntary actions and away from involuntary habit circuits. Unfortunately, very little opioid antagonist treatment is prescribed for opioid addicts.

Smoke Your Way to Quitting

This same phenomenon of "cheating" assisting the development of abstinence due to behavioral and pharmacological extinction has been seen in smoking cessation treatment as well. Many smokers who take treatments to stop smoking nevertheless simultaneously smoke. Thus, such patients "smoke over" their nicotine patch or bupropion and are able to quell craving and allow their habit to perpetuate in the face of treatment. However, with the nicotinic partial agonist varenicline, they cannot "smoke over" this treatment since it has higher affinity for nicotinic receptors than nicotine itself and the result is a lack of reinforcement from the cheating

while taking varenicline. If smoking on varenicline is no longer reinforcing and this is repeated again and again, as for alcohol and opioids, smoking becomes extinguished as a conditioned response as the brain "unlearns" the habit of smoking (Figure 13-29B).

"Therapeutic" Dissociation, Hallucinations, and Empathy?

The ability of dissociative agents, hallucinogens, and empathogens to produce mystical-like experiences has been utilized within ancient cultures and indigenous populations for religious and healing purposes for centuries. In the modern era, these same agents are starting to be used in a process called "dissociation-assisted psychotherapy" to produce these same experiences in a controlled setting with a psychotherapist. The idea is that mystical states with feelings of oceanic boundlessness, internal unity, external unity, sacredness, "noetic" insights, transcendence of time and space, deeply felt positive mood, and ineffability can be guided with psychotherapy to potentially "heal" some of the most treatment-resistant disorders in psychiatry.

These are early days for this approach, and the parameters that might lead to successful outcome are still being defined. Some of the variables are "set," "setting," and "cast." That is, what is the "mind-set" of the patient; what is the "setting" or environment, including sounds of the room where this experience occurs; and who are the "cast," including therapist and any others that are present. Preparation variables to be clarified include having established a trusting relationship between the patient and therapist in advance, explaining to the patient what to expect, and selection of drug, dose, and accompanying psychotherapy. Few of these variables are well established yet. Most of these approaches to date have used ketamine, psilocybin, or MDMA to induce the dissociative or mystical-like psychological state in a therapist's office, while conducting psychotherapy for up to several hours. Psychotherapies studied include nondirectedness/self-directedness, mindfulness-based behavioral modification, motivational enhancement therapy, and others.

Ketamine-Assisted Psychotherapy

Use of ketamine and esketamine without psychotherapy for treatment-resistant depression has been discussed in Chapter 7 and illustrated in Figures 7-59 to 7-62. Investigators are now evaluating subanesthetic infusions of ketamine for treating the craving and abuse of a wide range of substances including cocaine, nicotine, and alcohol, with some success. One of the ideas behind the use of ketamine is to promote prefrontal neural plasticity (see Figures 7-61 and 7-62) to reverse drug-related ventral to dorsal migration of neuronal control discussed extensively in this chapter (see Figure 13-29A), and to facilitate this with guidance from a psychotherapist.

Psilocybin-Assisted Psychotherapy

Originally utilized for the treatment of anxiety related to late-stage cancer, psilocybin use has been expanded to the treatment of other resistant anxiety disorders and notably to treatment-resistant depression, with some promising preliminary results. Psilocybin is also under investigation in OCD, pain, various addictions, sexual dysfunction, cluster headaches, mild traumatic brain injury, and many more conditions. It is not known whether the psychological state induced by psilocybin or the pharmacology of psilocybin is responsible for any therapeutic effects, or whether the differences between these variables and those induced by either ketamine or MDMA play a role in which patients, with which disorders, might respond. Any role of $5HT_{2A}$ receptors in triggering potentially favorable neuroplastic changes analogous to those seen with ketamine remains to be determined.

MDMA-Assisted Psychotherapy

The idea here is that an empathic state induced by MDMA may be even better than a mystical state induced by psilocybin or a dissociative state induced by ketamine, in that it renders the patient more amenable to exploring painful memories. MDMA has been mostly studied in PTSD, attempting to reduce traumatic memories and the symptoms they trigger. First-line treatment of PTSD is exposure therapy (fear extinction), but there are many patients for whom repeated exposure to the traumatic memory is either unsuccessful or too painful. Extinction of fearful memories was discussed in Chapter 8 on anxiety disorders and illustrated in Figures 8-21 and 8-22. MDMA can potentially provide a safe psychological state where there can be self-directed exploration of painful traumatic memories in the presence of a therapist, in order to contextualize them and thus reduce them. In Chapter 8, the process of reconsolidation of traumatic memories was also discussed and illustrated in Figure 8-21 and 8-22. In this formulation, emotional memories are thought to be amenable to weakening or even erasure at the time they are re-experienced. The notion is that re-experiencing the traumatic memory in a safe psychological state induced by MDMA, and accompanied

by a trusted and experienced therapist, can facilitate the blocking or weakening of reconsolidation of painful emotional memories.

BEHAVIORAL ADDICTIONS

Binge Eating Disorder

Can you become addicted to food? Can your brain circuits make you eat it? Although "food addiction" is not yet accepted as a formal diagnosis, binge eating disorder (BED) is now a formal DSM diagnosis. When external stimuli are triggers for maladaptive eating habits that are performed despite apparent satiety and adverse health consequences, this defines a compulsion and a habit, with the formation of aberrant eating behaviors in a manner that parallels drug addiction. Compulsive eating in BED and bulimia can be mirrored by compulsive rejection of food as in anorexia nervosa. BED is characterized by loss of control for eating, much as substance abuse has loss of control over seeking and taking a substance. For formal diagnostic criteria and clinical descriptions of BED as well as differentiation from the related disorder bulimia nervosa, the reader is referred to standard reference books. Here, we address the construct of BED as falling within the category of an impulsive–compulsive disorder.

Briefly, BED is defined as having recurrent episodes of binge eating, with binges being eaten in a discrete period of time, an amount of food larger than most people would eat in a similar amount of time under similar circumstances. What was once perhaps pleasurable eating to satisfy hunger and appetite has now become mindless, compulsive eating, out of control, and associated with marked distress. Not everyone with BED is obese and not everyone with obesity has BED even though about half of people with BED are obese. BED is the most common eating disorder but is commonly undiagnosed. Many clinicians do not inquire about this even if the patient is obese, perhaps because of fear that asking will be taken as offensive by the patient. It is a reality that most BED patients coming to a healthcare professional have a comorbid psychiatric condition, and are usually seeking treatment for that rather than for binge eating. In fact, 80% of patients with BED meet the criteria for a mood disorder, anxiety disorder, other substance abuse disorder, or ADHD. One thing for a clinician to remember is to ask about binge eating in patients with any of these conditions because treatment is available and the long-term complications of obesity are serious (discussed in Chapter 5 on drugs for psychosis). In fact, the D-amphetamine precursor lisdexamfetamine discussed in Chapter 11 on ADHD and illustrated in Figure 11-31 is the only currently approved treatment for BED.

Several agents with limited efficacy and side effects used off-label include topiramate, several drugs used to treat depression, and naltrexone. BED is another condition that belongs in the addictive disorders group and amongst the impulsive–compulsive disorders as it, too, is hypothesized to be linked to abnormalities in cortical striatal circuitry where impulsivity (Figure 13-1) leads to compulsivity (Figure 13-2). The mechanism of D-amphetamine reversing binge eating symptoms may not be due to suppressing appetite since appetite no longer really drives binge eating disorder when it becomes compulsive. Instead, it is known that stimulants induce neuroplasticity particularly in the striatum. Hypothetically, promotion of striatal neuroplasticity could help reverse food-related behaviors that have had their control migrate from ventral to dorsal control when impulsive eating became compulsive. As for most impulsive–compulsive disorders, most studies adding various psychotherapies to drug treatment of BED report enhancement of efficacy.

Other Behavioral Addictions

Although behaviors such as *gambling* and too much *internet gaming* have many parallels to BED and to substance abuse disorders, these are not yet generally recognized formally as behavioral "addictions." Internet addiction can involve an inability to stop the behavior, tolerance, withdrawal, and relief when reinitiating the behavior. Many experts believe gambling disorder should be classified along with drug addiction and BED as a nonsubstance abuse/behavioral addiction disorder. Gambling disorder is characterized by repeated unsuccessful efforts to stop despite adverse consequences, tolerance (gambling higher and higher dollar amounts), psychological withdrawal when not gambling, and relief when reinitiating gambling. Gambling has been observed after treatment with dopamine agonists and partial agonists, suggesting that stimulating the mesolimbic dopamine reward system can induce gambling in some patients. The neurobiology and treatment of other behavioral disorders listed in Table 13-1 are all under investigation as possible impulsive to compulsive and thus ventral to dorsal shifts of control of the abnormal or undesired behavior. The hope is that therapies useful for one of the impulsive–compulsive disorders might be helpful across the spectrum of other disorders in this group.

OBSESSIVE-COMPULSIVE AND RELATED DISORDERS

Obsessive–compulsive disorder (OCD) was once classified as an anxiety disorder (Figure 13-30) but is now placed in its own category by some diagnostic systems such as the DSM-5. In OCD, many patients experience an intense urge to perform stereotypic, ritualistic acts despite having full insight into how senseless and excessive these behaviors are, and having no real desire for the outcome of these actions. The most common types of compulsions are checking and cleaning. For OCD, a general propensity towards habit may be expressed solely as avoidance, deriving from the comorbid anxiety reported. In the context of high anxiety, superstitious avoidance responses may offer relief, which reinforces the behavior. Stress and anxiety may enhance the formation of habits, whether positively or negatively motivated. However, as the habit becomes progressively compulsive, the experience of relief may no longer be the driving force and instead the behavior comes under external control as a conditioned response. Excessive inflexible behaviors are often thought to be carried out in order to neutralize anxiety or distress evoked by particular obsessions. Paradoxically, although OCD patients feel compelled to perform these behaviors, they are often aware that they are more disruptive than helpful. So why do they do them? Rather than conceptualizing compulsive behaviors as goal-directed to reduce anxiety (Figure 13-30), these rituals might be better understood as habits provoked mindlessly from a stimulus in the environment. This is why some diagnostic systems no longer categorize OCD as an anxiety disorder.

The compulsive habits provoked by environmental stimuli in OCD are hypothetically the same phenomenon within the same neurocircuits as described throughout this chapter for addiction. So, are OCD patients addicted to their obsessions and to their compulsions? Certainly, that is one way to look at OCD symptoms. OCD patients have demonstrated lack of efficient information processing in their orbitofrontal cortex (Figure 13-2) and lack of cognitive flexibility, and thus cannot inhibit their compulsive responses/habits. Just like drug addicts. Such hypothesized habit learning in OCD – called addiction when applied to drugs, gambling, and binge eating – can be reduced or reversed in OCD with exposure and response prevention, involving graded exposure to anxiety-provoking stimuli/situations, and prevention of the associated avoidance compulsions. This type of cognitive behavioral therapy is thought to have its therapeutic effect by breaking the pattern of compulsive avoidance that confers dominant control to the external environment (such that the sight of a door elicits checking) and also maintains inappropriate anxiety. Instead of considering compulsions as behavioral reactions to abnormal obsessions, the reverse may be true: obsessions in OCD may in fact be post hoc rationalizations of otherwise inexplicable compulsive urges. Unfortunately, this same type of cognitive behavioral therapy has often proven less effective in drug and behavioral addictions. If successful, cognitive behavioral therapy reverses

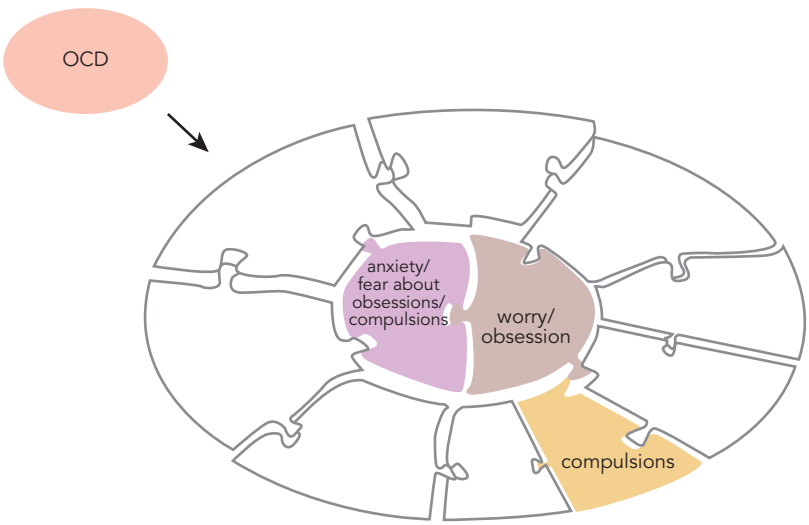


Figure 13-30 Obsessive–compulsive disorder (OCD). The symptoms typically associated with OCD are shown here and include obsessions that are intrusive and unwanted and that cause marked anxiety or distress, as well as compulsions that are aimed at preventing or suppressing the distress related to the obsessive thoughts. Compulsions can be repetitive behaviors (e.g., hand-washing, checking) or mental acts (e.g., praying, counting).

habits in OCD as it therapeutically helps to migrate the neurocircuit of control of OCD behaviors from dorsal back to ventral, where it belongs. Some other form of doing this same thing may be the key to developing robust treatments for addictions, most of which have little or no highly effective therapeutic drugs or interventions.

First-line drug treatment of OCD today is one of the SSRIs, although their efficacy is modest and half of patients treated with these agents show poor responses. Behavioral treatments such as exposure therapy with response prevention often have greater efficacy than serotonergic treatments. It seems as if serotonergic therapies suppress abnormal neurocircuitry, whereas exposure therapy may actually reverse abnormal neurocircuitry because symptoms continue to be improved after stopping exposure therapy but not after stopping SSRIs. Although second-line treatments with one of the tricyclic antidepressants with serotonergic properties, clomipramine, with serotonin–norepinephrine reuptake inhibitors (SNRIs) or with monoamine oxidase inhibitors (MAOIs) are all worthy of consideration, the best pharmacological option for a patient who has failed several SSRIs is often to consider very high doses with an SSRI or augmentation of an SSRI with a serotonin–dopamine blocker. The mechanisms of action of all of these agents are covered in detail in Chapter 5 and 7. Augmentation of an SSRI with a benzodiazepine, lithium, or buspirone can also be considered. Repetitive transcranial magnetic stimulation (rTMS) is an approved treatment for OCD. Experimental treatments for OCD include deep brain stimulation, or even stereotactic ablation of the impulsive–compulsive pathways shown in Figures 13-1 and 13-2, for the most resistant of cases.

Conditions related to OCD may respond somewhat to SSRIs, including hoarding, compulsive shopping, skin picking, and body dysmorphic disorder, but not especially trichotillomania (compulsive hair pulling). No agent is officially approved for any of these conditions (Table 13-1). Body dysmorphic disorder for example is preoccupation with perceived defects or flaws in appearance that cause repetitive behavior like looking in the mirror, grooming, reassurance seeking. Preoccupation with health, body function, and pain exist in hypochondriasis and somatization disorders and some experts consider these types of obsessions. It is clear that more robust treatments with a different mechanism of action are needed for the group of obsessive–compulsive related disorders.

IMPULSE CONTROL DISORDERS

A large variety of disorders that have lack of control of impulsivity are listed in Table 13-1. How many of these disorders can be conceptualized within the impulsive–compulsive spectrum, with abnormalities of cortico-striatal circuitry, remains to be shown, but the descriptive parallels between the impulsive symptoms of these various and sundry conditions gives face validity to this notion. Since the impulsivity of none of these conditions has an approved treatment, we are left with the hope that interventions that work in one of the impulsive–compulsive disorders may be effective across the spectrum of disorders that share this same dimension of psychopathology. However, this remains to be proven and has the risk of oversimplifying some very complex and very different disorders (Table 13-1). One general principle being tested and that may apply across the waterfront of these many and varied disorders is that interventions that can stop the frequent repetition of short-term rewarding impulsive behaviors may hopefully act to prevent converting them into long-term habits that lead to poor functional outcomes.

Aggression and *violence* have long been controversial issues in psychiatry. Experts categorize violence as psychotic, impulsive, or psychopathic, with the most common being impulsive (Figure 13-31). Perhaps somewhat surprisingly, the least frequent type of violent act is one due to cold, calculated psychopathy. Psychopathic violence seems to be the most lethal and the least responsive to treatment. Approximately 20% of violent acts are of the psychotic variety and require standard if not aggressive treatment for the underlying psychotic illness. The most frequent type of violent act is impulsive, especially in institutional settings and especially in patients with underlying psychotic illnesses (Figure 13-31).

Each type of aggression may be attributable to dysfunction in distinct neural circuits, with impulsive violence being linked to the same problems of balancing top-down inhibition with bottom-up emotional drives, as discussed in Chapter 12 on agitation in dementia and illustrated in Figures 12-43 and 12-44. Impulsive violence can occur in psychotic disorders of many types, including drug-induced psychosis, schizophrenia, and bipolar mania, as well as in borderline personality disorder and other impulsive–compulsive disorders (Table 13-1). Treatment of the underlying condition, often with drugs for psychosis (discussed in Chapter 5),

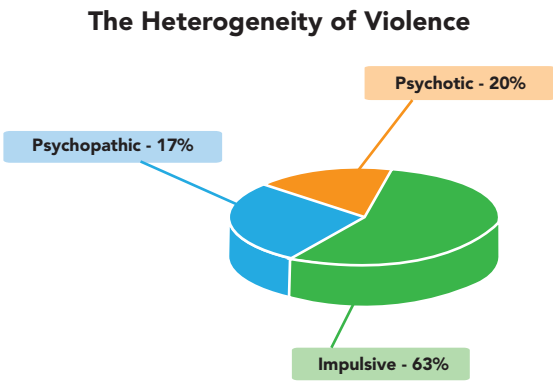


Figure 13-31 Heterogeneity of violence. Violence is categorized as psychotic, impulsive, or psychopathic. The most common form is impulsive and the least common is psychopathic. Approximately 20% of violent acts are of the psychotic variety.

can be helpful. Aggression and violence in such disorders can be considered examples of the imbalance between top-down "stop" signals, and bottom-up drives and "go" signals, as already discussed in dementia (Figures 12-43 and 12-44) and in several other impulsive–compulsive disorders (Table 13-1). Impulsive aggression can be considered a type of addictive behavior when it becomes increasingly compulsive, rather than manipulative and planned, and a habit that must be extinguished with behavioral interventions rather than with purely psychopharmacological approaches

SUMMARY

We have discussed the current conceptualization of impulsivity and compulsivity as dimensions of psychopathology that cut across many psychiatric disorders. Rewarding behaviors and addiction to drugs hypothetically share the same underlying circuitry. These disorders are characterized at first by impulsivity – defined as behaviors that are difficult to prevent because short-term reward is chosen over long-term gain. Such impulsivity is hypothetically mapped onto a prefrontal ventral striatal reward circuit. Impulsivity can transition to compulsivity – defined as an originally rewarding behavior becoming a habit that is difficult to stop because it reduces tension and withdrawal effects. Compulsivity is hypothetically mapped onto a prefrontal dorsal motor response inhibition circuit. Failure of the balance between top-down inhibition and bottom-up drives is the common underlying neurobiological mechanism of impulsivity and its transition to compulsivity.

Both drugs and behaviors can be associated with impulsivity/compulsivity and are dimensions of psychopathology for a wide range of drug addictions and psychiatric disorders. The chapter discusses the psychopharmacology of reward and the brain circuitry that regulates reward. We have attempted to explain the psychopharmacological mechanisms of actions of various drugs of abuse, from nicotine to alcohol, and also opioids, stimulants, sedative hypnotics, cannabis, hallucinogens, empathogens, and dissociative drugs. In the case of nicotine and alcohol, various novel psychopharmacological treatments are discussed, including the $\alpha_4\beta_2$ selective nicotine partial agonist (NPA) varenicline for smoking cessation, opioid replacement therapies for opioid addiction, and opioid antagonists for both alcohol and opioid addiction. Use of habit extinction in treatment of addiction is explored as is the evolving use of dissociative/hallucinogen-assisted psychotherapy for treatment-resistant conditions. Binge eating disorder is discussed as the prototypical behavioral addiction, and its treatment with stimulants. Impulsive violence is mentioned as a possible form of impulsive–compulsive disorder as well.

Suggested Reading and Selected References

General References: Specialty Textbooks

Brunton LL (ed.) (2018) *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 13th edition. New York, NY: McGraw Medical.

Schatzberg AF, Nemeroff CB (eds.) (2017) *Textbook of Psychopharmacology*, 5th edition. Washington, DC: American Psychiatric Publishing.

General References:Textbooks in the *Stahl's Essential Psychopharmacology* Series

Cummings M, Stahl SM (2021) *Management of Complex, Treatment-Resistant Psychiatric Disorders*. Cambridge: Cambridge University Press.

Goldberg J, Stahl SM (2021) *Practical Psychopharmacology*. Cambridge: Cambridge University Press.

Kalali A, Kwentus J, Preskorn S, Stahl SM (eds.) (2012) *Essential CNS Drug Development*. Cambridge: Cambridge University Press.

Marazzitti D, Stahl SM (2019) *Evil, Terrorism and Psychiatry*. Cambridge: Cambridge University Press.

Moutier C, Pisani A, Stahl SM (2021) *Stahl's Handbooks: Suicide Prevention Handbook*. Cambridge: Cambridge University Press.

Pappagallo M, Smith H, Stahl SM (2012) *Essential Pain Pharmacology: the Prescribers Guide*. Cambridge: Cambridge University Press.

Reis de Oliveira I, Schwartz T, Stahl SM. (2014) *Integrating Psychotherapy and Psychopharmacology*. New York, NY: Routledge Press.

Silberstein SD, Marmura MJ, Hsiangkuo Y, Stahl SM (2016) *Essential Neuropharmacology: the Prescribers Guide*, 2nd edition. Cambridge: Cambridge University Press.

Stahl SM (2009) *Stahl's Illustrated: Antidepressants*. Cambridge: Cambridge University Press.

Stahl SM (2009) *Stahl's Ilustrated: Mood Stabilizers*. Cambridge: Cambridge University Press.

Stahl SM (2009) *Stahl's Illustrated: Chronic Pain and Fibromyalgia*. Cambridge: Cambridge University Press.

Stahl SM, Mignon L (2009) *Stahl's Illustrated: Attention Deficit Hyperactivity Disorder*. Cambridge: Cambridge University Press.

Stahl SM, Mignon L (2010) *Stahl's Illustrated: Antipsychotics*, 2nd edition. Cambridge: Cambridge University Press.

Stahl SM, Grady MM (2010) *Stahl's Illustrated: Anxiety and PTSD*. Cambridge: Cambridge University Press.

Stahl SM (2011) *Essential Psychopharmacology Case Studies*. Cambridge: Cambridge University Press.

Stahl SM (2018) *Stahl's Essential Psychopharmacology: the Prescribers Guide Children and Adolescents*. Cambridge: Cambridge University Press.

Stahl SM (2019) *Stahl's Self-Assessment Examination in Psychiatry: Multiple Choice Questions for Clinicians*, 3rd edition. Cambridge: Cambridge University Press.

Stahl SM (2021) *Stahl's Essential Psychopharmacology: the Prescribers Guide*, 7th edition. Cambridge: Cambridge University Press.

Stahl SM, Davis RL (2011) *Best Practices for Medical Educators*, 2nd edition. Cambridge: Cambridge University Press.

Stahl SM, Grady MM (2012) *Stahl's Illustrated: Substance Use and Impulsive Disorders*. Cambridge: Cambridge University Press.

Stahl SM, Moore BA (eds.) (2013) *Anxiety Disorders: a Concise Guide and Casebook for Psychopharmacology and Psychotherapy Integration*. New York, NY: Routledge Press.

Stahl SM, Morrissette DA (2014) *Stahl's Illustrated: Violence: Neural Circuits, Genetics and Treatment*. Cambridge: Cambridge University Press.

Stahl SM, Morrissette DA (2016) *Stahl's Illustrated: Sleep and Wake Disorders*, Cambridge: Cambridge University Press.

Stahl SM, Morrissette DA (2018) *Stahl's Illustrated: Dementia*. Cambridge: Cambridge University Press..

Stahl SM, Schwartz T (2016) *Case Studies: Stahl's Essential Psychopharmacology*, Volume 2. Cambridge: Cambridge University Press.

Stein DJ, Lerer B, Stahl SM (eds.) (2012) *Essential Evidence Based Psychopharmacolgy*, 2nd edition. Cambridge: Cambridge University Press.

Warburton KD, Stahl SM (2016) *Violence in Psychiatry*. Cambridge: Cambridge University Press.

Warburton KD, Stahl SM (2021) *Decriminalizing Mental Illness*. Cambridge: Cambridge University Press.

Chapters 1–3 (Basic Neuroscience): Textbooks

Byrne JH, Roberts JL (eds.) (2004) *From Molecules to Networds: An Introduction to Cellular and Molecular Neuroscience*. New York, NY: Elsevier.

Charney DS, Buxbaum JD, Sklar P, Nestler EJ (2018) *Charney and Nestler's Neurbiology of Mental Illness*, 5th edition. New York, NY: Oxford University Press.

Iversen LL, Iversen SD, Bloom FE, Roth RH (2009) *Introduction to Neuropsychopharmacology*. New York, NY: Oxford University Press.

Meyer JS, Quenzer LF (2019) *Psychopharmacology: Drugs, the Brain, and Behavior*, 3rd edition. New York, NY: Sinauer Associates, Oxford University Press.

Nestler EJ, Kenny PJ, Russo SJ, Schaefer A (2020) *Molecular Neuropharmacology: A Foundation for Clinical Neuroscience*, 4th edition. New York, NY: McGraw Medical.

Purves D, Augustine GJ, Fitzpatrick D, et al. (2018) *Neuroscience*, 6th edition. New York, NY: Sinauer Associates, Oxford University Press.

Squire LR, Berg D, Bloom FE, et al. (eds.) (2012) *Fundamental Neuroscience*, 4th edition. San Diego, CA: Academic Press.

Chapters 4 (Psychosis, Schizophrenia, and the Neurotransmitter Networks Dopamine, Serotonin, and Glutamate) and 5 (Targeting Dopamine and Serotonin Receptors for Psychosis, Mood, and Beyond: So-called "Antipsychotics")

Neuronal Networks – Serotonin, Dopamine, and Glutamate: Selected References

Alex KD, Pehak EA (2007) Pharmacological mechanisms of serotoninergic regulation of dopamine neurotransmission. *Pharmacol Ther* 113: 296–320.

Amargos-Bosch M, Bortolozzi A, Buig MV, et al. (2004) Co-expression and in vivo interaction of serotonin 1A and serotonin 2A receptors in pyramidal neurons of prefrontal cortex. *Cerbral Cortex* 14: 281–99.

Baez MV, Cercata MC, Jerusalinsky DA (2018) NMDA receptor subunits change after synaptic plasticity induction and learning and memory acquisition. *Neural Plast*, doi. org/10,1155/2018/5093048.

Beaulier JM, Gainetdinov RR (2011) The physiology, signaling and pharmacology of dopamine receptors. *Pharmacol Rev* 63: 182–217.

Belmer A, Quentin E, Diaz SL, et al. (2018) Positive regulation of raphe serotonin neurons by serotonin 2B receptors. *Neuropsychopharmacology* 42: 1623–32.

Calabresi P, Picconi B, Tozzi A, Ghiglieri V, Di Fillippo M (2014) Direct and indirect pathways of basal ganglia: a critical reappraisal. *Nature Neurosci* 17: 1022–30.

Cathala A, Devroye C, Drutel G, et al. (2019) Serotonin 2B receptors in the rat dorsal raphe nucleus exert a GABA-mediated tonic inhibitor control on serotonin neurons. *Exp Neurol* 311: 57–66.

De Bartolomeis A, Fiore G, Iasevoli F (2005) Dopamine glutamate interaction and antipsychotics mechanism of action: implication for new pharmacologic strategies in psychosis. *Curr Pharmaceut Design* 11: 3561–94.

DeLong MR, Wichmann T (2007) Circuits and Ciruit disorders of the basal ganglia. *Arch Neurol* 64: 20–4.

Fink KB, Gothert M (2007) 5HT receptor regulation of neurotransmitter release. *Pharmacol Rev* 59: 360–417.

Hansen KB, Yi F, Perszyk RE, et al (2018) Structure, function and allosteric modulation of NMDA receptors. *J Gen Physiol* 150: 1081–105.

Homayoun H, Moghaddam B (2007) NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons. *J Neurosci* 27: 11496–500.

Nicoll RA (2017) A brief history of long-term potentiation. *Neuron* 93: 281–99.

Paoletti P, Neyton J (2007) NMDA receptor subunits: function and pharmacology. *Curr Opin Pharmacol* 7: 39–47.

Scheefhals N, MacGillavry HD (2018) Functional organization of postsynaptic glutamate receptors. *Mol Cell Neurosci* 91: 82–94.

Sokoloff P, Le Foil B (2017) The dopamine D_3 receptor: a quarter century later. *Eur J Neurosci* 45: 2–19.

Stahl SM (2017) Dazzled by the dominions of dopamine: clinical roles of D_3, D_2, and D_1 receptors. *CNS Spectrums* 22: 305–11.

Dopamine, Serotonin, and Glutamate Theories of Psychosis, Including Schizophrenia, Parkinson's Disease Psychosis, and Dementia-Related Psychosis

Aghajanian GK, Marek GJ (2000) Serotonin model of schizophrenia: emerging role of glutamate mechanisms. *Brain Res Rev* 31: 302–12.

Bloomfield MAP, Morgan CJA, Egerton A, et al. (2014) Dopaminergic function in cannabis users and its relationship to cannabis-induced psychotic symptoms. *Biol Psychiatry* 75: 470–8.

Brugger SP, Anelescu I, Abi-Dargham A, et al. (2020) Heterogeneity and striatal dopamine function in schizophrenia: meta analysis of variance. *Biol Psychiatry* 67: 215–24.

Bubenikova-Valesova V, Horacek J, Vrajova M, et al. (2008) Models of schizophrenia in humans and animals based on inhibition of NMDA receptors. *Neurosci Biobehav Rev* 32: 1014–23.

Demjaha A, Murray RM, McGuire PK (2012) Dopamine synthesis capacity in patients with treatment resistant schizophrenia. *Am J Psychiatry* 169: 1203–10.

Driesen N, McCarthy G, Bhagwagar Z, et al (2013) The impact of NMDA receptor blockade on human working memory-related prefrontal function and connectivity. *Neuropsychopharmacol* 38: 2613–22.

Egerton A, Chaddock CA, Winton-Brown TT, et al. (2013) Presynaptic striatal dopamine dysfunction in people at ultra high risk for psychosis: findings in a second cohort. *Biol Psychiatry* 74: 106–12.

Gellings Lowe N, Rapagnani MP, Mattei C, Stahl SM (2012)The psychopharmacology of hallucinations: ironic insights into mechanisms of action. In *The Neuroscience of Hallucinations*, Jardri R, Thomas P, Cachia A and Pins D. (eds.), Berlin: Springer, 471–92.

Howes OD, Bose SK, Turkheimer F, et al. (2011) Dopamine synthsis capacity before onset of psychosis: a prospective ^{18}F-DOPA PET imaging study. *Am J Psychiatry* 169: 1311–17.

Howes OD, Montgomery AJ, Asselin MC, et al. (2009) Elevated striatal dopamine function linked to prodromal signs of schizophrenia. *Arch Gen Psychiatry* 66: 13–20.

Juahar S, Nour MM, Veronese M, et al. (2017) A test of the transdiagnostic dopamine hypothesis of psychosis using positron emission tomographic imaging in bipolar affective disorder and schizophrenia. *JAMA Psychiatry* 74: 1206–13.

Lodge DJ, Grace AA (2011) Hippocampal dysregulation of dopamine system function and the pathophysiology of schizophrenia. *Trends Pharmacol Sci* 32: 507–13.

McCutcheon RA, Abi-Dargham A, Howes OD (2019) Schizophrenia, dopamine and the striatum: from biology to symptoms. *Trends Neurosci* 42: 205–20.

Mizrahi R, Kenk M, Suridjan I, et al (2014) Stress induced dopamine response in subjects at clinical high risk for schizophrenia with and without concurrent cannabis use. *Neuropsychopharmacology* 39: 1479–89.

Paz RD, Tardito S, Atzori M (2008) Glutamatergic dysfunction in schizophrenia: from basic neuroscience to clinical psychopharmacology. *Eur Neuropsychopharmacol* 18: 773–86.

Stahl SM (2016) Parkinson's disease psychosis as a serotonin–dopamine imbalance syndrome. *CNS Spectrums* 21: 355–9.

Stahl SM (2018) Beyond the dopamine hypothesis of schizophrenia to three neural networks of psychosis: dopamine, serotonin, and glutamate. *CNS Spectrums* 23: 187–91.

Weinstein JJ, Chohan MO, Slifstein M, et al. (2017) Pathway-specific dopamine abnormalities in schizophrenia. *Biol Psychiatry* 81: 31–42.

General Schizophrenia: Selected and Recent References

Alphs LD, Summerfelt A, Lann H, Muller RJ (1989) The Negative Symptom Assessment: A new instrument to assess negative symptoms of schizophrenia. *Psychopharmacol Bull* 25: 159–63.

Arango C, Rapado-Castro M, Reig S, et al. (2012) Progressive brain changes in children and adolescents with first-episode psychosis. *Arch Gen Psychiatry* 69: 16–26.

Cruz DA, Weawver CL, Lovallo EM, Melchitzky DS, Lewis DA. (2009) Selective alterations in postsynaptic markers of chandelier cell inputs to cortical pyramidal neurons in subjects with schizophrenia. *Neuropsychopharmacology* 34: 2112–24.

Dragt S, Nieman DH, Schultze-Lutter F, et al. (2012) Cannabis use and age at onset of symptoms in subjects at clinical high risk for psychosis. *Acta Psychiatr Scand* 125: 45–53.

Eisenberg DP, Berman KF (2010) Executive function, neural circuitry, and genetic mechanisms in schizophrenia. *Neuropsychopharmacology* 35: 258–77.

Foti DJ, Kotov R, Guey LT, Bromet EJ (2010) Cannabis use and the course of schizophrenia: 10-year follow-up after first hospitalization. *Am J Psychiatry* 167: 987–93.

Fusar-Poli P, Bonoldi I, Yung AR, et al. (2012) Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. *Arch Gen Psychiatry* 69: 220–9.

Goff DC, Zeng B, Ardelani BA, et al. (2018) Association of hippocampal atrophy with duration of untreated psychosis and molecular biomarkers during initial antipsychotic treatment of first episode psychosis. *JAMA Psychiatry* 75: 370–8.

Henry LP, Amminger GP, Harris MG, et al. (2010) The EPPIC follow up study of first episode psychosis: longer term clinical and functional outcome 7 years after index admission. *J Clin Psychiatry* 71: 716–28.

Kane JM, Robinson DG, Schooler NR, et al. (2016) Comprehensive versus usual community care for first-episode psychosis: 2-year outcomes from the NIMH RAISE early treatment program. *Am J Psychiatry* 173: 362–72.

Kendler KS, Ohlsson H, Sundquist J, et al. (2019) Prediction of onset of substance induced psychotic disorder and its progression to schizophrenia in a Swedish National Sample. *Am J Psychiatry* 176: 711–19.

Large M, Sharma S, Compton MT, Slade T, Nielssen O (2011) Cannabis use and earlier onset of psychosis. *Arch Gen Psychiatry* 68: 555–61.

Lieberman JA, Small SA, Girgis RR (2019) Early detection and preventive intervention in schizophrenia: from fantasy to reality. *Am J Psychiatry* 176: 794–810.

Mechelli A, Riecher-Rossler A, Meisenzahl EM, et al. (2011) Neuroanatomical abnormalities that predate the onset of psychosis. *Arch Gen Psychiatry* 68: 489–95.

Morrissette DA, Stahl SM (2014) Treating the violent patient with psychosis or impulsivity utilizing antipsychotic polypharmacy and high-dose monotherapy. *CNS Spectrums* 19: 439–48.

Stahl SM (2014) Deconstructing violence as a medical syndrome: mapping psychotic, impulsive, and predatory subtypes to malfunctioning brain circuits. *CNS Spectrums* 19: 357–65.

Stahl SM (2015) Is impulsive violence an addiction? The habit hypothesis. *CNS Spectrums* 20: 165–9.

Stahl SM, Morrissette DA, Cummings M (2014) California State Hospital Violence Assessment and Treatment (Cal-VAT) guidelines. *CNS Spectrums* 19: 449–65.

Wykes T, Huddy V, Cellard C, McGurk SR, Czobar P (2011) A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *Am J Psychiatry* 168: 472–85.

Tardive Dyskinesia and Treatments

Artukoglu BB, Li F, Szejko N, et al. (2020) Pharmacologic treatment of tardive dyskinesia: a meta analysis and systematic review. *J Clin Psychiatry* 81: e1–11.

Bhidayasin R, Jitkretsandakul O, Friedman JH (2018) Updating the recommendations for treatment of tardive syndromes: a systematic review of new evidence and practical treatment algorithm. *J Neurol Sci* 389: 67–75.

Carbon M, Kane JM, Leucht S, et al. (2018) Tardive dyskinesia risk with first- and second-generation antipsychotics in comparative randomized controlled trials: a meta analysis. *World Psychiatry* 173: 330–40.

Citrome L (2017) Valbenazine for tardive dyskinesia: a systematic review of the efficacy and safety profile for this newly approved novel medication – what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *Int J Clin Practice*, doi.org 10.1111/ijcp.12964.

Citrome L (2017) Deutetrabenazine for tardive dyskinesia: a systematic review of the efficacy and safety profile for this newly approved novel medication – what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *Int J Clin Practice*, doi.org 10.1111/ijcp.13030.

Jacobsen FM (2015) Second generation antipsychotics and tardive syndromes in affective illness: a public health problem with neuropsychiatric consequences. *Am J Public Health* 105: e10–16.

Niemann N, Jankovic J (2018) Treatment of tardive dyskinesia: a general overview with focus on the vesicular monoamine transporter 2 inhibitors. *Drugs* 78: 525–41.

Stahl SM (2017) Neuronal traffic signals in tardive dyskinesia: not enough "stop" in the motor striatum. *CNS Spectrums* 22: 427–34.

Stahl SM (2018) Mechanism of action of vesicular monoamine transporter 2 (VMAT2) inhibitors in tardive dyskinesia: reducing dopamine leads to less "go" and more "stop" from the motor striatum for robust therapeutic effects. *CNS Spectrums* 23: 1–6.

Stahl SM (2018) Comparing pharmacological mechanism of action for the vesicular monoamine transporter 2 (VMAT2) inhibitors valbenazine and deutetrabenazine in treating tardive dyskinesia: does one have advantages over the other? *CNS Spectrums* 23: 239–47.

Woods SW, Morgenstern H, Saksa JR, et al. (2010) Incidence of tardive dyskinesia with atypical versus conventional antipsychotic medications: a prospective cohort study. *J Clin Psychiatry* 71: 463–74.

Long-Acting Injectables

Brissos S, Veguilla MR, Taylor D, et al. (2014) The role of long-acting injectable antipsychotics in schizophrenia: a critical appraisal. *Ther Adv Psychopharmacol* 4: 198–219.

Kishimoto T, Nitto M, Borenstein M, et al. (2013) Long acting injectable versus oral antipsychotics in schizophrenia: a systematic review and meta analysis of mirror image studies. *J Clin Psychiatry* 74: 957–65.

MacEwan JP, Kamat SA, Duffy RA, et al. (2016) Hospital readmission rates among patients with schizophrenia treated with long acting injectables or oral antipsychotics. *Psychiatr Serv* 67: 1183–8.

Meyer JM (2013) Understanding depot antipsychotics: an illustrated guide to kinetics. *CNS Spectrums* 18: 58–68.

Meyer JM (2017) Converting oral to long acting injectable antipsychotics: a guide for the perplexed. *CNS Spectrums* 22: 17–27.

Stahl SM (2014) Long-acting injectable antipsychotics: shall the last be first? *CNS Spectrums* 19: 3–5.

Tiihonen J, Haukka J, Taylor M, et al. (2011) A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. *Am J Psychiatry* 168: 603–9.

Serotonin Dopamine Drugs for Psychosis and Mood: Updates and Newer Drugs

Berry MD, Gainetdinov RR, Hoener MC, et al. (2017) Pharmacology of human trace amine-associated receptors: therapeutic opportunities and challenges. *Pharmacol Ther* 180: 161–80.

Brannan S (2020) KarXT (a new mechanism antipsychotic based on xanomeline) is superior to placebo in patients with schizophrenia: phase 2 clinical trial results. Abstract, American Society of Clinical Psychopharmacology Annual Meeting.

Citrome L (2015) Brexpiprazole for schizophrenia and as adjunct for major depressive disorder: a systematic review of the efficacy and safety profile for the newly approved antipsychotic – what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *Int J Clin Pract* 69: 978–97.

Correll CU, Davis RE, Weingart M, et al. (2020) Efficacy and safety of lumateperone for treatment of schizophrenia: a randomized clinical trial. *JAMA Psychaitry* 77: 349–58.

Dedic N, Jones PG, Hopkins SC, et al. (2019) SEP363856: a novel psychotropic agent with unique non D_2 receptor mechanism of actions. *J Pharmacol Exp Ther* 371: 1–14.

Earley W, Burgess MV, Rekeda L, et al. (2019) Cariprazine treatment of bipolar depression: a randomized double-blind placebo-controlled phase 3 study, *Am J Psychiatry* 176: 439–48.

Gainetdinov RR, Hoener MC, Berry MD (2018) Trace amines and their receptors. *Pharmacol Rev* 70: 549–620.

Koblan KS, Kent J, Hopkins SC, Krystal JH, et al. (2020) A non-D_2-receptor-binding drug for the treatment of schizophrenia. *New Engl J Med* 382: 1407–506.

TD and Its Treatment

Lieberman JA, Davis RE, Correll CU, et al. (2016) ITI-007 for the treatment of schizophrenia: a 4-week randomized, double-blind, controlled trial. *Biol Psychiatry* 79: 952–6.

Loebel A, Cucchiaro J, Silva R, et al. (2014) Lurasidone monotherapy in the treatment of bipolar I depression: a randomized double-blind, placebo-controlled study. *Am J Psychiatry* 171: 160–8.

Loebel A, Cucchiaro J, Silva R, et al. (2014) Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: a randomized, double blind, placebo-controlled study. *Am J Psychiatry* 171: 169–77.

Marder SR, Davis JM, Couinard G (1997) The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the north American trials. *J Clin Psychiatry* 58: 538–46.

McIntyre RS, Suppes T, Early W, Patel M, Stahl SM (2020) Cariprazine efficacy in bipolar I depression with and without concurrent manic symptoms: post hoc analysis of three randomized, placebo-controlled studies. *CNS Spectrums* 25: 502–10.

Meyer JM, Cummings MA, Proctor G, Stahl SM (2016) Psychopharmacology of persistent violence and aggression. *Psychiatr Clin N Am* 39: 541–56.

Meyer JM, Stahl SM (2020) *Stahl's Handbooks: the Clozapine Handbook*. Cambridge: Cambridge University Press.

Nemeth G, Laszlovszky I, Czoboar P, et al. (2017) Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomized double-blind controlled trial. *Lancet* 389: 1103–13.

Pei Y, Asif-Malik A, Canales JJ (2016) Trace amines and the trace amine-associated receptor 1: pharmacology, neurochemistry and clinical implications. *Front Neurosci* 10: 148.

Perkins DO, Gu H, Boteva K, Lieberman JA (2005) Relationship between duration of untreated psychosis and outcome in first episode schizophrenia: a critical review and meta-analysis. *Am J Psychiatry* 162: 1785–804.

Roth BL. Ki determinations, receptor binding profiles, agonist and/or antagonist functional data, HERG data, MDR1 data, etc. as appropriate was generously provided by the National Institute of Mental Health's Psychoactive Drug Screening Program, Contract # HHSN-271–2008-00025-C (NIMH PDSP). The NIMH PDSP is directed by Bryan L. Roth MD, PhD at the University of North Carolina at Chapel Hill and Project Officer Jamie Driscol at NIMH, Bethesda MD, USA. For experimental details please refer to the PDSP website http://pdsp.med.unc.edu/

Schwartz MD, Canales JJ, Zucci R, et al. (2018) Trace amine associated receptor 1: a multimodal therapeutic target for neuropsychiatric diseases. *Expert Opin Ther Targets* 22: 513–26.

Shekar A, Potter WZ, Lightfoot J, et al. (2008) Seletive muscarinic receptor agonist xanomeline as a novel treatment approach for schizophrenia. *Am J Psychiatry* 165: 1033–9.

Snyder GL, Vanover KE, Zhu H, et al. (2014) Functional profile of a novel modulator of serotonin, dopamine and glutamate neurotransmission. *Psychopharmacology* 232: 605–21.

Stahl SM (2013) Classifying psychotropic drugs by mode of action and not by target disorder. *CNS Spectrums* 18: 113–17.

Stahl SM (2013) Role of α1 adrenergic antagonism in the mechanism of action of iloperidone: reducing extrapyramidal symptoms. *CNS Spectrums* 18: 285–8.

Stahl SM (2014) Clozapine: is now the time for more clinicians to adopt this orphan? *CNS Spectrums* 19: 279–81.

Stahl SM (2016) Mechanism of action of brexpiprazole: comparison with aripiprazole. *CNS Spectrums* 21: 1–6.

Stahl SM (2016) Mechanism of action of cariprazine. *CNS Spectrums* 21: 123–7.

Stahl SM (2016) Mechanism of action of pimavanserin in Parkinson's disease psychosis: targeting serotonin $5HT_{2A}$ and $5HT_{2C}$ receptors. *CNS Spectums* 21: 271–5.

Stahl SM (2017) Drugs for psychosis and mood: unique actions at D_3, D_2, and D_1 dopamine receptor subtypes. *CNS Spectrums* 22: 375–84.

Stahl SM, Cucchiaro J, Sinonelli D, et al. (2013) Effectiveness of lurasidone for patients with schizophrenia following 6 weeks of acute treatment with lurasidone, olanazapine, or placebo: a 6-month, open-label study. *J Clin Psychiatry* 74: 507–15.

Stahl SM, Laredo SA, Morrissette DA (2020) Cariprazine as a treatment across the bipolar I spectrum from depression to mania: mechanism of action and review of clinical data. *Ther Adv Psychopharmacol* 10: 1–11.

Stahl SM, Morrissette DA, Citrome L, et al. (2013) "Meta-guidelines" for the management of patients with schizophrenia. *CNS Spectrums* 18: 150–62.

Suppes T, Silva R, Cuccharino J, et al. (2016) Lurasidone for the treatment of major depressive disorder with mixed features: a randomized, double blind placebo controlled study. *Am J Psychiatry* 173: 400–7.

Tarazi F, Stahl SM (2012) Iloperidone, asenapine and lurasidone: a primer on their current status. *Expert Opin Pharmacother* 13: 1911–22.

Thase ME, Youakim JM, Skuban A, et al. (2015) Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder. *J Clin Psychiatry* 76: 1224–31.

Zhang L, Hendrick JP (2018) The presynaptic D2 partial agonist lumateperone acts as a postsynaptic D2 antagonist. *Matters*: doi: 10.19185/matters.201712000006.

Chapters 6 (Mood Disorders) and 7 (Treatment of Mood Disorders), including Norepinephrine and GABA

Neuronal Networks – Norepinephrine, GABA, and Neuroactive Steroids: Selected References

Alvarez LD, Pecci A, Estrin DA (2019) In searach of GABA A receptor's neurosteroid binding sites. *J Med Chem* 62: 5250–60.

Belelli D, Hogenkamp D, Gee KW, et al. (2020) Realising the therapeutic potential of neuroactive steroid modulators of the GABA A receptor. *Neurobiol Stress* 12: 100207.

Botella GM, Salitur FG, Harrison BL, et al. (2017) Neuroactive steroids. 2. 3α-hydroxy-3β-methyl-21-(4-cyano-1H-pyrazol-1′-yl)-19-nor-5β-pregnan-20-one (SAGE 217): a clinical next generation neuroactive steroid positive allosteric modulator of the GABA A receptor. *J Med Chem* 60: 7810–19.

Chen ZW, Bracomonies JR, Budelier MM, et al. (2019) Multiple functional neurosteroid binding sites on GABA A receptors. *PLOS Biol* 17: e3000157; doi.org/10.137/journal.pbio.3000157.

Gordon JL, Girdler SS, Meltzer-Brody SE, et al. (2015) Ovarian hormone fluctuation, neurosteroids and HPA axis dysregulation in perimenopausal depression: a novel heuristic model. *Am J Psychiatry* 172: 227–36.

Gunduz-Bruce H, Silber C, Kaul I, et al. (2019) Trial of SAGE 217 in patients with major depressive disorder. *New Engl J Med* 381: 903–11.

Luscher B, Mohler H (2019) Brexanolone, a neurosteroid antidepressant, vindicates the GABAergic deficit hypothesis of depression and may foster reliance. *F1000Research* 8: 751.

Marek GJ, Aghajanian GK (1996) Alpha 1B-adrenoceptor-mediated excitation of piriform cortical interneurons. *Eur J Pharmacol* 305: 95–100.

Marek GJ, Aghajanian GK (1999) $5HT_{2A}$ receptor or alpha 1-adrenoceptor activation induces excitatory postsynaptic currents in layer V pyramidal cells of the medial prefrontal cortex. *Eur J Pharmacol* 367: 197–206.

Meltzer-Brody S, Kanes SJ (2020) Allopregnanolone in postpartum depression: role in pathophysiology and treatment. *Neurobiol Stress* 12: 100212.

Pieribone VA, Nicholas AP, Dagerlind A, et al. (1994) Distribution of alpha 1 adrenoceptors in rat brain revealed by in situ hybridization experiments utilizing subtype specific probes. *J Neurosci* 14: 4252–68.

Price DT, Lefkowitz RJ, Caron MG, et al. (1994) Localization of mRNA for three distinct alpha1 adrenergic receptor sybtypes in human tissues: implications for human alpha adrenergic physiology. *Mol Pharmacol* 45: 171–5.

Ramos BP, Arnsten AFT (2007) Adrenergic pharmacology and cognition: focus on the prefrontal cortex. *Pharmacol Ther* 113: 523–36.

Santana N, Mengod G, Artigas F (2013) Expression of alpha1 adrenergic receptors in rat prefrontal cortex: cellular colocalization with $5HT_{2A}$ receptors. *Int J Neuropsychopharmacol* 16: 1139–51.

Zorumski CF, Paul SM, Covey DF, et al. (2019) Neurosteroids as novel antidepressants and anxiolytics: GABA A receptors and beyond. *Neurobiol Stress* 11: 100196.

Mood Disorders – Depression, Bipolar Disorder: Selected and Recent References

Bergink V, Bouvy PF, Vervoort JSP, et al. (2012) Prevention of postpartum psychosis and mania in women at high risk. *Am J Psychiatry* 169: 609–16.

Bogdan R, Williamson DE, Hariri AR. (2012) Mineralocorticoid receptor Iso/Val (rs5522) genotype moderates the association between previous childhood emotional neglect and amygdala reactivity. *Am J Psychiatry* 169: 515–22.

Brites D, Fernandes A (2015) Neuroinflammation and depression: microglia activion, extracellular microvesicles and micro RNA dysregulation. *Front Cell Neurosci* 9: 476.

Fiedorowicz JG, Endicott J, Leon AC, et al. (2011) Subthreshold hypomanic symptoms in progression from unipolar major depression to bipolar disorder. *Am J Psychiatry* 168: 40–8.

Goldberg JF, Perlis RH, Bowden CL, et al. (2009) Manic symptoms during depressive episodes in 1,380 patients with bipolar disorder: findings from the STEP-BD. *Am J Psychiatry* 166: 173–81.

McIntyre RS, Anderson N, Baune BT, et al. (2019) Expert consensus on screening assessment of cognition in psychiatry. *CNS Spectrums* 24: 154–62.

Price JL, Drevets WC (2010) Neurocircuitry of mood disorders. *Neuropsychopharmacology* 35: 192–216.

Rao U, Chen LA, Bidesi AS, et al. (2010) Hippocampal changes associated with early-life adversity and vulnerability to depression. *Biol Psychiatry* 67: 357–64.

Roiser JP, Elliott R, Sahakian BJ (2012) Cognitive mechanisms of treatment in depression. *Neuropsychopharmacology* 37: 117–36.

Roiser JP, Sahakian BJ (2013) Hot and cold cognition in depression. *CNS Spectrums* 18: 139–49.

Roy A, Gorodetsky E, Yuan Q, Goldman D, Enoch MA (2010) Interaction of *FKBP5*, a stress-related gene, with childhood trauma increases the risk for attempting suicide. *Neuropsychopharmacology* 35: 1674–83.

Semkovska M, Quinlivan L, Ogrady T, et al. (2019) Cognitive function following a major depressive episode: a systematic review and meta-analysis. *Lancet Psychiatry* 6: 851–61.

Stahl SM (2017) Psychiatric pharmacogenomics: how to integrate into clinical practice. *CNS Spectrums* 22: 1–4.

Stahl SM (2017) Mixed-up about how to diagnose and treat mixed features in major depressive episodes. *CNS Spectrums* 22: 111–15.

Stahl SM, Morrissette DA (2017) Does a "whiff" of mania in a major depressive episode shift treatment from a classical antidepressant to an atypical/second-generation antipsychotic? *Bipolar Disord* 19: 595–6.

Stahl SM, Morrissette DA (2019) Mixed mood states: baffled, bewildered, befuddled and bemused.*Bipolar Disord* 21: 560–1.

Stahl SM, Morrissette DA, Faedda G, et al. (2017) Guidelines for the recognition and management of mixed depression. *CNS Spectrums* 22: 203–19.

Yatham LN, Liddle PF, Sossi V, et al. (2012) Positron emission tomography study of the effects of tryptophan depletion on brain serotonin$_2$ receptors in subjects recently remitted from major depression. *Arch Gen Psychiatry* 69: 601–9.

Serotonin Dopamine Drugs for Mood

See above references for Chapters 4 and 5

Ketamine/Esketamine and NMDA Antagonists (Dextromethorphan, Dextromethadone)

Aan het Rot M, Collins KA, Murrough JW, et al. (2010) Safety and efficacy of repeated dose intravenous ketamine for treatment resistant depression. *Biol Psychiatry* 67: 139–45.

Abdallah CG, DeFeyter HM, Averill LA, et al. (2018) The effects of ketamine on prefrontal glutamate neurotransmission in healthy and depressed subjects. *Neuropsychopharmacology* 43: 2154–60.

Anderson A, Iosifescu DV, Macobsen M, et al. (2019) Efficacy and safety of AXS-05, an oral NMDA receptor antagonist with multimodal activity, in major depressive disorder: results of a phase 2, double blind active controlled trial. Abstract, American Society of Clincal Psychopharmacology Annual Meeting.

Deyama S, Bang E, Wohleb ES, et al. (2019) Role of neuronal VEGF signaling in the prefrontal cortex in the rapid antidepressant effects of ketamine. *Am J Psychiatry* 176: 388-400.

DiazGranados N, Ibrahim LA, Brutsche NE, et al. (2010) Rapid resolution of suicidal ideation after a single infusion of an *N*-methyl-D-aspartate antagonist in patients with treatment-resistant depressive disorder. *J Clin Psychiatry* 71: 1605–11.

Duman RS, Voleti B (2012) Signaling pathways underlying the pathophysiology and treatment of depression: novel mechanisms for rapid-acting agents. *Trends Neurosci* 35: 47–56.

Dwyer JM, Duman RS (2013) Activation of mammalian target of rapamycin and synaptogenesis: role in the actions of rapid acting antidepressants. *Biol Psychiatry* 73: 1189–98.

Fu DJ, Ionescu DF, Li X, et al. (2020) Esketamine nasal spray for rapid reduction of major depressive disorder symptoms in patients who have active suicidal ideation with intent: double blind randomized study (ASPIRE K). *J Clin Psychiatry* 61: doi.org/10.4088/JCP.19m13191.

Hanania T, Manfredi P, Inturrisi C, et al. (2020) The NMDA antagonist dextromethadone acutely improves depressive like behavior in the forced swim test performance of rats. *AA Rev Public Health* 34: 119–38.

Hasler G (2020) Toward specific ways to combine ketamine and psychotherapy in treating depression. *CNS Spectrums* 25: 445–7.

Ibrahim L, Diaz Granados N, Franco-Chaves J (2012) Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs. add-on riluzole: results from a 4-week, double-blind, placebo-controlled study. *Neuropsychopharmacology* 37: 1526–33.

Li N, Lee, Lin RJ, et al. (2010) mTor-dependent synapse formation underlies the rapid antidepressant effects of NMDA antgonists. *Science* 329: 959–64.

Monteggia LM, Gideons E, Kavalali EG (2013) The role of eukaryotic elongation factor 2 kinase in rapid antidepressant action of ketamine. *Biol Psychiatry* 73: 1199–203.

Mosa-Sava RN, Murdock MH, Parekh PK, et al. (2019) Sustained rescue of prefrontal circuit dysfunction by antidepressant induced spine formation. *Science* 364: doi: 10.1126/Science.aat80732019.

Murrough JW, Perez AM, Pillemer S, et al. (2013) Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment resistant major depression. *Biol Psychiatry* 74: 250–6.

O'Gorman C, Iosifescu DV, Jones A, et al. (2018) Clinical development of AXS-05 for treatment resistant depression and agitation associated with Alzheimer's disease. Abstract, American Society of Clinical Psychopharmacology Annual Meeting.

O'Gorman C, Jones A, Iosifescu DV, et al. (2020) Efficacy and safety of AXS-05, an oral NMDA receptor antagonist with multimodal activity in major depressive disorder: results from the GEMINI phase 3, double blind placebo-controlled trial. Abstract, American Society of Clinical Psychopharmacology Annual Meeting.

Phillips JL, Norris S, Talbot J, et al. (2019) Single, repeated and maintenance ketamine infusions for treatment resistant depression: a randomized controlled trial. *Am J Psychiatry* 176: 401–9.

Price RB, Nock MK, Charney DS, Mathew SJ (2009) Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. *Biol Psychiatry* 66: 522–6.

Salvadore G, Cornwell BR, Sambataro F, et al. (2010) Anterior cingulate desynchronization and functional connectivity with the amygdala during a working memory task predict rapid antidepressant response to ketamine. *Neuropsychopharmacology* 35: 1415–22.

Stahl SM (2013) Mechanism of action of ketamine. *CNS Spectrums* 18: 171–4.

Stahl SM (2013) Mechanism of action of dextromethorphan/quinidine: comparison with ketamine. *CNS Spectrums* 18: 225–7.

Stahl SM (2016) Dextromethorphan–quinidine-responsive pseudobulbar affect (PBA): psychopharmacological model for wide-ranging disorders of emotional expression? *CNS Spectrums* 21: 419–23.

Stahl SM (2019) Mechanism of action of dextromethorphan/bupropion: a novel NMDA antagonist with multimodal activity. *CNS Spectrums* 24: 461–6.

Wajs E, Aluisio L, Holder R, et al. (2020) Esketamine nasal spray plus oral antidepressant in patients with treatment resistant depression: assessment of long term safety in a phase 3 open label study (SUSTAIN2). *J Clin Psychiatry* 81: 19m12891.

Williams NR, Heifets B, Blasey C, et al. (2018) Attenuation of antidepressant effects of ketamine by opioid receptor antagonism. *Am J Psychiatry* 175: 1205–15

Zarate Jr. CA, Brutsche NE, Ibrahim L (2012) Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. *Biol Psychiatry* 71: 939–46.

Mood Disorder Treatments: Updates and Other Newer Drugs

Alvarez E, Perez V, Dragheim M, Loft H, Artigas F (2012) A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. *Int J Neuropsychopharmacol* 15: 589–600.

BALANCE investigators and collaborators, et al. (2010) Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomized open-label trial. *Lancet* 375: 385–95.

Baldessarini RJ, Tondo L, Vazquez GH (2019) Pharmacological treatment of adult bipolar disorder. *Mol Psychiatry* 24: 198–217.

Bang-Andersen B, Ruhland T, Jorgensen M, et al. (2011) Discovery of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl] piperazine (LuAA21004): a novel multimodal compound for the treatment of major depressive disorder. *J Med Chem* 54: 3206–21.

Carhart-Harris RL, Bolstridge M, Day CMG, et al. (2018) Psilocybin with psychological support for treatment-resistant depression: six month follow up. *Psychopharmacology* 235: 399–408.

Carhart-Harris RL, Bolstridge M, Rucker J, et al. (2016) Psilocybin with psychological support for treatment resistant depression: an open label feasibility study. *Lancet Psychiatry* 3: 619–27.

Carhart-Harris RL, Goodwin GM (2017) The therapeutic potential of psychedelic drugs: past, present and future, *Neuropsychopharmacology* 42: 2105–13.

Carhart-Harris RL, Leech R, Williams TM, et al. (2012) Implications for psychedelic assisted psychotherapy: a functional magnetic resonance imaging study with psilocybin. *Br J Psychiatry*: doi:10.1192/bjp.bp.111.103309.

Chiu CT, Chuan DM (2010) Molecular actions and therapeutic potential of lithium in preclinical and clinical studies of CNS disorders. *Pharmacol Ther* 128: 281–304.

Cipriani A, Pretty H, Hawton K, Geddes JR (2005) Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials. *Am J Psychiatry* 162: 1805–19.

Frye MA, Grunze H, Suppes T, et al. (2007) A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression. *Am J Psychiatry* 164: 1242–9.

Grady M, Stahl SM (2012) Practical guide for prescribing MAOI: Debunking myths and removing barriers. *CNS Spectrums* 17: 2–10.

Mork A, Pehrson A, Brennum LT, et al. (2012) Pharmacological effects of Lu AA21004: a novel multimodal compound for the treatment of major depressive disorder. *J Pharmacol Exp Ther* 340: 666–75.

Pasquali L, Busceti CL, Fulceri F, Paparelli A, Fornai F (2010) Intracellular pathways underlying the effects of lithium. *Behav Pharmacol* 21: 473–92.

Perlis RH, Ostacher MJ, Goldberg JF, et al. (2010) Transition to mania during treatment of bipolar depression. *Neuropsychopharmacology* 35: 2545–52.

Pompili M, Vazquez GH, Forte A, Morrissette DA, Stahl SM (2020) Pharmacological treatment of mixed states. *Psychiatr Clin N Am* 43: 157–86. doi:10.1016/j.psc.2019.10.015

Schwartz TL, Siddiqui US, Stahl SM (2011) Vilazodone: a brief pharmacologic and clinical review of the novel SPARI (serotonin partial agonist and reuptake inhibitor). *Ther Adv Psychopharmacol* 1: 81–7.

Settimo L, Taylor D (2018) Evaluating the dose-dependent mechanism of action of trazodone by estimation of occupancies for different brain neurotransmitter targets. *J Psychopharmacol* 32: 960104.

Stahl SM (2009) Mechanism of action of trazodone: a multifunctional drug. *CNS Spectrums* 14: 536–46.

Stahl SM (2012) Psychotherapy as an epigenetic "drug": psychiatric therapeutics target symptoms linked to malfunctioning brain circuits with psychotherapy as well as with drugs. *J Clin Pharm Ther* 37: 249–53.

Stahl SM (2014) Mechanism of action of the SPARI vilazodone: (serotonin partial agonist reuptake inhibitor). *CNS Spectrums* 19: 105–9.

Stahl SM (2014) Mechanism of action of agomelatine: a novel antidepressant exploiting synergy between monoaminergic and melatonergic properties. *CNS Spectrums* 19: 207–12.

Stahl SM (2015) Modes and nodes explain the mechanism of action of vortioxetine, a multimodal agent (MMA): enhancing serotonin release by combining serotonin (5HT) transporter inhibition with actions at 5HT receptors ($5HT_{1A}$, $5HT_{1B}$, $5HT_{1D}$, $5HT_7$ receptors). *CNS Spectrums* 20: 93–7.

Stahl SM (2015) Modes and nodes explain the mechanism of action of vortioxetine, multimodal agent (MMA): actions at serotonin receptors may enhance downstream release of four pro-cognitive neurotransmitters. *CNS Spectrums* 20: 515–19.

Stahl SM, Fava M, Trivedi M (2010) Agomelatine in the treatment of major depressive disorder: an 8 week, multicenter, randomized, placebo-controlled trial. *J Clin Psychiatry* 71: 616–26.

Undurraga J, Baldessarini RJ, Valenti M, et al. (2012) Bipolar depression: clinical correlates of receiving antidepressants. *J Affect Disord* 139: 89–93.

Zajecka J, Schatzberg A, Stahl SM, et al. (2010) Efficacy and safety of agomelatine in the treatment of major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled trial. *J Clin Psychopharmacol* 30: 135–44.

Chapter 8 (Anxiety and Trauma)

Anxiety Disorders: Psychopharmacology and Psychotherapy

Batelaan NM, Van Balkom AJLM, Stein DJ (2010) Evidence-based pharmacotherapy of panic disorder: an update. *Int J Neuropsychopharmacol* 15: 403–15.

De Oliveira IR, Schwartz T, Stahl SM (eds.) (2014) *Integrating Psychotherapy and Psychopharmacology*. New York, NY: Routledge Press.

Etkin A, Prater KE, Hoeft F, et al. (2010) Failure of anterior cingulate activation and connectivity with the amygdala during implicit regulation of emotional processing in generalized anxiety disorder. *Am J Psychiatry* 167: 545–54.

Monk S, Nelson EE, McClure EB, et al. (2006) Ventrolateral prefrontal cortex activation and attentional bias in response to angry faces in adolescents with generalized anxiety disorder. *Am J Psychiatry* 163: 1091–7.

Otto MW, Basden SL, Leyro TM, McHugh K, Hofmann SG (2007) Clinical perspectives on the combination of D-cycloserine and cognitive behavioral therapy for the treatment of anxiety disorders. *CNS Spectrums* 12: 59–61.

Otto MW, Tolin DF, Simon NM, et al. (2010) Efficacy of D-cycloserine for enhancing response to cognitive-behavior therapy for panic disorder. *Biol Psychiatry* 67: 365–70.

Stahl SM (2010) *Stahl's Illustrated: Anxiety and PTSD*. Cambridge: Cambridge University Press.

Stahl SM (2012) Psychotherapy as an epigenetic "drug": psychiatric therapeutics target symptoms linked to malfunctioning brain circuits with psychotherapy as well as with drugs. *J Clin Pharm Ther* 37: 249–53.

Stahl SM, Moore BA (eds.) (2013) *Anxiey Disorders: A Guide for Integrating Psychopharmacology and Psychotherapy*. New York, NY: Routledge Press.

Stress/Early Life Adversity

Chen Y, Baram TZ (2016) Toward understanding how early life stress reprograms cognitive and emotional brain networks. *Neuropsychopharm Rev* 41: 187–296.

Hanson JL, Nacewicz BM, Suggerer MJ, et al. (2015) Behavioral problems after early life stress: contributions of the hippocampus and amygdala. *Biol Psychiatry* 77: 314–23.

Kundakavic M, Champagne FA (2015) Early life experience, epigenetics and the developing brain. *Neuropsychopharmacol Rev* 40: 141–53.

Marusak HA, Martin K, Etkin A, et al. (2015) Childhood trauma exposure disrupts the automatic regulation of emotional processing. *Neuropsychopharmacology* 40: 1250–8.

McEwen BS, Nasca C, Gray JD (2016) Stress effects on neuronal structure: hippocampus, amygdala and prefrontal cortex. *Neuropsychopharm Rev* 41: 3–23.

McLaughlin KA, Sheridan MA, Gold AL, et al. (2016) Maltreatment exposure, brain structure and fear conditioning in children and adolescents. *Neuropsychopharmacology* 41: 1956–65.

Teicher MH, Anderson CM, Ohashi K, et al. (2014) Childhood maltreatment: altered network centrality of cingulate precuneus, temporal pole and insula. *Biol Psychiatry* 76: 297–305.

Tyrka AR, Burgers DE, Philip NS (2013) The neurobiological correlates of childhood adversity and implications for treatment. *Acta Psychiatr Scand* 138: 434–47.

Zhang JY, Liu TH, He Y, et al. (2019) Chronic stress remodels synapses in an amygdala circuit-specific manner. *Biol Psychiatry* 85: 189–201.

Fear Conditioning/Fear Extinction/ Reconsolidation/Circuitry

Anderson KC, Insel TR (2006) The promise of extinction research for the prevention and treatment of anxiety disorders. *Biol Psychiatry* 60: 319–21.

Barad M, Gean PW, Lutz B. (2006) The role of the amygdala in the extinction of conditioned fear. *Biol Psychiatry* 60: 322–8.

Bonin RP, De Koninck Y (2015) Reconsolidation and the regulation of plasticity: moving beyond memory. *Trends Neurosci* 38: 336–44.

Dejean C, Courtin J, Rozeaske RR, et al. (2015) Neuronal circuits for fear expression and recovery: recent advances and potential therapeutic strategies. *Biol Psychiatry* 78: 298–306.

Feduccia AA, Mithoefer MC (2018) MDMA-assisted psychotherapy for PTSD: are memory reconsolidation and fear extinction underlying mechanisms. *Prog Neuropsychopharmacol Biol Psychiatry* 84: 221–8.

Fox AS, Oler JA, Tromp DPM, et al. (2015) Extending the amygdala in theories of threat processing. *Trends Neurosci* 38: 319–29.

Giustino RF, Seemann JR, Acca GM, et al. (2017) Beta adrenoceptor blockade in the basolateral amygdala, but not the medial prefrontal cortex, rescues the immediate extinction deficit. *Neuropsychopharmacol* 42: 2537–44.

Graham BM, Milad MR (2011) The study of fear extinction: implications for anxiety disorder. *Am J Psychiatry* 168: 1255–65.

Hartley CA, Phelps EA (2010) Changing fear: the neurocircuitry of emotion regulation. *Neuropsychopharmacol Rev* 35: 136–46.

Haubrich J, Crestani AP, Cassini LF, et al. (2015) Reconsolidation allows fear memory to be updated to a less aversive level through the incorporation of appetitive information. *Neuropsychopharmacology* 40: 315–26.

Hermans D, Craske MG, Mineka S, Lovibond PF (2006) Extinction in human fear conditioning. *Biol Psychiatry* 60: 361–8.

Holbrook TL, Galarneau ME, Dye JL, et al. (2010) Morphine use after combat injury in Iraq and post traumatic stress disorder. *New Engl J Med* 362: 110–17.

Keding TJ, Herringa RJ (2015) Abnormal structure of fear circuitry in pediatric post traumatic stress disorder. *Neuropsychopharmacology* 40: 537–45.

Krabbe S, Grundemann J, Luthi A (2018) Amygdala inhibitory circuits regulate associative fear conditioning. *Biol Psychiatry* 83: 800–9.

Kroes MCW, Tona KD, den Ouden HEM, et al. (2016) How administration of the beta blocker propranolol before extinction can prevent the return of fear. *Neuropsychopharmacology* 41: 1569–78.

Kwapis JL, Wood MA (2014) Epigenetic mechanisms in fear conditioning: implications for treating post traumatic stress disorder. *Trends Neurosci* 37: 706–19.

Lin HC, Mao SC, Su CL, et al. (2010) Alterations of excitatory transmission in the lateral amygdala during expression and extinction of fear memory. *Int J Neuropsychopharmacol* 13: 335–45.

Linnman C, Zeidan MA, Furtak SC, et al. (2012) Resting amygdala and medial prefrontal metabolism predicts functional activation of the fear extinction circuit. *Am J Psychiatry* 169: 415–23.

Mahan AL, Ressler KJ (2012) Fear conditioning, synaptic plasticity and the amygdala: implications for post traumatic stress disorder. *Trends Neurosci* 35: 24–35.

Mithoefer MC, Wagner MT, Mithoefer AT, et al. (2011) The safety and efficacy of {+/−} 3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. *J Psychopharmacol* 25: 439–52.

Myers KM, Carlezon WA Jr. (2012) D-Cycloserine effects on extinction of conditioned responses to drug-related cues. *Biol Psychiatry* 71: 947–55.

Onur OA, Schlaepfer TE, Kukolja J, et al. (2010) The *N*-methyl-D-aspartate receptor co-agonist D-cycloserine facilitates declarative learning and hippocampal activity in humans. *Biol Psychiatry* 67: 1205–11.

Otis JM, Werner CR, Muelier D (2015) Noradrenergic regulation of fear and drug-associated memory reconsolidation. *Neuropsychopharmacology* 40: 793–803.

Ressler KJ (2020) Translating across circuits and genetics toward progress in fear- and anxiety-related disorders. *Am J Psychiatry* 177: 214–22.

Sandkuher J, Lee J (2013) How to erase memory traces of pain and fear. *Trends Neurosci* 36: 343–52.

Schwabe L, Nader K, Pruessner JC (2011) Reconsolidation of human memory: brain mechanisms and clinical relevance. *Biol Psychiatry* 76: 274–80.

Schwabe L, Nader K, Wold OT (2012) Neural signature of reconsolidation impairments by propranolol in humans. *Biol Psychiatry* 71: 380–6.

Shin LM, Liberzon I (2010) The neurocircuitry of fear, stress and anxiety disorders. *Neuropsychopharmacol Rev* 35: 169–91.

Soeter M, Kindt M (2012) Stimulation of the noradrenergic system during memory formation impairs extinction learning but not the disruption of reconsolidation. *Neuropsychopharmacology* 37: 1204–15.

Stern CAJ, Gazarini L, Takahashi RN, et al. (2012) On disruption of fear memory by reconsolidation blockade: evidence from cannabidiol treatment. *Neuropsychopharmacology* 37: 2132–42.

Tamminga CA (2006) The anatomy of fear extinction. *Am J Psychiatry* 163: 961.

Tronson NC, Corcoran KA, Jovasevic V, et al. (2011) Fear conditioning and extinction: emotional states encoded by distinct signaling pathways. *Trends Neurosci* 35: 145–55.

PTSD

Aupperle RL, Allard CB, Grimes EM, et al. (2012) Dorsolateral prefrontal cortex activation during emotional anticipation and neuropsychological performance in posttraumatic stress disorder. *Arch Gen Psychiatry* 69: 360–71.

Bonne O, Vythilingam M, Inagaki M, et al. (2008) Reduced posterior hippocampal volume in posttraumatic stress disorder. *J Clin Psychiatry* 69: 1087–91.

De Kleine RA, Hendriks GJ, Kusters WJC, Broekman TG, van Minnen A (2012) A randomized placebo-controlled trial of D-cycloserine to enhance exposure therapy for posttraumatic stress disorder. *Biol Psychiatry* 71: 962–8.

Feduccia AA, Mithoefer MC (2018) MDMA-assisted psychotherapy for PTSD: are memory reconsolidation and fear extinction underlying mechanisms. *Prog Neuropsychopharmacol Biol Psychiatry* 84: 221–8.

Ipser JC, Stein DJ (2012) Evidence-based pharmacotherapy of post-traumatic stress disorder (PTSD). *Int J Neuropsychopharmacol* 15: 825–40.

Jovanovic T, Ressler KJ (2010) How the neurocircuitry and genetics of fear inhibition may inform our understanding of PTSD. *Am J Psychiatry* 167: 648–62.

Mercer KB, Orcutt HK, Quinn JF, et al. (2012) Acute and posttraumatic stress symptoms in a prospective gene X environment study of a university campus shooting. *Arch Gen Psychiatry* 69: 89–97.

Mithoefer MC, Wagner MT, Mithoefer AT, et al. (2011) The safety and efficacy of {+/−} 3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. *J Psychopharmacol* 25: 439–52.

Orr SP, Milad MR, Metzger LJ (2006) Effects of beta blockade, PTSD diagnosis, and explicit threat on the extinction and retention of an aversively conditioned response. *Biol Psychol* 732: 262–71.

Perusini JN, Meyer EM, Long VA, et al. (2016) Induction and expression of fear sensitization caused by acute traumatic stress. *Neuropsychopharm Rev* 41: 45–57.

Raskind MA, Peskind ER, Hoff DJ (2007) A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. *Biol Psychiatry* 61: 928–34.

Rauch SL, Shin LM, Phelps EA. (2006) Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research – past, present and future. *Biol Psychiatry* 60: 376–82.

Reist C, Streja E, Tang CC, et al. (2020) Prazocin for treatment of post traumatic stress disorder: a systematic review and met analysis. *CNS Spectrums*: doi.org/10.1017/S1092852920001121.

Sandweiss DA, Slymen DJ, Leardmann CA, et al. (2011) Preinjury psychiatric status, injury severity, and postdeployment posttraumatic stress disorder. *Arch Gen Psychiatry* 68: 496–504.

Sauve W, Stahl SM (2019) Psychopharmacological and neuromodulation treatment of PTSD. In *Treating PTSD in Military Personnel*, 2nd edition, Moore BA and Penk WE (eds.), Guilford Press: 155–72.

Shin LM, Bush G, Milad MR, et al. (2011) exaggerated activation of dorsal anterior cingulate cortex during cognitive interference: a monozygotic twin study of posttraumatic stress disorder. *Am J Psychiatry* 168: 979–85.

Stein MB, McAllister TW (2009) Exploring the convergence of posttraumatic stress disorder and mild traumatic brain injury. *Am J Psychiatry* 166: 768–76.

Vaiva G, Ducrocq F, Jezequel K, et al. (2003) Immediate treatment with propranolol decreases postraumatic stress disorder two months after trauma. *Biol Psychiatry* 54: 947–9.

van Zuiden M, Geuze E, Willemen HLD, et al. (2011) Pre-existing high glucocorticoid receptor number predicting development of posttraumatic stress symptoms after military deployment. *Am J Psychiatry* 168: 89–96.

Chapter 9 (Pain)

Apkarian AV, Sosa Y, Sonty S, et al. (2004) Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. *J Neurosci* 24: 10410–15.

Bar KJ, Wagner G, Koschke M, et al. (2007) Increased prefrontal activation during pain perception in major depression. *Biol Psychiatry* 62: 1281–7.

Benarroch EE (2007) Sodium channels and pain. *Neurology* 68: 233–6.

Brandt MR, Beyer CE, Stahl SM (2012) TRPV1 antagonists and chronic pain: beyond thermal perception. *Pharmaceuticals* 5: 114–32.

Davies A, Hendrich J, Van Minh AT, et al. (2007) Functional biology of the alpha 2 beta subunits of voltage gated calcium channels. *Trends Pharmacol Sci* 28: 220–8.

Descalzi G, Ikegami D, Ushijima T, et al. (2015) Epigenetic mechanisms of chronic pain *Trends Neurosci* 38: 237–46.

Dooley DJ, Taylor CP, Donevan S, Feltner D (2007) Ca^{2+} Channel alpha 2 beta ligands: novel modulators of neurotransmission. *Trends Pharmacol Sci* 28: 75–82.

Farrar JT (2006) Ion channels as therapeutic targets in neuropathic pain. *J Pain* 7 (Suppl 1): S38–47.

Gellings-Lowe N, Stahl SM (2012) *Antidepressants in pain, anxiety and depression.* In *Pain Comorbidities*, Giamberardino MA and Jensen TS (eds.), Washington, DC: IASP Press, 409–23.

Gracely RH, Petzke F, Wolf JM, Clauw DJ (2002) Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis Rheum* 46: 1222–343.

Khoutorsky A, Price TJ (2018) Translational control mechanism in persistent pain. *Trends Neuosci* 41: 100–14.

Luo C, Kuner T, Kuner R (2014) Synaptic plasticity in pathological pain. *Trends Neurosci* 37: 343–55.

McLean SA, Williams DA, Stein PK, et al. (2006) Cerebrospinal fluid corticotropin-releasing factor concentration is associated with pain but not fatigue symptoms in patients with fibromyalgia. *Neuropsychopharmacology* 31: 2776–82.

Nickel FT, Seifert F, Lanz S, Maihofner C (2012) Mechanisms of neuropathic pain. *Eur Neuropsychopharmacol* 22: 81–91.

Norman E, Potvin S, Gaumond I, et al. (2011) Pain inhibition is deficient in chronic widespread pain but normal in major depressive disorder. *J Clin Psychiatry* 72: 219–24.

Ogawa K, Tateno A, Arakawa R, et al. (2014) Occupancy of serotonin transporter by tramadol: a positron

emission tomography study with ^{11}C-DSDB. *Int J Neuropsychopharmacol* 17: 845–50.

Stahl SM (2009) Fibromyalgia: pathways and neurotransmitters. *Hum Psychopharmacol* 24: S11–17.

Stahl SM, Eisenach JC, Taylor CP, et al. (2013) The diverse therapeutic actions of pregabalin: is a single mechanism responsible for several pharmacologic activities. *Trends Pharmacol Sci* 34: 332–9.

Wall PD, Melzack R (eds.) (1999) *Textbook of Pain*, 4th edition. London: Harcourt Publishers Limited.

Williams DA, Gracely RH (2006) Functional magnetic resonance imaging findings in fibromyalgia. *Arthritis Res Ther* 8: 224–32.

Chapter 10 (Sleep/Wake Disorders and Their Treatment Including Histamine and Orexin)

Histamine

Broderick M, Masri T (2011) Histamine H_3 receptor (H_{3R}) antagonists and inverse agonists in the treatment of sleep disorders. *Curr Pharm Design* 17: 1426–9.

Kotanska M, Kuker KJ, Szcaepanska K, et al. (2018) The histamine H_3 receptor inverse agonist pitolisant reduces body weight in obese mice. *Arch Pharmacol* 391: 875–81.

Nomura H, Mizuta H, Norimoto H, et al. (2019) Central histamine boosts perirhinal cortex activity and restores forgotten object memories. *Biol Psychiatry* 86: 230–9.

Romig A, Vitran G, Giudice TL, et al. (2018) Profile of pitolisant in the management of narcolepsy: design, development and place in therapy. *Drug Des Devel Ther* 12: 2665–75.

Schwartz JC (2011) The histamine H_3 receptor: from discovery to clinical trials with pitolisant. *Br J Pharmacol* 163: 713–21.

Szakacs Z, Dauvilliers Y, Mikhaulov V, et al. (2017) Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomized, double-blind placebo controlled trial. *Lancet Neurol* 16: 200–7.

Orexin

Bennett T, Bray D, Neville MW (2014) Suvorexant, a dual orexin receptor antagonist for the management of insomnia. *PT* 39: 264–6.

Bettica P, Squassante L, Groeger JA, et al. (2012) Differential effects of a dual orexin receptor antagonist (SB-649868) and zolpidem on sleep initiation and consolidation, SWS, REM sleep, and EEG power spectra in a model of situational insomnia. *Neuropsychopharmacology* 37: 1224–33.

Beuckmann CT, Suzuki M, Ueno T, et al. (2017) In vitro and in silico characterization of lemborexant (E2006), a novel dual orexin receptor antagonist. *J Pharmacol Exp Ther* 362: 287–95.

Beuckmann CT, Ueno T, Nakagawa M, et al. (2019) Preclinical in vivo characterization of lemborexant (E2006) a novel dual orexin receptor antagonist for sleep/wake regulation. *Sleep*: doi 10.1093/sleep/zsz076.

Bonnavion P, de Lecea L (2010) Hypocretins in the control of sleep and wakefulness. *Curr Neurol Neurosci Rep* 10: 174–9.

Bourgin P, Zeitzer JM, Mignot E (2008) CSF hypocretin-1 assessment in sleep and neurological disorders. *Lancet Neurol* 7: 649–62.

Brisbare-Roch C, Dingemanse J, Koberstein R, et al. (2007) Promotion of sleep by targeting the orexin system in rats, dogs and humans. *Nat Med* 13: 150–5.

Cao M, Guilleminault C (2011) Hypocretin and its emerging role as a target for treatment of sleep disorders. *Curr Neurol Neurosci Rep* 11: 227–34.

Citrome L (2014) Suvorexant for insomnia: a systematic review of the efficacy and safety profile for this newly approved hypnotic – what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *Int J Clin Pract* 68: 1429–41.

Coleman PJ, Schreier JD, Cox CD, et al. (2012) Discovery of [(2R, 5R)-5-{[(5-fluoropyridin-2-yl)oxy]methyl}-2-methylpiperidin-1-yl] [5-methyl-2-(pyrimidin-2-yl)phenyl] methanone (MK-6096): a dual orexin receptor antagonist with potent sleep-promoting properties. *Chem Med* 7, 415–24.

Dauvilliers Y, Abril B, Mas E, et al. (2009) Normalization of hypocretin-1 in narcolepsy after intravenous immunoglobulin treatment. *Neurology* 73: 1333–4.

de Lecea L, Huerta R (2015) Hypocretin (orexin) regulation of sleep-to-wake transitions. *Front Pharmacol* 5: 1–7.

DiFabio R, Pellacani A, Faedo S (2011) Discovery process and pharmacological characterization of a novel dual orexin 1 and orexin 2 receptor antagonist useful for treatment of sleep disorders. *Bioorg Med Chem Lett* 21: 5562–7.

Dubey AK, Handu SS, Mediratta PK (2015) Suvorexant: the first orexin receptor antagonist to treat insomnia. *J Pharmacol Pharmacother* 6: 118–21.

Equihua AC, De la Herran-Arita AK, Drucker-Colin R (2013) Orexin receptor antagonists as therapeutic agents for insomnia. *Front Pharmacol* 4: 1–10.

Gentile TA, Simmons SJ, Watson MN, et al. (2018) Effects of suvorexant, a dual orexin hypocretin receptor antagonist on impulsive behavior associated with cocaine. *Neuropsychopharmacology* 43: 1001–9.

Gotter AL, Winrow CJ, Brunner J, et al. (2013) The duration of sleep promoting efficacy by dual orexin receptor antagonists is dependent upon receptor occupancy threshold. *BMC Neurosci* 14: 90.

Griebel G, Decobert M, Jacquet A, et al. (2012) Awakening properties of newly discovered highly selective H_3 receptor antagonists in rats. *Behav Brain Res* 232: 416–20.

Herring WJ, Connor KM, Ivgy-May N, et al. (2016) Suvorexant in patients with insomnia: results from two 3-month randomized controlled clinical trials. *Biol Psychiatry* 79: 136–48.

Hoever P, Dorffner G, Benes H, et al. (2012) Orexin receptor antagonism, a new sleep-enabling paradigm: a proof-of-concept clinical trial. *Clin Pharmacol Ther* 91: 975–85.

Hoyer D, Jacobson LH (2013) Orexin in sleep, addiction, and more: is the perfect insomnia drug at hand? *Neuropeptides* 47: 477–88.

Jones BE, Hassani OK (2013) The role of Hcrt/Orx and MCH neurons in sleep–wake state regulation. *Sleep* 36: 1769–72.

Krystal AD, Benca RM, Kilduff TS (2013) Understanding the sleep–wake cycle: sleep, insomnia, and the orexin system. *J Clin Psychiatry* 74 (Suppl 1): 3–20.

Mahler SV, Moorman DE, Smith RJ, et al. (2014) Motivational activation: a unifying hypothesis of orexin/hypocretin function. *Nat Neurosci* 17: 1298–303.

Michelson D, Snyder E, Paradis E, et al. (2014) Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 13: 461–71.

Nixon JP, Mavanji V, Butterick TA, et al. (2015) Sleep disorders, obesity, and aging: the role of orexin. *Aging Res Rev* 20: 63–73.

Rosenberg R, Murphy P, Zammit G, et al. (2019) Comparison of lemborexant with placebo and zolpidem tartrate extended release for the treatment of older adults with insomnia disorder: a phase 3 randomized clinical trial. *JAMA Network Open* 2: e1918254

Ruoff C, Cao M, Guilleminault C (2011) Hypocretin antagonists in insomnia treatment and beyond. *Curr Pharm Design* 17: 1476–82.

Sakurai T, Mieda M (2011) Connectomics of orexin-producing neurons: interface of systems of emotion, energy homeostasis and arousal. *Trends Pharmacol Sci* 32: 451–62.

Scammel TE, Winrow CJ (2011) Orexin receptors: pharmacology and therapeutic opportunities. *Annu Rev Pharmacol Toxicol* 51: 243–66.

Stahl SM (2016) Mechanism of action of suvorexant. *CNS Spectrums* 21: 215–18.

Steiner MA, Lecourt H, Strasser DS, Brisbare-Roch C, Jenck F (2011) Differential effects of the dual orexin receptor antagonist almorexant and the $GABA_A$-α1 receptor modulator zolpidem, alone or combined with ethanol, on motor performance in the rat. *Neuropsychopharmacology* 36: 848–56.

Vermeeren A, Jongen S, Murphy P, et al. (2019) On the road driving performance the morning after bedtime administration of lemborexant in healthy adult and elderly volunteers. *Sleep*: doi: 10.1093.sleep/zsy260.

Willie JT, Chemelli RM, Sinton CM, et al. (2003) Distinct narcolepsy syndromes in *orexin recepter-2* and *orexin* null mice: molecular genetic dissection of non-REM and REM sleep regulatory processes. *Neuron* 38: 715–30.

Winrow CJ, Gotter AL, Cox CD, et al. (2012) Pharmacological characterization of MK-6096: a dual orexin receptor antagonist for insomnia. *Neuropharmacology* 62: 978–87.

Yeoh JW, Campbell EJ, James MH, et al. (2014) Orexin antagonists for neuropsychiatric disease: progress and potential pitfalls. *Front Neurosci* 8: 1–12.

Sleep/General/Disorders/Insomia/Restless Legs

Abadie P, Rioux P, Scatton B, et al. (1996) Central benzodiazepine receptor occupancy by zolpidem in the human brain as assessed by positron emission tomography. *Science* 295: 35–44.

Allen RP, Burchell BJ, MacDonald B, et al. (2009) Validation of the self-completed Cambridge–Hopkins questionnaire (CH-RLSq) for ascertainment of restless legs syndrome (RLS) in a population survey. *Sleep Med* 10: 1079–100.

Bastien CH, Vallieres A, Morin CM (2001) Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med* 2: 297–307.

Bonnet MH, Burton GG, Arand DL (2014) Physiological and medical findings in insomnia: implications for diagnosis and care. *Sleep Med Rev* 18: 95–8.

Burke RA, Faulkner MA (2011) Gabapentin enacarbil for the treatment of restless legs syndrome (RLS). *Expert Opin Pharmacother* 12: 2905–14.

Buysse DJ, Reynolds CF III, Monk TH, et al. (1989) The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 28: 193–213.

Cappuccio FP, D'Elia L, Strazzullo P, et al. (2010) Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. *Sleep* 33: 585–92.

Chahine LM, Chemali ZN (2006) Restless legs syndrome: a review. *CNS Spectrums* 11: 511–20.

Dawson GR, Collinson N, Atack JR (2005) Development of subtype selective $GABA_A$ modulators. *CNS Spectrums* 10: 21–7.

De Lecea L, Winkelman JW (2020) Sleep and neuropsychiatric illness. *Neuropsychopharmacol Rev* 45: 1–216.

Drover DR (2004) Comparative pharmacokinetics and pharmacodynamics of short-acting hypnosedatives – zaleplon, zolpidem and zopiclone. *Clin Pharmacokinet* 43: 227–38.

Durmer JS, Dinges DF (2005) Neurocognitive consequences of sleep deprivation. *Semin Neurol* 25: 117–29.

Espana RA, Scammell TE (2011) Sleep neurobiology from a clinical perspective. *Sleep* 34: 845–58.

Fava M, McCall WV, Krystal A, et al. (2006) Eszopiclone co-administered with fluoxetine in patients with insomnia coexisting with major depressive disorder. *Biol Psychiatry* 59: 1052–60.

Freedom T (2011) Sleep-related movement disorders. *Dis Mon* 57: 438-47.

Frenette E (2011) Restless legs syndrome in children: a review and update on pharmacological options. *Curr Pharm Design* 17: 1436–42.

Garcia-Borreguero D, Allen R, Kohnen R, et al. (2010) Loss of response during long-term treatment of restless legs syndrome: guidelines approved by the International Restless Legs Syndrome Study Group for use in clinical trials. *Sleep Med* 11: 956–9.

Green CB, Takahashi JS, Bass J (2008) The meter of metabolism. *Cell* 134: 728–42.

Harris J, Lack L, Kemo K, et al. (2012) A randomized controlled trial of intensive sleep retraining (ISR): a brief conditioning treatment for chronic insomnia. *Sleep* 35: 49–60.

Hening W, Walters AS, Allen RP, et al. (2004) Impact, diagnosis and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS Epidemiology, Symptoms, and Treatment) Primary Care Study. *Sleep Med* 5: 237–46.

Koffel EA, Koffel JB, Gehrman PR (2015) A meta-analysis of group cognitive behavioral therapy for insomnia. *Sleep Med Rev* 19: 6–16.

Krystal AD, Walsh JK, Laska E, et al. (2003) Sustained efficacy of eszopiclone over 6 months of nightly treatment: results of a randomized, double-blind, placebo-controlled study in adults with chronic insomnia. *Sleep* 26: 793–9.

Morin CM, Benca R (2012) Chronic insomnia. *Lancet* 379: 1129–41.

Nofzinger EA, Buysse DJ, Germain A, et al. (2004) Functional neuroimaging evidence for hyperarousal in insomnia. *Am J Psychiatry* 161: 2126–9.

Nutt D, Stahl SM (2010) Searching for perfect sleep: the continuing evolution of $GABA_A$ receptor modulators as hypnotics. *J Psychopharmacol* 24: 1601–2.

Orzel-Gryglewska J (2010) Consequences of sleep deprivation. *Int J Occup Med Environ Health* 23: 95–114.

Palma JA, Urrestarazu E, Iriarte J (2013) Sleep loss as a risk factor for neurologic disorders: a review. *Sleep Med* 14: 229–36.

Parthasarathy S, Vasquez MM, Halonen M, et al. (2015) Persistent insomnia is associated with mortality risk. *Am J Med* 128: 268–75.

Pinto Jr LR, Alves RC, Caixeta E, et al. (2010) New guidelines for diagnosis and treatment of insomnia. *Arq Neuropsiquiatr* 68: 666–75.

Plante DT (2017) Sleep propensity in psychiatric hypersomnolence: a systematic review and meta-analysis of multiple sleep latency findings. *Sleep Med Rev* 31: 48–57.

Reeve K, Bailes B. (2010) Insomnia in adults: etiology and management. *JNP* 6: 53–60.

Richey SM, Krystal AD (2011) Pharmacological advances in the treatment of insomnia. *Curr Pharm Design* 17: 1471–5.

Roth T, Roehrs T (2000) Sleep organization and regulation. *Neurology* 54 (Suppl 1): S2–7.

Sahar S, Sassone-Corsi P (2009) Metabolism and cancer: the circadian clock connection. *Nature* 9: 886–96.

Schutte-Rodin S, Broch L, Buysse D, et al. (2008) Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med* 4: 487–504.

Sehgal A, Mignot E (2011) Genetics of sleep and sleep disorders. *Cell* 146: 194–207.

Tafti M (2009) Genetic aspects of normal and disturbed sleep. *Sleep Med* 10: S17–21.

Thorpe AJ, Clair A, Hochman S, et al. (2011) Possible sites of therapeutic action in restless legs syndrome: focus on dopamine and α2δ ligands. *Eur Neurol* 66: 18–29.

Vgontzas AN, Fernadez-Mendoza J, Bixler EO, et al. (2012) Persistent insomnia: the role of objective short sleep duration. *Sleep* 35: 61–8.

Wu JC, Gillin JC, Buchsbaum MS, et al. (2006) Frontal lobe metabolic decreases with sleep deprivation not totally reversed by recovery sleep. *Neuropsychopharmacology* 31: 2783–92.

Zeitzer JM, Morales-Villagran A, Maidment NT (2006) Extracellular adenosine in the human brain during sleep and sleep deprivation: an in vivo microdialysis study. *Sleep* 29: 455–61.

Wake Disorders/Sleepiness/OSA/ Narcolepsy/Circadian/Shift Work

Abad VC, Guilleminault C (2011) Pharmacological treatment of obstructive sleep apnea. *Curr Pharm Design* 17: 1418–25.

Adenuga O, Attarian H (2014) Treatment of disorders of hypersomnolence. *Curr Treat Options Neurol* 16: 302.

Ahmed I, Thorpy M (2010) Clinical features, diagnosis and treatment of narcolepsy. *Clin Chest Med* 31: 371–81.

Aloia MS, Arnedt JT, Davis JD, Riggs RL, Byrd D (2004) Neuropsychological sequelae of obstructive sleep apnea–hypopnea syndrome: a critical review. *J Int Neuropsychol Soc* 10: 772–85.

Arallanes-Licea E, Caldelas I, De Ita-Perez D, et al. (2014) The circadian timing system: a recent addition in the physiological mechanisms underlying pathological and aging processes. *Aging Dis* 5: 406–18.

Artioli P, Lorenzi C, Priovano A, et al. (2007) How do genes exert their role? Period 3 gene variants and possible influences on mood disorder phenotypes. *Eur Neuropsychopharmacol* 17: 587–94.

Aurora RN, Chowdhuri S, Ramar K, et al. (2012) The treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses. *Sleep* 35: 17–40.

Banerjee S, Wang Y, Solt LA, et al. (2014) Pharmacological targeting of the mammalian clock regulates sleep architecture and emotional behaviour. *Nat Commun* 5: 5759.

Barger LK, Ogeil RP, Drake CL, et al. (2012) Validation of a questionnaire to screen for shift work disorder. *Sleep* 35: 1693–703.

Benedetti F, Serretti A, Colombo C, et al. (2003) Influence of *CLOCK* gene polymorphisms on circadian mood fluctuation and illness recurrence in bipolar depression. *Am J Med Genet B, Neuropsychiatr Genet* 123 : 23–6.

Black JE, Hull SG, Tiller J, et al. (2010) The long-term tolerability and efficacy of armodafinil in patients with excessive sleepiness associated with treated obstructive sleep apnea, shift work disorder, or narcolepsy: an open-label extension study. *J Clin Sleep Med* 6: 458–66.

Bogan RK (2010) Armodafinil in the treatment of excessive sleepiness. *Expert Opin Pharmacother* 11: 993–1002.

Bonacci JM, Venci JV, Ghandi MA (2015) Tasimelteon (HetliozTM): a new melatonin receptor agonist for the treatment of non-24 sleep-wake disorder. *J Pharm Pract* 28: 473–8.

Brancaccio M, Enoki R, Mazuki CN, et al. (2014) Network-mediated encoding of circadian time: the suprachiasmatic nucleus (SCN) from genes to neurons to circuits, and back. *J Neurosci* 34: 15192–9.

Carocci A, Catalano A, Sinicropi MS (2014) Melatonergic drugs in development. *Clin Pharmacol Adv Applications* 6: 127–37.

Cauter EV, Plat L, Scharf MB, et al. (1997) Simultaneous stimulation of slow-wave sleep and growth hormone secretion by gamma-hydroxybutyrate in normal young men. *J Clin Invest* 100: 745–53.

Cermakian N, Lange T, Golombek D, et al. (2013) Crosstalk between the circadian clock circuitry and the immune system. *Chronobiol Int* 30: 870–88.

Cirelli C (2009) The genetic and molecular regulation of sleep: from fruit flies to humans. *Nat Rev Neurosci* 10: 549–60.

Colwell CS (2011) Linking neural activity and molecular oscillators in the SCN. *Nat Rev Neurosci* 12: 553–69.

Cook H et al. (2003) A 12-month, open-label, multicenter extension trial of orally administered sodium oxybate for the treatment of narcolepsy. *Sleep* 26: 31–5.

Crowley SJ, Lee C, Tseng CY, et al. (2004) Complete or partial circadian re-entrainment improves performance, alertness, and mood during night-shift work. *Sleep* 27: 1077–87.

Czeisler CA, Walsh JK, Roth T, et al. (2005) Modafinil for excessive sleepiness associated with shift-work sleep disorder. *New Engl J Med* 353: 476–86.

Dallaspezia S, Benedetti F (2011) Chronobiological therapy for mood disorders. *Expert Rev Neurother* 11: 961–70.

Darwish M, Bond M, Ezzet F (2012) Armodafinil in patients with excessive sleepiness associated with shift work disorder: a pharmacokinetic/pharmacodynamic model for predicting and comparing their concentration-effect relationships. *J Clin Pharmacol* 52: 1328–42.

Darwish M, Kirby M, D'Andrea DM, et al. (2010) Pharmacokinetics of armodafinil and modafinil after single and multiple doses in patients with excessive sleepiness associated with treated obstructive sleep apnea: a randomized, open-label, crossover study. *Clin Ther* 32: 2074–87.

Dauvilliers Y, Tafti M (2006) Molecular genetics and treatment of narcolepsy. *Ann Med* 38: 252–62.

De la Herran-Arita AK, Garcia-Garcia F (2014) Narcolepsy as an immune-mediated disease. *Sleep Disord* 2014: 792687.

Dinges DF, Weaver TE (2003) Effects of modafinil on sustained attention performance and quality of life in OSA patients with residual sleepiness while being treated with CPAP. *Sleep Med* 4: 393–402.

Dresler M, Spoormaker VI, Beitinger P, et al. (2014) Neuroscience-driven discovery and development of sleep therapeutics. *Pharmacol Ther* 141: 300–34.

Eckel-Mahan KL, Patel VR, de Mateo S, et al. (2013) Reprogramming of the circadian clock by nutritional challenge. *Cell* 155: 1464–78.

Ellis CM, Monk C, Simmons A, et al. (1999) Functional magnetic resonance imaging neuroactivation studies in normal subjects and subjects with the narcoleptic syndrome. Actions of modafinil. *J Sleep Res* 8: 85–93.

Epstein LJ, Kristo D, Strollo PJ, et al. (2009) Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med* 5: 263–76.

Erman MK, Seiden DJ, Yang R, et al. (2011) Efficacy and tolerability of armodafinil: effect on clinical condition late in the shift and overall functioning of patients with excessive sleepiness associated with shift work disorder. *J Occup Environ Med* 53: 1460–5.

Froy O (2010) Metabolism and circadian rhythms: implications for obesity. *Endocr Rev* 31: 1–24.

Golombek DA, Casiraghi LP, Agostino PV, et al. (2013) The times they are a-changing: effects of circadian desynchronization on physiology and disease. *J Physiol Paris* 107: 310–22.

Guo X, Zheng L, Wang J, et al. (2013) Epidemiological evidence for the link between sleep duration and high blood pressure: a systematic review and meta-analysis. *Sleep Med* 14: 324–32.

Hampp G, Ripperger JA, Houben T, et al. (2008) Regulation of monoamine oxidase A by circadian-clock components implies influence on mood. *Curr Biol* 18: 678–83.

Harrison EM, Gorman MR (2012) Changing the waveform of circadian rhythms: considerations for shift-work. *Front Neurol* 3: 1–7.

Hart CL, Haney M, Vosburg SK, et al. (2006) Modafinil attentuates disruptions in cognitive performance during simulated night-shift work. *Neuropsychopharmacology* 31: 1526–36.

He B, Peng H, Zhao Y, et al. (2011) Modafinil treatment prevents REM sleep deprivation-induced brain function impairment by increasing MMP-9 expression. *Brain Res* 1426: 38–42.

Hirai N, Nishino S (2011) Recent advances in the treatment of narcolepsy. *Curr Treat Options Neurol* 13: 437–57.

Horne JA, Ostberg O (1976) A self-assessment questionnaire to determine morningness–eveningness in human circadian rhythms. *Int J Chronobiol* 4: 97–100.

Johansson C, Willeit M, Smedh C, et al. (2003) Circadian clock-related polymorphisms in seasonal affective disorder and their relevance to diurnal preference. *Neuropsychopharmacology* 28: 734–9.

Khalsa SB, Jewett ME, Cajochen C, et al. (2003) A phase response curve to single bright light pulses in human subjects. *J Physiol* 549(pt 3): 945–52.

Knudsen S, Biering-Sorensen B, Kornum BR, et al. (2012) Early IVIg treatment has no effect on post-H1N1 narcolepsy phenotype or hypocretin deficiency. *Neurology* 79: 102–3.

Krakow B, Ulibarri VA (2013) Prevalence of sleep breathing complaints reported by treatment-seeking chronic insomnia disorder patients on presentation to a sleep medical center: a preliminary report. *Sleep Breath* 17: 317–22.

Kripke DE, Nievergelt CM, Joo E, et al. (2009) Circadian polymorphisms associated with affective disorders. *J Circadian Rhythms* 27: 2.

Krystal AD, Harsh JR, Yang R et al. (2010) A double-blind, placebo-controlled study of armodafinil for excessive sleepiness in patients with treated obstructive sleep apnea and comorbid depression. *J Clin Psychiatry* 71: 32–40.

Lallukka T, Kaikkonen R, Harkanen T, et al. (2014) Sleep and sickness absence: a nationally representative register-based follow-up study. *Sleep* 37: 1413–25.

Landrigan CP, Rothschild JM, Cronin JW, et al. (2004) Effect of reducing interns work hours on serious medical errors in intensive care units. *New Engl J Med* 351: 1838–48.

Larson-Prior LJ, Ju Y, Galvin JE (2014) Cortical–subcortical interactions in hypersomnia disorders: mechanisms underlying cognitive and behavioral aspects of the sleep–wake cycle. *Front Neurol* 5: 1–13.

Laudon M, Frydman-Marom A (2014) Therapeutic effects of melatonin receptor agonists on sleep and comorbid disorders. *Int J Mol Sci* 15: 15924–50.

Liira J, Verbeek JH, Costa G, et al. (2014) Pharmacological interventions for sleepiness and sleep disturbances caused by shift work. *Cochrane Database Syst Rev* 8: CD009776.

Lim DC, Veasey SC (2010) Neural injury in sleep apnea. *Curr Neurol Neurosci Rep* 10: 47–52.

Liu Y, Wheaton AG, Chapman DP, et al. (2013) Sleep duration and chronic disease among US adults age 45 years and older: evidence from the 2010 behavioral risk factor surveillance system. *Sleep* 36: 1421–7.

Madras BK, Xie Z, Lin Z, et al. (2006) Modafinil occupies dopamine and norepinephrine transporters in vivo and modulates the transporters and trace amine activity in vitro. *J Pharmacol Exp Ther* 319: 561–9.

Makris AP, Rush CR, Frederich RC, Kelly TH (2004) Wake-promoting agents with different mechanisms of action: comparison of effects of modafinil and amphetamine on food intake and cardiovascular activity. *Appetite* 42: 185–95.

Mansour HA, Wood J, Logue T, et al. (2006) Association of eight circadian genes with bipolar I disorder, schizoaffective disorder and schizophrenia. *Genes Brain Behav* 5: 150–7.

Martin JL, Hakim AD (2011) Wrist actigraphy. *Chest* 139: 1514–27.

Masri S, Kinouchi K, Sassone-Corsi P (2015) Circadian clocks, epigenetics, and cancer. *Curr Opin Oncol* 27: 50–6.

Mignot EJM (2012) A practical guide to the therapy of narcolepsy and hypersomnia syndromes. *Neurotherapeutics* 9: 739–52.

Miletic V, Relja M (2011) Restless legs syndrome. *Coll Antropol* 35: 1339–47.

Morgenthaler TI, Kapur VK, Brown T, et al. (2007) Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. *Sleep* 30: 1705–11.

Morgenthaler TI, Lee-Chiong T, Alessi C, et al. (2007) Practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders. *Sleep* 30: 1445–59.

Morrissette DA (2013) Twisting the night away: a review of the neurobiology, genetics, diagnosis, and treatment of shift work disorder. *CNS Spectrums* 18 (Suppl 1): 45–53.

Niervergelt CM, Kripke DF, Barrett TB, et al. (2006) Suggestive evidence for association of circadian genes *PERIOD3* and *ARNTL* with bipolar disorder. *Am J Med Genet B, Neuropsychiatr Genet* 141: 234–41.

Norman D, Haberman PB, Valladares EM (2012) Medical consequences and associations with untreated sleep-related breathing disorders and outcomes of treatments. *J Calif Dent Assoc* 40: 141–9.

O'Donoghue FJ, Wellard RM, Rochford PD, et al. (2012) Magnetic resonance spectroscopy and neurocognitive dysfunction in obstructive sleep apnea before and after CPAP treatment. *Sleep* 35: 41–8.

Ohayon MM (2012) Determining the level of sleepiness in the American population and its correlates. *J Psychiatr Res* 46: 422–7.

Oosterman JE, Kalsbeek A, la Fleur SE, et al. (2015) Impact of nutrition on circadian rhythmicity. *Am J Physiol Regul Integr Comp Physiol* 308: R337–50.

Pail G, Huf W, Pjrek E, et al. (2011) Bright-light therapy in the treatment of mood disorders. *Neuropsychobiology* 64: 152–62.

Palagini L, Biber K, Riemann D (2014) The genetics of insomnia: evidence for epigenetic mechanisms? *Sleep Med Rev* 18: 225–35.

Partonen T, Treutlein J, Alpman A, et al. (2007) Three circadian clock genes *Per2*, *Arntl*, and *Npas2* contribute to winter depression. *Ann Med* 39: 229–38.

Pigeon WR, Pinquart M, Conner K (2012) Meta-analysis of sleep disturbance and suicidal thoughts and behaviors. *J Clin Psychiatry* 73: e1160–7.

Qureshi IA, Mehler MF (2014) Epigenetics of sleep and chronobiology. *Curr Neurol Neurosci Rep* 14: 432.

Rogers RR (2012) Past, present, and future use of oral appliance therapies in sleep-related breathing disorders. *J Calif Dent Assoc* 40: 151–7.

Sangal RB, Thomas L, Mitler MM (1992) Maintenance of wakefulness test and multiple sleep latency test. Measurement of different abilities in patients with sleep disorders. *Chest* 101: 898–902.

Saper CB, Lu J, Chou TC, Gooley J (2005) The hypothalamic integrator for circadian rhythms. *Trends Neurosci* 3: 152–7.

Saper CB, Scammell TE, Lu J (2005) Hypothalamic regulation of sleep and circadian rhythms. *Nature* 437: 1257–63.

Schwartz JRL, Nelson MT, Schwartz ER, Hughes RJ (2004) Effects of modafinil on wakefulness and executive function in patients with narcolepsy experiencing late-day sleepiness. *Clin Neuropharmacol* 27: 74–9.

Severino G, Manchia M, Contu P, et al. (2009) Association study in a Sardinian sample between bipolar disorder and the nuclear receptor REV-ERBalpha gene, a critical component of the circadian clock system. *Bipolar Disord* 11: 215–20.

Soria V, Martinez-Amoros E, Escaramis G, et al. (2010) Differential association of circadian genes with mood disorders: CRY1 and NPAS2 are associated with unipolar major depression and CLOCK and VIP with bipolar disorder. *Neuropsychopharmacology* 35: 1279–89.

Stahl SM (2014) Mechanism of action of tasimelteon in non-24 sleep–wake syndrome: treatment for a circadian rhythm disorder in blind patients. *CNS Spectrums* 19: 475–87.

Stippig A, Hubers U, Emerich M (2015) Apps in sleep medicine. *Sleep Breath* 19: 411–17.

Tafti M, Dauvilliers Y, Overeem S (2007) Narcolepsy and familial advanced sleep-phase syndrome: molecular genetics of sleep disorders. *Curr Opin Genet Dev* 17: 222–7.

Tahara Y, Shibata S (2014) Chrono-biology, chrono-pharmacology, and chrononutrition. *J Pharmacol Sci* 124: 320–35.

Takahashi S, Hong HK, McDearmon EL (2008) The genetic of mammalian circadian order and disorder: implications for physiology and disease. *Nat Rev Genet* 9: 764–75.

Takao T, Tachikawa H, Kawanishi Y, et al. (2007) *CLOCK* gene *T3111C* polymorphism is associated with Japanese schizophrenics: a preliminary study. *Eur Neuropsychopharmacol* 17: 273–6.

Tarasiuk A, Reuveni H (2013) The economic impact of obstructive sleep apnea. *Curr Opin Pulm Med* 19: 639–44.

Thaiss CA, Zeevi D, Levy M, et al. (2014) Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis. *Cell* 159: 514–29.

Thomas RJ, Kwong K (2006) Modafinil activates cortical and subcortical sites in the sleep-deprived state. *Sleep* 29: 1471–81.

Thomas RJ, Rosen BR, Stern CE, Weiss JW, Kwong KK (2005) Functional imaging of working memory in obstructive sleep-disordered breathing. *J Appl Physiol* 98: 2226–34.

Thorpy MJ, Dauvilliers Y (2015) Clinical and practical consideration in the pharmacologic management of narcolepsy. *Sleep Med* 16: 9–18.

Trotti LM, Saini P, Bliwise DL, et al. (2015) Clarithromycin in gamma-aminobutyric acid-related hypersomnolence: a randomized, crossover trial. *Ann Neurol* 78: 454–65.

Trotti LM, Saini P, Freeman AA, et al. (2013) Improvement in daytime sleepiness with clarithromycin in patients with GABA-related hypersomnia: clinical experience. *J Psychopharmacol* 28: 697–702.

Van Someren EJ, Riemersma-Van Der Lek RF (2007) Live to the rhythm, slave to the rhythm. *Sleep Med Rev* 11: 465–84.

Wulff K, Gatti S, Wettstein JG, Foster RG (2010) Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. *Nat Rev Neurosci* 11: 589–99.

Zaharna M, Dimitriu A, Guilleminault C (2010) Expert opinion on pharmacotherapy of narcolepsy. *Expert Opin Pharmacother* 11: 1633–45.

Zawilska JB, Skene DJ, Arendt J. (2009) Physiology and pharmacology of melatonin in relation to biological rhythms. *Pharmacol Rep* 61: 383–410.

Chapter 11 (Attention Deficit Hyperactivity Disorder)

Arnsten AFT (2006) Fundamentals of attention deficit/hyperactivity disorder: circuits and pathways. *J Clin Psychiatry* 67 (Suppl 8): 7–12.

Arnsten AFT (2006) Stimulants: therapeutic actions in ADHD. *Neuropsychopharmacology* 31: 2376–83.

Arnsten AFT (2009) Stress signaling pathways that impair prefrontal cortex structure and function. *Nat Rev Neurosci* 10: 410–22.

Arnsten AFT, Li BM (2005) Neurobiology of executive functions: catecholamine influences on prefrontal cortical functions. *Biol Psychiatry* 57: 1377–84.

Avery RA, Franowicz JS, Phil M, et al. (2000) The alpha 2a adrenoceptor agonist, guanfacine, increases regional cerebral blood flow in dorsolateral prefrontal cortex of monkeys performing a spatial working memory task. *Neuropsychopharmacology* 23: 240–9.

Berridge CW, Devilbiss DM, Andrzejewski ME, et al. (2006) Methylphenidate preferentially increases catecholamine neurotransmission within the prefrontal cortex at low doses that enhance cognitive function. *Biol Psychiatry* 60: 1111–20.

Berridge CW, Shumsky JS, Andrzejewski ME, et al. (2012) Differential sensitivity to psychostimulants across prefrontal cognitive tasks: differential involvement of noradrenergic α_1- and α_2-receptors. *Biol Psychiatry* 71: 467–73.

Biederman J (2004) Impact of comorbidity in adults with attention deficit/hyperactivity disorder. *J Clin Psychiatry* 65 (Suppl 3): 3–7.

Biederman J, Petty CR, Fried R, et al. (2007) Stability of executive function deficits into young adult years: a prospective longitudinal follow-up study of grown up males with ADHD. *Acta Psychiatr Scand* 116: 129–36.

Clerkin SM, Schulz KP, Halperin JM (2009) Guanfacine potentiates the activation of prefrontal cortex evoked by warning signals. *Biol Psychiatry* 66: 307–12.

Cortese S, Adamo N, Del Giovane C, et al. (2018) Comparative efficacy and tolerability of medications for attention deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. *Lancet Psychiatry* 5: 727–38.

Easton N, Shah YB, Marshall FH, Fone KC, Marsden CA (2006) Guanfacine produces differential effects in frontal cortex compared with striatum: assessed by phMRI BOLD contrast. *Psychopharmacology* 189: 369–85.

Faraone SV, Biederman J, Spencer T (2006) Diagnosing adult attention deficit hyperactivity disorder: are late onset and subthreshold diagnoses valid? *Am J Psychiatry* 163: 1720–9.

Franke B, Nucgekubu G, Asherson P, et al. (2018) Live fast, die young? A review on the developmental trajectories of ADHD across the lifespan. *Eur Neuropsychopharmacol* 28: 1059–88.

Fusar-Poli P, Rubia K, Rossi G, Sartori G, Balottin U (2012) Striatal dopamine transporter alterations in ADHD: pathophysiology or adaptation to psychostimulants? a meta-analysis. *Am J Psychiatry* 169: 264–72.

Grady M, Stahl SM (2012) A horse of a different color: how formulation influences medication effects. *CNS Spectrums* 17: 63–9.

Hannestad J, Gallezot JD, Planeta-Wilson B, et al. (2010) Clinically relevant doses of methylphenidate significantly occupy norepinephrine transporters in humans in vivo. *Biol Psychiatry* 68: 854–60.

Jakala P, Riekkinen M, Sirvio J, et al. (1999) Guanfacine, but not clonidine, improves planning and working memory performance in humans. *Neuropsychopharmacology* 20: 460–70.

Johnson K, Liranso T, Saylor K, et al. (2020) A phase II double blind placebo controlled efficacy and safety study of SPN-812 (extended release vilaxazine) in children with ADHD. *J Atten Disord* 24: 348–58.

Kessler RC, Adler L, Barkley R (2006) The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *Am J Psychiatry* 163: 716–23.

Kessler RC, Green JG, Adler LA, et al. (2010) Structure and diagnosis of adult attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 67: 1168–78.

Kollins SH, McClernon JM, Fuemmeler BF (2005) Association between smoking and attention deficit/hyperactivity disorder symptoms in a population based sample of young adults. *Arch Gen Psychiatry* 62: 1142–7.

Madras BK, Miller GM, Fischman AJ (2005) The dopamine transporter and attention deficit/hyperactivity disorder. *Biol Psychiatry* 57: 1397–409.

Matthijssen AFM, Dietrich A, Bierens M, et al. (2019) Continued benefits of methylphenidate in ADHD after 2 years in clinical practice: a randomized placebo-controlled discontinuation study. *Am J Psychiatry* 176: 754–62.

Mattingly G, Anderson RH (2016) Optimizing outcomes of ADHD treatment: from clinical targets to novel delivery systems. *CNS Spectrums* 21: 48–58.

Pinder RM, Brogden RN, Speight TM, et al. (1977) Voloxazine: a review of its pharmacological properties and therapeutic efficacy in depressive illness. *Drugs* 13: 401–21.

Pingault JB, Tremblay RE, Vitaro F, et al. (2011) Childhood trajectories of inattention and hyperactivity and prediction of educational attainment in early adulthood: a 16-year longitudinal population-based study. *Am J Psychiatry* 168: 1164–70.

Seidman LJ, Valera EM, Makris N, et al. (2006) Dorsolateral prefrontal and anterior cingulate cortex volumetric abnormalities in adults with attention-deficit/hyperactivity disorder identified by magnetic resonance imaging. *Biol Psychiatry* 60: 1071–80.

Shaw P, Stringaris A, Nigg J, et al. (2014) Emotion dysregulation in attention deficit hyperactivity disorder. *Am J Psychiatry* 171: 276–93.

Spencer TJ, Biederman J, Madras BK, et al. (2005) In vivo neuroreceptor imaging in attention deficit/hyperactivity disorder: a focus on the dopamine transporter. *Biol Psychiatry* 57: 1293–300.

Spencer TJ, Bonab AA, Dougherty DD, et al. (2012) Understanding the central pharmacokinetics of spheroidal oral drug absorption system (SODAS) dexmethylphenidate: a positron emission tomography study of dopamine transporter receptor occupancy measured with C-11 altropane. *J Clin Psychiatry* 73: 346–52.

Stahl SM (2009) The prefrontal cortex is out of tune in attention-deficit/hyperactivity disorder. *J Clin Psychiatry* 70: 950–1.

Stahl SM (2009) Norepinephrine and dopamine regulate signals and noise in the prefrontal cortex. *J Clin Psychiatry* 70: 617–18.

Stahl SM (2010) Mechanism of action of stimulants in attention deficit/hyperactivity disorder. *J Clin Psychiatry* 71: 12–13.

Stahl SM (2010) Mechanism of action of α2A-adrenergic agonists in attention-deficit/hyperactivity disorder with or without oppositional symptoms. *J Clin Psychiatry* 71: 223–24.

Steere JC, Arnsten AFT (1997) The alpha 2A noradrenergic receptor agonist guanfacine improves visual object discrimination reversal performance in aged rhesus monkeys. *Behav Neurosci* 111: 883–91.

Surman CBH, Biederman J, Spencer T (2011) Deficient emotional self regulation and adult attention deficit hyperactivity disorder: a family risk analysis. *Am J Psychiatry* 168: 617–23.

Swanson J, Baler RD, Volkow ND (2011) Understanding the effects of stimulant medications on cognition in individuals with attention-deficit hyperactivity disorder: a decade of progress. *Neuropsychopharmacology* 36: 207–26.

Turgay A, Goodman DW, Asherson P, et al. (2012) Lifespan persistance of ADHD: the lift transition model and its application. *J Clin Psychiatry* 73: 192–201.

Turner DC, Clark L, Dowson J, Robbins TW, Sahakian BJ (2004) Modafinil improves cognition and response inhibition in adult attention deficit/hyperactivity disorder. *Biol Psychiatry* 55: 1031–40.

Turner DC, Robbins TW, Clark L, et al. (2003) Cognitive enhancing effects of modafinil in healthy volunteers. *Psychopharmacology* 165: 260–9.

Vaughan BS, March JS, Kratochvil CJ (2012) The evidence-based pharmacological treatment of pediatric ADHD. *Int J Neuropsychopharmacol* 15: 27–39.

Volkow ND, Wong GJ, Kollins SH, et al. (2009) Evaluating dopamine reward pathway in ADHD: Clinical implications. *JAMA* 302: 1084–91.

Wang M, Ramos BP, Paspalas CD, et al. (2007) α2A-Adrenoceptors strengthen working memory networks by inhibiting cAMP-HCN channel signaling in prefrontal cortex. *Cell* 129: 397–410.

Wigal T, Brams M, Gasior M, et al. (2010) Randomized, double-blind, placebo-controlled, crossover study of the efficacy and safety of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder: novel findings using a simulated adult workplace environment design. *Behav Brain Funct* 6: 34–48.

Wilens TE (2007) Lisdexamfetamine for ADHD. *Curr Psychiatry* 6: 96–105.

Yang L, Cao Q, Shuai L (2012) Comparative study of OROS-MPH and atomoxetine on executive function improvement in ADHD: a randomized controlled trial. *Int J Neuropsychopharmacol* 15: 15–16.

Zang YF, Jin Z, Weng XC, et al. (2005) Functional MRI in attention deficit hyperactivity disorder: evidence for hypofrontality. *Brain Dev* 27: 544–50.

Zuvekas SH, Vitiello B (2012) Stimulant medication use in children: a 12-year perspective. *Am J Psychiatry* 169: 160–6.

Chapter 12 (Dementia) and Acetylcholine

Neuronal Networks: Acetylcholine

Bacher I, Rabin R, Woznica A, Sacvco KA, George TP (2010) Nicotinic receptor mechanisms in neuropsychiatric disorders: therapeutic implications. *Prim Psychiatry* 17: 35–41.

Fryer AD, Christopoulos A, Nathanson NM (eds.) (2012) *Muscarinic Receptors*. Berlin: Springer-Verlag.

Geldmacher DS, Provenano G, McRae T, et al. (2003) Donepezil is associated with delayed nursing home placement in patients with Alzheimer's disease. *J Am Geriatr Soc* 51: 937–44.

Grothe M, Heinsen H, Teipel SF (2012) Atrophy of the cholinergic basal forebrain over the adult age range and in early states of Alzheimer's disease. *Biol Psychiatry* 71: 805–13.

Hasselmo ME, Sarter M (2011) Nodes and models of forebrain cholinergic neuromodulation of cognition. *Neuropsychopharmacology* 36: 52–73.

Lane RM, Potkin SG, Enz A (2006) Targeting acetylcholinesterase and butyrylcholinesterase in dementia. *Int J Neuropsychopharmacol* 9: 101–24.

Ohta Y, Darwish M, Hishikawa N, et al. (2017) Therapeutic effects of drug switching between acetylcholinesterase inhibitors in patients with Alzheimer's disease. *Geriatr Gerontol Int* 17: 1843–8.

Pepeu G, Giovannini M (2017) The fate of the brain cholinergic neurons in neurodegenerative diseases. *Brain Res* 1670: 173–84.

Tariot PN, Farlow MR, Grossberg GT, et al. (2004) Memantine treatment in patients with moderate to severe Alzheimer's disease already receiving donepezil. *JAMA* 291: 317–24.

Diet/Exercise/Genetics/Aging

Anastasiou CA, Yannakoulia M, Kosmidis MH, et al. (2017) Mediterranean diet and cognitive health: initial results from the Hellenic Longitudinal Investigation of ageing and diet. *PLOS ONE* 12: e0182048.

Aridi YS, Walker JL, Wright ORL (2017) The association between the Mediterranean dietary pattern and cognitive health: a systematic review. *Nutrients* 9: E674.

Ballard C, Khan Z, Clack H, et al. (2011) Nonpharmacological treatment of Alzheimer disease. *Can J Psychiatry* 56: 589–95.

Buchman AS, Boyle PA, Yu L, et al. (2012) Total daily physical activity and the risk of AD and cognitive decline in older adults. *Neurology* 78: 1323–9.

Burmester B, Leathem J, Merrick P (2016) Subjective cognitive complaints and objective cognitive function in aging: a systematic review and meta-analysis of recent cross-sectional findings. *Neuropsychol Rev* 26: 376–93.

Cederholm T (2017) Fish consumption and omega-3 fatty acid supplementation for prevention or treatment of cognitive decline, dementia or Alzheimer's disease in older adults: any news? *Curr Opin Clin Nutr Metab Care* 20: 104–9.

Cepoiu-Martin M, Tam-Tham H, Patten S, et al. (2016) Predictors of long-term care placement in persons with dementia: a systematic review and metaanalysis. *Int J Geriatr Psychiatry* 31: 1151–71.

Ercoli L, Siddarth P, Huang SC, et al. (2006) Perceived loss of memory ability and cerebral metabolic decline in persons with the apolipoprotein E-IV genetic risk for Alzheimer disease. *Arch Gen Psychiatry* 63: 442–8.

Gu Y, Brickman AM, Stern Y, et al. (2015) Mediterranean diet and brain structure in a multiethnic elderly cohort. *Neurology* 85: 1744–51.

Hardman RJ, Kennedy G, Macpherson H, et al. (2016) Adherence to a Mediterranean-style diet and effects on cognition in adults: a qualitative evaluation and systematic review of longitudinal and prospective trials. *Front Nutr* 3: 1–13.

Hinz FI, Geschwind DH (2017) Molecular genetics of neurodegenerative dementias. *Cold Spring Harb Perspect Biol* 9: a023705.

Knight A, Bryan J, Murphy K (2016) Is the Mediterranean diet a feasible approach to preserving cognitive function and reducing risk of dementia for older adults in Western countries? New insights and future directions. *Ageing Res Rev* 25: 85–101.

Kullmann S, Heni M, Hallschmid M, et al. (2016) Brain insulin resistance at the crossroads of metabolic and cognitive disorders in humans. *Physiol Rev* 96: 1169–209.

Larson EB, Wang L, Bowen JD, et al. (2006) Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Ann Intern Med* 144: 73–81.

Lee HS, Park SW, Park YJ (2016) Effects of physical activity programs on the improvement of dementia symptom: a meta-analysis. *Biomed Res Int* 2016: 2920146.

Lee SH, Zabolotny JM, Huang H, et al. (2016) Insulin in the nervous system and the mind: functions in metabolism, memory, and mood. *Mol Metab* 5: 589–601.

Li Y, Sekine T, Funayama M, et al. (2014) Clinicogenetic study of GBA mutations in patients with familial Parkinson's disease. *Neurobiol Aging* 35: 935.e3–8.

Lim SY, Kim EJ, Kim A, et al. (2016) Nutritional factors affecting mental health. *Clin Nutr Res* 5: 143–52.

Marcason W (2015) What are the components of the MIND diet? *J Acad Nutr Diet* 115: 1744.

Matsuzaki T, Sasaki K, Tanizaki Y, et al. (2010) Insulin resistance is associated with the pathology of Alzheimer disease. *Neurology* 75: 764–70.

Ngandu T, Lehtisalo J, Solomon A, et al. (2015) A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomized controlled trial. *Lancet* 385: 2255–63.

O'Donnell CA, Browne S, Pierce M, et al. (2015) Reducing dementia risk by targeting modifiable risk factors in mid-life: study protocol for the Innovative Midlife Intervention for Dementia Deterrence (In-MINDD) randomized controlled feasibility trial. *Pilot Feasibility Stud* 1: 40.

Olszewska DA, Lonergan R, Fallon EM, et al. (2016) Genetics of frontotemporal dementia. *Curr Neurol Neurosci Rep* 16: 107.

Petersson SD, Philippou E (2016) Mediterranean diet, cognitive function, and dementia: a systematic review of the evidence. *Adv Nutr* 7: 889–904.

Qosa H, Mohamed LA, Batarseh YS, et al. (2015) Extra-virgin olive oil attenuates amyloid-β and tau pathologies in the brains of *TgSwD1* mice. *J Nutr Biochem* 26: 1479–90.

Rigacci S (2015) Olive oil phenols as promising multi-targeting agents against Alzheimer's disease. *Adv Exp Med Biol* 863: 1–20.

Rosenberg RN, Lambracht-Washington D, Yu G, et al. (2016) Genomics of Alzheimer disease: a review. *JAMA Neurol* 73: 867–74.

Schellenberg GD, Montine TJ (2012) The genetics and neuropathology of Alzheimer's disease. *Acta Neuropathol* 124: 305–23.

Valenzuela MJ, Matthews FE, Brayne C, et al. for the Medical Research Council Cognitive Function and Ageing Study (2012) Multiple biological pathways link cognitive lifestyle to protection from dementia. *Biol Psychiatry* 71: 783–91.

Yang T, Sun Y, Lu Z, et al. (2017) The impact of cerebrovascular aging on vascular cognitive impairment and dementia. *Ageing Res Rev* 34: 15–29.

Zillox LA, Chadrasekaran K, Kwan JY, et al. (2016) Diabetes and cognitive impairment. *Curr Diab Rep* 16: 1–11.

Alzheimer Disease/Vascular Dementia/ Dementia with Lewy Bodies/Parkinson's Disease Dementia/Frontotemporal Dementia/Other Dementias/General Dementia

Annus A, Csati A, Vecsei L (2016) Prion diseases: new considerations. *Clin Neurol Neurosurg* 150: 125–32.

Arai T (2014) Significance and limitation of the pathological classification of TDP-43 proteinopathy. *Neuropathology* 34: 578–88.

Arendt T, Steiler JT, Holzer M (2016) Tau and tauopathies. *Brain Res Bull* 126: 238–92.

Asken BM, Sullan MJ, Snyder AR, et al. (2016) Factors influencing clinical correlates of chronic traumatic encephalopathy (CTE): a review. *Neuropsychol Rev* 26: 340–63.

Atri A (2016) Imaging of neurodegenerative cognitive and behavioral disorders: practical considerations for dementia clinical practice. *Handb Clin Neurol* 136: 971–84.

Azizi SA, Azizi SA (2018) Synucleinopathies in neurodegenerative diseases: accomplices, an inside job and selective vulnerability. *Neurosci Lett* 672: 150–2.

Ballard C, Mobley W, Hardy J, Williams G, Corbett A (2016) Dementia in Down's syndrome. *Lancet Neurol* 15: 622–36.

Ballard C, Ziabreva I, Perry R, et al. (2006) Differences in neuropathologic characteristics across the Lewy body dementia spectrum. *Neurology* 67: 1931–4.

Benskey MJ, Perez RG, Manfredsson FP (2016) The contribution of alpha synuclein to neuronal survival and function: implications for Parkinson's disease. *J Neurochemistry* 137: 331–59.

Bonifacio G, Zamboni G (2016) Brain imaging in dementia. *Postgrad Med J* 92: 333–40.

Boxer AL, Yu JT, Golbe LI, et al. (2017) Advances in progressive supranuclear palsy: new diagnostic criteria, biomarkers, and therapeutic approaches. *Lancet Neurol* 166: 552–63.

Braak H, Del Tredici K, Rub U, et al. (2003) Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 24: 197–211.

Burchell JT, Panegyres PK (2016) Prion diseases: immunotargets and therapy. *ImmunoTargets Ther* 5: 57–68.

Cheung CY, Ikram MK, Chen C, et al. (2017) Imaging retina to study dementia and stroke. *Prog Brain Retinal Eye Res* 57: 89–107.

Chutinet A, Rost NS (2014) White matter disease as a biomarker for long-term cerebrovascular disease and dementia. *Curr Treat Options Cardiovasc Med* 16: 292.

Dugger BN, Dickson DW (2017) Pathology of neurodegenerative diseases. *Cold Springs Harb Perspect Biol* 9: a028035.

Eddy CM, Parkinson EG, Rickards HE (2016) Changes in mental state and behavior in Huntington's disease. *Lancet Psychiatry* 3: 1079–86.

Emre M (2007) Treatment of dementia associated with Parkinson's disease. *Parkinsonism Relat Disord* 13 (Suppl 3): S457–61.

Eusebio A, Koric L, Felician O, et al. (2016) Progressive supranuclear palsy and corticobasal degeneration: diagnostic challenges and clinicopathological considerations. *Rev Neurol (Paris)* 172: 488–502.

Foo H, Mak E, Yong TT (2017) Progression of subcortical atrophy in mild Parkinson's disease and its impact on cognition. *Eur J Neurol* 24: 341–8.

Ford AH (2016) Preventing delirium in dementia: managing risk factors. *Maturitas* 92: 35–40.

Galvin JE (2015) Improving the clinical detection of Lewy body dementia with the Lewy Body Composite Risk Score. *Alzheimers Dement (Amst)* 1: 316–24.

Giri M, Zhang M, Lu Y (2016) Genes associated with Alzheimer's disease: an overview and current status. *Clin Interv Aging* 11: 665–81.

Goetz CG, Emre M, Dubois B (2008) Parkinson's disease dementia: definitions, guidelines, and research perspectives in diagnosis. *Ann Neurol* 64 (Suppl 2): S81–92.

Goodman RA, Lochner KA, Thambisetty M, et al. (2017) Prevalence of dementia subtypes in United States Medicare fee-for-service beneficiaries, 2011-2013. *Alzheimers Dement* 13: 28–37.

Gordon E, Rohrer JD, Fox NC (2016) Advances in neuroimaging in frontotemporal dementia. *J Neurochem* 138 (Suppl 1): 193–210.

Gray SL, Hanlon JT (2016) Anticholinergic medication use and dementia: latest evidence and clinical implications. *Ther Adv Drug Saf* 7: 217–24.

Harper L, Barkhof F, Scheltens P, et al. (2014) An algorithmic approach to structural imaging in dementia. *J Neurol Neurosurg Psychiatry* 85: 692–8.

Hasegawa M, Nonaka T, Masuda-Suzukake M (2017) Prion-like mechanisms and potential therapeutic targets in neurodegenerative disorders. *Pharmacol Ther* 172: 22–33.

Hithersay R, Hamburg S, Knight B, et al. (2017) Cognitive decline and dementia in Down syndrome. *Curr Opin Psychiatry* 30: 102–7.

Huey ED, Putnam KT, Grafman J (2006) A systematic review of neurotransmitter deficits and treatments in frontotemporal dementia. *Neurology* 66: 17–22.

Ince PG, Perry EK, Morris CM (1998) Dementia with Lewy bodies: a distinct non-Alzheimer dementia syndrome? *Brain Pathol* 8: 299–324.

Jellinger KA (2018) Dementia with Lewy bodies and Parkinson's disease-dementia: current concepts and controversies. *J Neural Transm* 125: 615–50.

Jena A, Renjen PN, Taneja S, et al. (2015) Integrated (18) F-fluorodeoxyglucose positron emission tomography magnetic resonance imaging ([18]F-FDG PET/MRI), a multimodality approach for comprehensive evaluation of dementia patients: a pictorial essay. *Indian J Radiol Imaging* 25: 342–52.

Jennings LA, Palimaru A, Corona MG, et al. (2017) Patient and caregiver goals for dementia care. *Qual Life Res* 26: 685–93.

Johnson BP, Westlake KP (2018) Link between Parkinson disease and rapid eye movement sleep behavior disorder with dream enactment: possible implications for early rehabilitation. *Arch Phys Med Rehab* 99: 410–15.

Kapasi A, DeCarli C, Schneider JA (2017) Impact of multiple pathologies on the threshold for clinically overt dementia. *Acta Neuropathol* 134: 171–86.

Karantzoulis S, Galvin JE (2011) Distinguishing Alzheimer's disease from other major forms of dementia. *Expert Rev Neurother* 11: 1579–91.

Kertesz A, Munoz DG (2002) Frontotemporal dementia. *Med Clin North Am* 86: 501–18.

Knopman DS, Kramer JH, Boeve BF, et al. (2008) Development of methodology for conducting clinical trials in frontotemporal lobar degeneration. *Brain* 131 (Pt 11): 2957–68.

Kobylecki C, Jones M, Thompson JC, et al. (2015) Cognitive-behavioural features of progressive supranuclear palsy syndrome overlap with frontotemporal dementia. *J Neurol* 262: 916–22.

Kolb HC, Andres JI (2017) Tau positron emission tomography imaging. *Cold Spring Harb Perspect Biol* 9: a023721.

Koronyo Y, Biggs D, Barron E, et al. (2017) Retinal amyloid pathology and proof-of-concept imaging trial in Alzheimer's disease. *JCI Insight* 2: 93621.

Landin-Romero R, Tan R, Hodges HR, et al. (2016) An update on semantic dementia: genetics, imaging, and pathology. *Alz Res Ther* 8: 52.

Levy RH, Collins C (2007) Risk and predictability of drug interactions in the elderly. *Int Rev Neurobiol* 81: 235–51.

Ling H (2016) Clinical approach to progressive supranuclear palsy. *J Mov Disord* 9: 3–13.

Lippmann S, Perugula ML (2016) Delirium or dementia? *Innov Clin Neurosci* 13: 56–7.

Liscic RM, Srulijes K, Groger A, et al. (2013) Differentiation of progressive supranuclear palsy: clinical, imaging and laboratory tools. *Acta Neurol Scand* 127: 361–70.

Llorens F, Karch A, Golanska E, et al. (2017) Cerebrospinal fluid biomarker-based diagnosis of sporadic Creutzfeldt–Jakob disease: a validation study for previously established cutoffs. *Dement Geriatr Cogn Disord* 43: 71–80.

Mackenzie IR, Neumann M (2016) Molecular neuropathology of frontotemporal dementia: insights into disease mechanisms from postmortem studies. *J Neurochem* 138 (Suppl 1): 54–70.

Mackenzie IR, Munoz DG, Kusaka H, et al. (2011) Distinct subtypes of FTLD-FUS. *Acta Neuropathol* 121: 207–18.

Maloney B, Lahiri DK (2016) Epigenetics of dementia: understanding the disease as a transformation rather than a state. *Lancet Neurol* 15: 760–74.

McCarter S, St Louis EK, Boeve BF (2016) Sleep disturbances in frontotemporal dementia. *Curr Neurol Neurosci Rep* 16: 85.

McCleery J, Cohen DA, Sharpley AL (2016) Pharmacotherapies for sleep disturbances in dementia (review). *Cochrane Database Syst Rev* 11: CD009178.

McGirt MJ, Woodworth G, Coon AL, et al. (2005) Diagnosis, treatment, and analysis of long-term outcomes in idiopathic normal-pressure hydrocephalus. *Neurosurgery* 57: 699–705.

McKeith IG, Dickson DW, Lowe J, et al. (2005) Diagnosis and management of dementia with Lewy bodies: third report of the DLB consortium. *Neurology* 65: 1863–72.

Meyer PT, Frings L, Rucker G, et al. (2017) ^{18}F-FDG PET in Parkinsonism: differential diagnosis and evaluation of cognitive impairment. *J Nucl Med* 58: 1888–98.

Michel J-P (2016) Is it possible to delay or prevent age-related cognitive decline? *Korean J Fam Med* 37: 263–6.

Mioshi E, Flanagan E, Knopman D (2017) Detecting change with the CDR-FTLD: differences between FTLD and AD dementia. *Int J Geriatr Psychiatry* 32: 977–82.

Mioshi E, Hsieh S, Savage S, et al. (2010) Clinical staging and disease progression in frontotemporal dementia. *Neurology* 74: 1591–7.

Montenigro PH, Baugh CM, Daneshvar DH, et al. (2014) Clinical subtypes of chronic traumatic encephalopathy: literature review and proposed research diagnostic criteria for traumatic encephalopathy syndrome. *Alz Res Ther* 6: 68.

Nalbandian A, Donkervoort S, Dec E, et al. (2011) The multiple faces of valosin-containing protein-associated diseases: inclusion body myopathy with Paget's disease of bone, frontotemporal dementia, and amyotrophic lateral sclerosis. *J Mol Neurosci* 45: 522–31.

Noe E, Marder K, Bell KL, et al. (2004) Comparison of dementia with Lewy bodies to Alzheimer's disease and Parkinson's disease with dementia. *Movement Disorders* 19: 60–7.

Pandya SY, Clem MA, Silva LM, et al. (2016) Does mild cognitive impairment always lead to dementia? A review. *J Neurol Sci* 369: 58–62.

Paoli RA, Botturi A, Ciammola A, et al. (2017) Neuropsychiatric burden in Huntington's disease. *Brain Sci* 7: 67.

Park HK, Park KH, Yoon B, et al. (2017) Clinical characteristics of parkinsonism in frontotemporal dementia according to subtypes. *J Neurol Sci* 372: 51–6.

Purandare N, Burns A, Morris J, et al. (2012) Association of cerebral emboli with accelerated cognitive deterioration in Alzheimer's disease and vascular dementia. *Am J Psychiatry* 169: 300–8.

Ransohoff RM (2016) How neuroinflammation contributes to neurodegeneration. *Science* 353: 777–83.

Raz L, Knoefel J, Bhaskar K (2016) The neuropathology and cerebrovascular mechanisms of dementia. *J Cereb Blood Flow Metab* 36: 179–86.

Roalf D, Moberg MJ, Turetsky BI, et al. (2017) A quantitative meta-analysis of olfactory dysfunction in mild cognitive impairment. *J Neurol Neurosurg Psychiatry* 88: 226–32.

Sachdeva A, Chandra M, Choudhary M, et al. (2016) Alcohol-related dementia and neurocognitive impairment: a review study. *Int J High Risk Behav Addict* 5: e27976.

Sarro L, Tosakulwong N, Schwarz CG, et al. (2017) An investigation of cerebrovascular lesions in dementia with Lewy bodies compared to Alzheimer's disease. *Alzheimers Dement* 13: 257–66.

Schott JM, Warren JD, Barhof F, et al. (2011) Suspected early dementia. *BMJ* 343: d5568.

Schroek JL, Ford J, Conway EL, et al. (2016) Review of safety and efficacy of sleep medicines in older adults. *Clin Ther* 38: 2340–72.

Schwartz M, Deczkowska A (2016) Neurological disease as a failure of brain-immune crosstalk: the multiple faces of neuroinflammation. *Trends Immunol* 37: 668–79.

Stahl SM (2017) Does treating hearing loss prevent or slow the progress of dementia? Hearing is not all in the ears, but who's listening? *CNS Spectrums* 22: 247–50.

Takada LT, Kim MO, Cleveland RW, et al. (2017) Genetic prion disease: experience of a rapidly progressive dementia center in the United States and a review of the literature. *Am J Med Genet B Neuropsychiatr Genet* 174: 36–69.

Tartaglia MC, Rosen JH, Miller BL (2011) Neuroimaging in dementia. *Neurotherapeutics* 8: 82–92.

Thomas AJ, Attems J, Colloby SJ, et al. (2017) Autopsy validation of ^{123}I-FP-CIT dopaminergic neuroimaging for the diagnosis of DLB. *Neurology* 88: 1–8.

Thomas AJ, Taylor JP, McKeith I, et al. (2017) Development of assessment toolkits for improving the diagnosis of Lewy body dementias: feasibility study within the DIAMOND Lewy study. *Int J Geriatr Psychiatry* 32: 1280–304.

Todd TW, Petrucelli L (2016) Insights into the pathogenic mechanisms of chromosome 9 open reading frame 72 (C9orf72) repeat expansions. *J Neurochem* 138 (Suppl 1): 145–62.

Togo T, Isojima D, Akatsu H, et al. (2005) Clinical features of argyrophilic grain disease: a retrospective survey of cases with neuropsychiatric symptoms. *Am J Geriatr Psychiatry* 13: 1083–91.

Tsai RM, Boxer AL (2016) Therapy and clinical trials in frontotemporal dementia: past, present, and future. *J Neurochem* 138 (Suppl 1): 211–21.

Tyebi S, Hannan AJ (2017) Synaptopathic mechanisms of neurodegeneration and dementia: insights from Huntington's disease. *Prog Neurobiol* 153: 18–45.

Weishaupt JH, Hyman T, Dikic I (2016) Common molecular pathways in amyotrophic lateral sclerosis and frontotemporal dementia. *Trends Mol Med* 22: 769–83.

Wenning GK, Tison F, Seppi K, et al. (2004) Development and validation of the Unified Multiple System Atrophy Rating Scale (UMSARS). *Mov Disord* 19: 1391–402.

Williams DR, Holton JL, Strand C, et al. (2007) Pathological tau burden and distribution distinguishes progressive supranuclear palsy-parkinsonism from Richardson's syndrome. *Brain* 130 (Pt 6): 1566–76.

Wimo A, Guerchet M, Ali GC, et al. (2017) The worldwide costs of dementia 2015 and comparisons with 2010. *Alzheimers Dement* 13: 1–7.

Xu Y, Yang J, Shang H (2016) Meta-analysis of risk factors for Parkinson's disease dementia. *Transl Neurodegen* 5: 1–8.

Yang L, Yan J, Jin X, et al. (2016) Screening for dementia in older adults: comparison of Mini-Mental State Examination, Min-Cog, Clock Drawing Test and AD8. *PLOS ONE* 11: e0168949.

Yang W, Yu S (2017) Synucleinopathies: common features and hippocampal manifestations. *Cell Mol Life Sci* 74: 8466–80.

Dementia/Memory/Cognition/Amyloid/Alzheimer

Albert MS, DeKosky ST, Dickson D, et al. (2011) The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging and Alzheimer's Association Workgroup. *Alzheimers Dement* 7: 270–9.

Arbor SC, LaFontaine M, Cumbay M (2016) Amyloid-beta Alzheimer targets: protein processing, lipid rafts, and amyloid-beta pores. *Yale J Biol Med* 89: 5–21.

Bronzuoli MR, Iacomino A, Steardo L, et al. (2016) Targeting neuroinflammation in Alzheimer's disease. *J Inflamm Res* 9: 199–208.

Cardenas-Aguayo M. del C, Silva-Lucero, M. del C, Cortes-Ortiz M, et al. (2014) Physiological role of amyloid beta in neural cells: the cellular trophic activity. In *Neurochemistry*, Heinbockel T (ed.) InTech Open Access Publisher, doi:10.5772/57398.

Chakraborty A, de Wit NM, van der Flier WM, et al. (2017) The blood brain barrier in Alzheimer's disease. *Vasc Pharmacol* 89: 12–18.

Chetelat G, Villemagne VL, Villain N, et al. (2012) Accelerated cortical atrophy in cognitively normal elderly with high β-amyloid deposition. *Neurology* 78: 477–84.

Citron M (2004) β-Secretase inhibition for the treatment of Alzheimer's disease: promise and challenge. *Trends Pharmacol Services* 25: 92–7.

Clark CM, Schneider JA, Bedell BJ, et al. (2011) Use of florbetapir-PET for imaging β-amyloid pathology. *JAMA* 305: 275–83.

Cummings JL (2011) Biomarkers in Alzheimer's disease drug development. *Alzheimers Dement* 7: e13–44.

Cummings J (2011) Alzheimer's disease: clinical trials and the amyloid hypothesis. *Ann Acad Med Singapore* 40: 304–6.

Deutsch SI, Rosse RB, Deutsch LH (2006) Faulty regulation of tau phosphorylation by the reelin signal transduction pathway is a potential mechanism of pathogenesis and therapeutic target in Alzheimer's disease. *Eur Neuropsychopharmacol* 16: 547–51.

Dickerson BC, Stoub TR, Shah RC, et al. (2011) Alzheimer-signature MRI biomarker predicts AD dementia in cognitively normal adults. *Neurology* 76: 1395–402.

Ewers M, Sperling RA, Klunk WE, Weiner MW, Hampel H (2011) Neuroimaging markers for the prediction and early diagnosis of Alzheimer's disease dementia. *Trends Neurosci* 34: 430–42.

Fajardo VA, Fajardo VA, LeBlanc PJ, et al. (2018) Examining the relationship between trace lithium in drinking water and the rising rates of age-adjusted Alzheimer's disease mortality in Texas. *J Alzheimers Dis* 61: 425–34.

Fleisher AS, Chen K, Liu X, et al. (2011) Using positron emission tomography and florbetapir F 18 to image amyloid in patients with mild cognitive impairment or dementia due to Alzheimer disease. *Arch Neurol* 68: 1404–11.

Forster S, Grimmer T, Miederer I, et al. (2012) Regional expansion of hypometabolism in Alzheimer's disease follows amyloid deposition with temporal delay. *Biol Psychiatry* 71: 792–7.

Gehres SW, Rocha A, Leuzy A, et al. (2016) Cognitive intervention as an early nonpharmacological strategy in Alzheimer's disease: a translational perspective. *Front Aging Neurosci* 8: 1–4.

Gitlin LN, Hodgson NA (2016) Who should assess the needs of and care for a dementia patient's caregiver? *AMA J Ethics* 18: 1171–81.

Godyn J, Jonczyk J, Panek D, et al. (2016) Therapeutic strategies for Alzheimer's disease in clinical trials. *Pharmacol Rep* 68: 127–38.

Gomar JJ, Bobes-Bascaran MT, Conejero-Goldberg C, et al. (2011) Utility of combinations of biomarkers, cognitive markers, and risk factors to predict conversion from mild cognitive impairment to Alzheimer disease in patients in the Alzheimer's Disease Neuroimaging Initiative. *Arch Gen Psychiatry* 68: 961–9.

Grimmer T, Tholen S, Yousefi BH, et al (2010) Progression of cerebral amyloid load is associated with the apolipoprotein E ε4 genotype in Alzheimer's disease. *Biol Psychiatry* 68: 879–84.

Gurnani AS, Gavett BE (2017) The differential effects of Alzheimer's disease and Lewy body pathology on cognitive performance: a meta-analysis. *Neuropsychol Rev* 27: 1–17.

Harrison JR, Owen MJ (2016) Alzheimer's disease: the amyloid hypothesis on trial. *Br J Psychiatry* 208: 1–3.

Herukka SK, Simonsen AH, Andreasen N, et al. (2017) Recommendations for CSF AD biomarkers in the diagnostic evaluation of MCI. *Alzheimers Dement* 13: 285–95.

Jack CR Jr., Albsert MS, Knopman DS, et al. (2011) Introduction to the recommendations from the National Institute on Aging and the Alzheimer's Association Workgroup on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 7: 257–62.

Jack CR Jr., Lowe VJ, Weigand SD, et al. (2009) Serial PIB and MRI in normal, mild cognitive impairment and Alzheimer's disease: implications for sequence of pathological events in Alzheimer's disease. *Brain* 132: 1355–65.

Jonsson T, Atwal JK, Steinberg S, et al. (2012) A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. *Nature* 488: 96–9.

Kokjohn TA, Maarouf CL, Roher AE (2012) Is Alzheimer's disease amyloidosis a result of a repair mechanism gone astray? *Alzheimers Dement* 8: 574–83.

Kovari E, Herrmann FR, Hof PR, et al. (2013) The relationship between cerebral amyloid angiopathy and cortical microinfarcts in brain ageing and Alzheimer's disease. *Neuropathol Appl Neurobiol* 39: 498–509.

Li Y, Li Y, Li X, et al. (2017) Head injury as a risk factor for dementia and Alzheimer's disease: a systematic review and meta-analysis of 32 observational studies. *PLOS ONE* 12: e0169650.

Lieberman A, Deep A, Shi J, et al. (2018) Downward finger displacement distinguishes Parkinson disease dementia from Alzheimer disease. *Int J Neurosci* 128: 151–4.

Lim JK, Li QX, He Z, et al. (2016) The eye as a biomarker for Alzheimer's disease. *Front Neurosci* 10: 1–14.

MacLeod R, Hillert EK, Cameron RT, et al. (2015) The role and therapeutic targeting of α-, β-, and γ-secretase in Alzheimer's disease. *Future Sci OA* 1: FS011.

Mallik A, Drzezga A, Minoshima S (2017) Clinical amyloid imaging. *Semin Nucl Med* 47: 31–43.

Marciani DJ (2015) Alzheimer's disease vaccine development: a new strategy focusing on immune modulation. *J Neuroimmunol* 287: 54–63.

McKhann GM, Knopman DS, Chertkow H (2011) The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging and the Alzheimer's Association Workgroup. *Alzheimers Dement* 7: 263–9.

Mendiola-Precoma J, Berumen LC, Padilla K, et al. (2016) Therapies for prevention and treatment of Alzheimer's disease. *BioMed Res Int* 2016: 2589276.

Panza F, Solfrizzi V, Seripa D, et al. (2016) Tau-centric targets and drugs in clinical development for the treatment of Alzheimer's disease. *BioMed Res Int* 2016: 3245935.

Pascoal TA, Mathotaarachchi S, Shin M, et al. (2017) Synergistic interaction between amyloid and tau predicts the progression to dementia. *Alzheimers Dement* 13: 644–53.

Rabinovici GD, Rosen HJ, Alkalay A, et al. (2011) Amyloid vs. FDG-PET in the differential diagnosis of AD and FTLD. *Neurology* 77: 2034–42.

Rapp MA, Schnaider-Beeri M, Grossman HT, et al. (2006) Increased hippocampal plaques and tangles in patients with Alzheimer disease with a lifetime history of major depression. *Arch Gen Psychiatry* 63: 161–7.

Reisberg B, Doody R, Stöffle A, et al. (2003) Memantine in moderate-to-severe Alzheimer's disease. *New Engl J Med* 348: 1333–41.

Ritter AR, Leger GC, Miller JB, et al. (2017) Neuropsychological testing in pathologically verified Alzheimer's disease and frontotemporal dementia. *Alzheimer Dis Assoc Disord* 31: 187–91.

Rodrigue KM, Kennedy KM, Devous MD Sr., et al. (2012) B-Amyloid burden in healthy aging. Regional distribution and cognitive consequences. *Neurology* 78: 387–95.

Ruthirakuhan M, Herrmann N, Seuridjan I, et al. (2016) Beyond immunotherapy: new approaches for disease modifying treatments for early Alzheimer's disease. *Expert Opin Pharmacother* 17: 2417–29.

Sabbagh MN, Schauble B, Anand K, et al. (2017) Histopathology and florbetaben PET in patients incorrectly diagnosed with Alzheimer's disease. *J Alzheimers Dis* 56: 441–6.

Scheinin NM, Aalto S, Kaprio J, et al. (2011) Early detection of Alzheimer disease. *Neurology* 77: 453–60.

Sharma N, Singh AN (2016) Exploring biomarkers for Alzheimer's disease. *J Clin Diag Res* 10: KE01–06.

Simonsen AH, Herukka SK, Andreasen N, et al. (2017) Recommendations for CSF AD biomarkers in the diagnostic evaluation of dementia. *Alzheimers Dement* 13: 285–95.

Sperling RA, Aisen PS, Beckett LA, et al. (2011) Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging and the Alzheimer's Association Workgroup. *Alzheimers Dement* 7: 280–92.

Spies PE, Claasen JA, Peer PG, et al. (2013) A prediction model to calculate probability of Alzheimer's disease using cerebrospinal fluid biomarkers. *Alzheimers Dement* 9: 262–8.

Spies PE, Verbeek MM, van Groen T, et al. (2012) Reviewing reasons for the decreased CSF Abeta42 concentration in Alzheimer disease. *Front Biosci (Landmark Ed)* 17: 2024–34.

Spira AP, Gottesman RF (2017) Sleep disturbance: an emerging opportunity for Alzheimer's disease prevention? *Int Psychogeriatr* 29: 529–31.

Tarawneh R, Holtzman DM (2012) The clinical problem of symptomatic Alzheimer disease and mild cognitive impairment. *Cold Spring Harbor Perspect Med* 2: a006148.

Tariot PN, Aisen PS (2009) Can lithium or valproate untie tangles in Alzheimer's disease? *J Clin Psychiatry* 70: 919–21.

Uzun S, Kozumplik O, Folnegovic-Smalc V (2011) Alzheimer's dementia: current data review. *Coll Antropol* 35: 1333–7.

Venkataraman A, Kalk N, Sewell G, et al. (2017) Alcohol and Alzheimer's disease: does alcohol dependence contribute to beta-amyloid deposition, neuroinflammation and neurodegeneration in Alzheimer's disease? *Alcohol Alcoholism* 52: 151–8.

Villemagne VL, Doré V, Bourgeat P, et al. (2017) Aβ-amyloid and tau imaging in dementia. *Semin Nucl Med* 47: 75–88.

Wagner M, Wolf S, Reischies FM, et al. (2012) Biomarker validation of a cued recall memory deficit in prodromal Alzheimer disease. *Neurology* 78: 379–86.

Weintraub S, Wicklund AH, Salmon DP (2012) The neuropsychological profile of Alzheimer disease. *Cold Spring Harb Perspect Med* 2 :a006171.

Williams MM, Xiong C, Morris JC, Galvin JE (2006) Survival and mortality differences between dementia with Lewy bodies vs. Alzheimer's disease. *Neurology* 67: 1935–41.

Wishart HA, Saykin AJ, McAllister TW, et al. (2006) Regional brain atrophy in cognitively intact adults with a single APOE ε4 allele. *Neurology* 67: 1221–4.

Wolk DA, Grachev ID, Buckley C, et al. (2011) Association between in vivo fluorine 18-labeled flutemetamol amyloid positron emission tomography imaging and in vivo cerebral cortical histopathology. *Arch Neurol* 68: 1398–403.

Yaffe K, Tocco M, Petersen RC, et al. (2012) The epidemiology of Alzheimer's disease: laying the foundation for drug design, conduct, and analysis of clinical trials. *Alzheimers Dement* 8: 237–42.

Yan R (2016) Stepping closer to treating Alzheimer's disease patients with BACE1 inhibitor drugs. *Transl Neurodegen* 5: 13.

Yeh HL, Tsai SJ (2008) Lithium may be useful in the prevention of Alzheimer's disease in individuals at risk of presenile familial Alzheimer's disease. *Med Hypotheses* 71: 948–51.

Behavioral Symptoms of Dementia

Alexopoulos GS (2003) Role of executive function in late life depression. *J Clin Psychiatry* 64 (Suppl 14): 18–23.

Ballard C, Oyebode F (1995) Psychotic symptoms in patients with dementia. *Int J Geriatr Psychiatry* 10: 743–52.

Ballard C, Neill D, O'Brien J, et al. (2000) Anxiety, depression and psychosis in vascular dementia: prevalence and associations. *J Affect Disord* 59: 97–106.

Bao AM, Meynen G, Swaab DF (2008) The stress system in depression and neurodegeneration: focus on the human hypothalamus. *Brain Res Rev* 57: 531–53.

Barnes DE, Yaffe K, Byers AL, et al. (2012) Midlife vs. late-life depressive symptoms and risk of dementia. *Arch Gen Psychiatry* 6: 493–8.

Bassetti CL, Bargiotas P (2018) REM sleep behavior disorder. *Front Neurol Neurosci* 41: 104–16.

Bennett S, Thomas AJ (2014) Depression and dementia: cause, consequence or coincidence? *Maturita* 79:184–90.

Buoli M, Serati M, Caldiroli A, et al. (2017) Pharmacological management of psychiatric symptoms in frontotemporal dementia: a systematic review. *J Geriatr Psychiatry* 30: 162–9.

Burns A, Jacoby R, Levy R (1990) Psychiatric phenomena in Alzheimer's disease. II: disorders of perception. *Br J Psychiatry* 157: 76–81, 92–4.

Canevelli M, Valleta M, Trebbastoni A, et al. (2016) Sundowning in dementia: clinical relevance, pathophysiological determinants, and therapeutic approaches. *Front Med (Lausanne)* 3: 73.

Caraci F, Copani A, Nicoletti F, et al. (2010) Depression and Alzheimer's disease: neurobiological links and common pharmacological targets. *Eur J Pharmacol* 626: 64–71.

Cohen-Mansfield J, Billig N (1986) Agitated behaviors in the elderly. I. A conceptual review. *J Am Geriatr Soc* 34: 711–21.

Corcoran C, Wong ML, O'Keane V (2004) Bupropion in the management of apathy. *J Psychopharm* 18: 133–5.

Cummings J, Kohegyi E, Mergel V, et al. (2018) Efficacy and safety of flexibly dosed brexpiprazole for the treatment of agitation in Alzheimer type dementia: a randomized, double blind fixed dose 12 week placebo controlled global clinical trial. Abstract for the American Association of Geriatric Psychiatry, Honolulu, Hawaii.

Cummings JL, Lyketsos CG, Peskind ER, et al. (2015) Effect of dextromethorphan–quinidine on agitation in patients with Alzheimer's disease dementia: a randomized clinical trial. *JAMA* 314: 1242–54.

Dennis M, Shine L, John A, et al. (2017) Risk of adverse outcomes for older people with dementia prescribed antipsychotic medication: a population based e-cohort study. *Neurol Ther* 6: 57–77.

Ducharme S, Price BH, Dickerson BC (2018) Apathy: a neurocircuitry model based on frontotemporal dementia. *J Neural Neurosurg Psychiatry* 89: 389–96.

Evan C, Weintraub D (2010) Case for and against specificity of depression in Alzheimer's disease. *Psychiatry Clin Neurosci* 64: 358–66.

Farina N, Morrell L, Banerjee S (2017) What is the therapeutic value of antidepressants in dementia? A narrative review. *Geriatr Psychiatry* 32: 32–49.

Fernandez-Matarrubia M, Matias-Guiu JA, Cabrera-Martin MN, et al. (2018) Different apathy clinical profile and neural correlates in behavioral variant frontotemporal dementia and Alzheimer's disease. *Int J Geriatr Psychiatry* 33: 141–50.

Fernandez-Matarrubia M, Matias-Guiu JA, Moreno-Ramos T, et al. (2016) Validation of the Lille's Apathy Rating Scale in very mild to moderate dementia. *Am J Geriatr Psychiatry* 24: 517–27.

Ford AH, Almeida OP (2017) Management of depression in patients with dementia: is pharmacological treatment justified? *Drugs Aging* 34: 89–95.

Fraker J, Kales HC, Blazek M (2014) The role of the occupational therapist in the management of neuropsychiatric symptoms of dementia in clinical settings. *Occup Ther Health Care* 28: 4–20.

Frakey LL, Salloway S, Buelow M, Malloy P (2012) A randomized, double-blind, placebo-controlled trial of modafinil for the treatment of apathy in individuals with mild-to-moderate Alzheimer's disease. *J Clin Psychiatry* 73: 796–801.

Garay RP, Grossberg GT (2017) AVP-786 for the treatment of agitation in dementia of the Alzheimer's type. *Expert Opin Invest Drugs* 26: 121–32.

Geerlings MI, den Hijer T, Koudstaal PJ, et al. (2008) History of depression, depressive symptoms, and medial temporal lobe atrophy and the risk of Alzheimer's disease. *Neurology* 70: 1258–64.

Gessing LV, Sondergard L, Forman JL, et al. (2009) Antidepressants and dementia. *J Affect Disord* 117: 24–9.

Goldman JG, Holden S (2014) Treatment of psychosis and dementia in Parkinson's disease. *Curr Treat Options Neurol* 16: 281.

Goodarzi Z, Mele B, Guo S, et al. (2016) Guidelines for dementia or Parkinson's disease with depression or anxiety: a systematic review. *BMC Neurol* 16(1): 244.

Grossberg G, Kohegyi E, Amatniek J, et al. (2018) Efficacy and safety of fixed dose brexpiprazole for the treatment of agitation in Alzheimer type dementia: a randomized, double blind fixed dose 12-week placebo controlled global clinical trial. Abstract for the American Association of Geriatric Psychiatry, Honolulu, Hawaii.

Hacksell U, Burstein ES, McFarland K, et al. (2014) On the discovery and development of pimavanserin: a novel drug candidate for Parkinson's disease. *Neurochem Res* 39: 2008–17.

Hongiston K, Hallikainen I, Seldander T, et al. (2018) Quality of life in relation to neuropsychiatric symptoms in Alzheimer's disease: 5-year prospective ALSOVA cohort study. *Int J Geriatr Psychiatry* 33: 47–57.

Jack Jr. CR, Wiste HJ, Weigland SD, et al. (2017) Defining imaging biomarker cut point for brain aging and Alzheimer's disease. *Alzheimers Dement* 13: 205–16.

Johnson DK, Watts AS, Chapin BA, et al. (2011) Neuropsychiatric profiles in dementia. *Alzheimer Dis Assoc Disord* 25: 326–32.

Kales, HC, Kim HM, Zivin K, et al. (2012) Risk of mortality among individual antipsychotics in patients with dementia. *Am J Psychiatry* 169: 71–9.

Kales HC, Lyketsos CG, Miller EM, et al. (2019) Management of behavioral and psychological symptoms in people with Alzheimer's disease: an international Delphi consensus. *Int Psychogeriatr* 31: 83–90.

Kok RM, Reynolds CF (2017) Management of depression in older adults: a review. *JAMA* 317: 2114–22.

Kong EH (2005) Agitation in dementia: concept clarification. *J Adv Nurs* 52: 526–36.

Kumfor F, Zhen A, Hodges JR, et al. (2018) Apathy in Alzheimer's disease and frontotemporal dementia: distinct clinical profiles and neural correlates. *Cortex* 103: 350–9.

Lanctot KL, Amatniek J, Ancoli-Israel S, et al. (2017) Neuropsychiatric signs and symptoms of Alzheimer's disease: new treatment paradigms. *Alzheimers Dement (NY)* 3: 440–9.

Lee GJ, Lu PH, Hua X, et al. (2012) Depressive symptoms in mild cognitive impairment predict greater atrophy in Alzheimer's disease-related regions. *Biol Psychiatry* 71: 814–21.

Leroi I, Voulgari A, Breitner JC, et al. (2003) The epidemiology of psychosis in dementia. *Am J Geriatr Psychiatry* 11: 83–91.

Lochhead JD, Nelson MA, Maguire GA (2016) The treatment of behavioral disturbances and psychosis associated with dementia. *Psychiatr Pol* 50: 311–22.

Lopez OL, Becker JT, Sweet RA, et al. (2003) Psychiatric symptoms vary with the severity of dementia in probable Alzheimer's disease. *J Neuropsychiatry Clin Neurosci* 15: 346–53.

Lyketsos CG, Carillo MC, Ryan JM, et al. (2011) Neuropsychiatric symptoms in Alzheimer's disease. *Alzheimers Dement* 7: 532–9.

Lyketsos CG, Lopez O, Jones B, et al. (2002) Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. *JAMA* 288: 1475–83.

Lyketsos CG, Steinberg M, Tschanz JT, et al. (2000) Mental and behavioral disturbances in dementia: findings from the Cache County Study on memory in aging. *Am J Psychiatry* 157: 704–7.

Macfarlane S, O'Connor D (2016) Managing behavioural and psychological symptoms in dementia. *Aust Prescr* 39: 123–5.

Marin RS, Fogel BS, Hawkins J, et al. (1995) Apathy: a treatable symptom. *J Neuropsychiatry* 7: 23–30.

Maust DT, Kim HM, Seyfried LS, et al. (2015) Antipsychotics, other psychotropics, and the risk of death in patients with dementia: number needed to harm. *JAMA Psychiatry* 72: 438–45.

Moraros J, Nwankwo C, Patten SB, et al. (2017) The association of antidepressant drug usage with cognitive impairment or dementia, including Alzheimer disease: a systematic review and meta-analysis. *Depress Anxiety* 34: 217–26.

Mossello E, Boncinelli M, Caleri V, et al. (2008) Is antidepressant treatment associated with reduced cognitive decline in Alzheimer's disease? *Dement Geriatr Cogn Disord* 25: 372–9.

Norgaard A, Jensen-Dahm C, Gasse C, et al. (2017) Psychotropic polypharmacy in patients with dementia: prevalence and predictors. *J Alz Dis* 56: 707–16.

O'Gorman C (2020) Advance 1 phase 2/3 trial of AXS-05 in Alzheimer's disease agitation, personal communication.

Porsteinsson AP, Antonsdottir IM (2017) An update on the advancements in the treatment of agitation in Alzheimer's disease. *Expert Opin Pharmacother* 18: 611–20.

Preuss UW, Wong JW, Koller G (2016) Treatment of behavioral and psychological symptoms of dementia: a systematic review. *Psychiatr Pol* 50: 679–715.

Rosenberg PB, Nowrangi MA, Lyketsos CG (2015) Neuropsychiatric symptoms in Alzheimer's disease: what might be associated brain circuits? *Mol Aspects Med* 43–44: 25–37.

Sadowsky CH, Galvin JE (2012) Guidelines for the management of cognitive and behavioral problems in dementia. *J Am Board Fam Med* 25: 350–66.

Schneider LS, Dagerman KS, Insel P (2005) Risk of death with atypical antipsychotic drug treatment for dementia. *JAMA* 294: 1935–43.

Siever LJ (2008) Neurobiology of aggression and violence. *Am J Psychiatry* 165: 429–42.

Sink KM, Holden KF, Yaffe K (2005) Pharmacological treatment of neuropsychiatric symptoms of dementia. *JAMA* 293: 596–608.

Stahl SM (2016) Parkinson's disease psychosis as a serotonin-dopamine imbalance syndrome. *CNS Spectrums* 21: 271–5.

Stahl SM (2016) Mechanism of action of pimavanserin in Parkinson's disease psychosis: targeting serotonin $5HT_{2A}$ and $5HT_{2C}$ receptors. *CNS Spectrums* 21: 271–5.

Stahl SM (2018) New hope for Alzheimer's dementia as prospects for disease modification fade: symptomatic treatments for agitation and psychosis. *CNS Spectrums* 23: 291–7.

Stahl SM, Morrissette DA, Cummings M, et al. (2014) California State Hospital violence assessment and treatment (Cal-VAT) guidelines. *CNS Spectrums* 19: 449–65.

Torrisi M, Cacciola A, Marra A, et al. (2017) Inappropriate behaviors and hypersexuality in individuals with dementia: an overview of a neglected issue. *Geriatr Gerontol Int* 17: 865–74.

Tsuno N, Homma A (2009) What is the association between depression and Alzheimer's disease? *Exp Rev Neurother* 9: 1667–76.

Van der Linde RM, Dening T, Stephan BC, et al. (2016) Longitudinal course of behavioural and psychological symptoms of dementia: systematic review. *Br J Psychiatry* 209: 366–77.

Van der Spek K, Gerritsen DL, Smallbrugge M, et al. (2016) Only 10% of the psychotropic drug use for neuropsychiatric symptoms in patients with dementia is fully appropriate: the PROPER I-study. *Int Psychogeriatr* 28: 1589–95.

Vigen CLP, Mack WJ, Keefe RSE, et al. (2011) Cognitive effects of atypical antipsychotic medications in patients with Alzheimer's disease: outcomes from CATIE-AD. *Am J Psychiatry* 168: 831–9.

Volicer L, Citrome L, Volavka J (2017) Measurement of agitation and aggression in adult and aged neuropsychiatric patients: review of definitions and frequently used measurement scales. *CNS Spectrums* 22: 407–14.

Wisniewski T, Drummond E (2016) Developing therapeutic vaccines against Alzheimer's disease. *Expert Rev Vaccines* 15: 401–15.

Wuwongse S, Chang RC, Law AC (2010) The putative neurodegenerative links between depression and Alzheimer's disease. *Prog Neurobiol* 92: 362–75.

Zhang Y, Cai J, An L, et al. (2017) Does music therapy enhance behavioral and cognitive function in elderly dementia patients? A systematic review and metaanalysis.*Ageing Res Rev* 35: 1–11.

Chapter 13 (Impulsivity, Compulsivity, and Addiction)

OCD

Bloch MH, Wasylink S, Landeros A, et al. (2012) Effects of ketamine in treatment refractory obsessive compulsive disorder. *Biol Psychiatry* 72: 964–70.

Chamberlain SR, Menzies L, Hampshire A, et al. (2008) Orbitofrontal dysfunction in patients with obsessive-compulsive disorder and their unaffected relatives. *Science* 321: 421–2.

Dougherty DD, Brennan BP, Stewart SE, et al. (2018) Neuroscientifically informed formulation and treatment planning for patients with obsessive compulsive disorder: a review. *JAMA Psychiatry* 75: 1081–7.

Fineberg NA, Potenza MN, Chamberlain SR, et al. (2010) Probing compulsive and impulsive behaviors, from animal models to endophenotypes: a narrative review. *Neuropsychopharmacology* 35: 591–604.

Gillan CM, Papmeyer M, Morein-Zamir S, et al. (2011) Disruption in the balance between goal-directed behavior and habit learning in obsessive–compulsive disorder. *Am J Psychiatry* 168: 719–26.

Greenberg BD, Malone DA, Friehs GM, et al. (2006) Three year outcomes in deep brain stimulation for highly resistant obsessive–compulsive disorder. *Neuropsychopharmacology* 31: 2384–93.

Greenberg BD, Rauch SL, Haber SN (2010) Invasive circuitry-based neurotherapeutics: stereotactic ablation and deep brain stimulation for OCD. *Neuropsychopharmacology* 35: 317–36.

Greeven A, van Balkom AJLM, van Rood YR, van Oppen P, Spinhoven P (2006) The boundary between hypochondriasis and obsessive–compulsive disorder: a cross-sectional study from the Netherlands. *J Clin Psychiatry* 67: 1682–9.

Kisely S, Hall K, Siskind D, et al. (2014) Deep brain stimulation for obsessive compulsive disorder: a systematic review and meta analysis. *Psychol Med* 44: 3533–42.

Menzies L, Chamberlain SR, Laird AR, et al. (2008) Integrating evidence from neuroimaging and neuropsychological studies of obsessive–compulsive disorder: the orbito-fronto-striatal model revisited. *Neurosci Biobehav Rev* 32: 525–49.

Milad MR, Rauch SL (2012) Obsessive–compulsive disorder: beyond segregated cortico-striatal pathways. *Trends Cogn Sci* 16: 43–51.

Rasmussen SA, Noren G, Greenberg BD (2018) Gamma ventral capsulotomy in intractable obsessive–compulsive disorder. *Biol Psychiatry* 84: 355–64.

Richter MA, de Jesus DR, Hoppenbrouwers S, et al. (2012) Evidence for cortical inhibitory and excitatory dysfunction in obsessive compulsive disorder. *Neuropsychopharmacology* 37: 1144–51.

Wilhelm S, Buhlmann U, Tolin DF (2008) Augmentation of behavior therapy with D-cycloserine for obsessive compulsive disorder. *Am J Psychiatry* 165: 335–41.

Yin D, Zhang C, Lv Q, et al. (2018) Dissociable frontostriatal connectivity: mechanism and predictor of the clinical efficacy of capsulotomy in obsessive compulsive disorder. *Biol Psychiatry* 84: 926–36.

Substance Abuse: General

Bedi G (2018) 3, 4-Methylenedioxymethamphetamine as a psychiatric treatment. *JAMA Psychiatry* 75: 419–20.

Clark L, Robbins TW, Ersche KD, Sahakian BJ (2006) Reflection impulsivity in current and former substance users. *Biol Psychiatry* 60: 515–22.

Dalley JW, Everitt BJ (2009) Dopamine receptors in the learning, memory and drug reward circuitry. *Semin Cell Dev Biol* 20: 403–10.

Ersche KD, Turton AJ, Pradhan S, Bullmore ET, Robbins TW (2010) Drug addiction endophenotypes: impulsive versus sensation-seeking personality traits. *Biol Psychiatry* 68: 770–3.

Field M, Marhe R, Franken I (2014) The clinical relevance of attentional bias in substance use disorders. *CNS Spectrums* 19: 225–30.

Haber SN, Knutson B (2010) The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology* 35: 4–26.

Koob GF, Le Moal M (2008) Addiction and the brain antireward system. *Ann Rev Psychol* 59: 29–53.

Koob GF, Volkow ND (2010) Neurocircuitry of addiction. *Neuropsychopharmacology* 35: 217–38.

Mandyam CD, Koob GF (2012) The addicted brain craves new neurons: putative role for adult-born progenitors in promoting recovery. *Trends Neurosci* 35: 250–60.

Nestler EJ (2005) Is there a common molecular pathway for addiction? *Nat Neurosci* 11: 1445–9.

Nutt DJ, Hughes AL, Erritzoe D, et al. (2015) The dopamine theory of addiction: 40 years of highs and lows. *Nat Rev Neurosci* 16: 305–22.

Schneider S, Peters J, Bromberg U, et al. (2012) Risk taking and the adolescent reward system: a potential common link to substance abuse. *Am J Psychiatry* 169: 39–46.

Solway A, Gu X, Montague PR (2017) Forgetting to be addicted: reconsolidation and the disconnection of things past. *Biol Psychiatry* 82: 774–5

Volkow ND, Wang GJ, Fowler JS, Tomasi D, Telang F (2011) Addiction: beyond dopamine reward circuitry. *Proc Natl Acad Sci USA* 108: 15037–42.

Substance Abuse: Alcohol

Anton RF, O'Malley SS, Ciraulo DA, et al. (2006) Combined pharmacotherapies and behavioral interventions for alcohol dependence. The combine study: a randomized controlled trial. *JAMA* 295: 2003–17.

Anton RF, Pettinati H, Zweben A, et al. (2004) A multi site dose ranging study of nalmefene in the treatment of alcohol dependence. *J Clin Psychopharmacol* 24: 421–8.

Braus DH, Schumann G, Machulla HJ, Bares R, Mann K (2005) Correlation of stable elevations in striatal μ-opioid receptor availability in detoxified alcoholic patients with alcohol craving. A positron emission tomography study using carbon 11-labeled carfentanil. *Arch Gen Psychiatry* 62: 57–64.

Crevecoeur D, Cousins SJ, Denering L, et al. (2018) Effectiveness of extended release naltrexone to reduce alcohol cravings and use behaviors during treatment and at follow-up. *J Subst Abuse Treat* 85: 105–8.

Dahchour A, DeWitte P (2003) Effects of acamprosate on excitatory amino acids during multiple ethanol withdrawal periods. *Alcohol Clin Exp Res* 3: 465–70.

Dakwar E, Levin F, Hart CL, et al. (2020) A single ketamine infusion combined with motivational enhancement therapy for alcohol use disorder: a randomized midazolam controlled pilot study. *Am J Psychiatry* 172: 125–33.

DeWitte P (2004) Imbalance between neuroexcitatory and neuroinhibitory amino acids causes craving for ethanol. *Addict Behav* 29: 1325–39.

DeWitte P, Littleton J, Parot P, Koob G (2005) Neuroprotective and abstinence-promoting effects of acamprosate. Elucidating the mechanism of action. *CNS Drugs* 6: 517–37.

Garbutt JC, Kranzler HR, O'Malley SS, et al. (2005) Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence. A randomized controlled trial. *JAMA* 293: 1617–25.

Kiefer F, Wiedemann K (2004) Combined therapy: what does acamprosate and naltrexone combination tell us? *Alcohol Alcohol* 39: 542–7.

Kiefer F, Jahn H, Tarnaske T, et al. (2003) Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism. *Arch Gen Psychiatry* 60: 92–9.

Mann K, Bladstrom A, Torup T, et al. (2013) Extending the treatment options in alcohol dependence: a randomized controlled study of as-needed nalmefene. *Biol Psychiatry* 73: 706–13.

Martinez D, Gil R, Slifstein M, et al. (2005) Alcohol dependence is associated with blunted dopamine transmission in the ventral striatum. *Biol Psychiatry* 58: 779–86.

Mason BJ (2003) Acamprosate and naltrexone treatment for alcohol dependence: an evidence-based risk-benefits assessment. *Eur Neuropsychopharmacol* 13: 469–75.

Mason BJ (2005) Acamprosate in the treatment of alcohol dependence. *Expert Opin Pharmacother* 6: 2103–15.

Mason BJ, Goodman AM, Chabac S, Lehert P (2006) Effect of oral acamprosate on abstinence in patients with alcohol dependence in a double-blind, placebo-controlled trial: the role of patient motivation. *J Psychiatr Res* 40: 382–92.

Netzeband JG, Gruol DL (1995) Modulatory effects of acute ethanol on metabotropic glutamate responses in cultured Purkinje neurons. *Brain Res* 688: 105–13.

O'Brien CO (2015) In treating alcohol use disorders, why not use evidence-based treatment? *Am J Psychiatry* 172: 305–7.

Palpacuer C, Duprez R, Huneau A, et al. (2017) Pharmacologically controlled drinking in the treatment of alcohol dependence or alcohol use disorders: a systematic review with direct and network meta analyses on nalmefene, naltrexone, acamprosate, baclofen and topiramate. *Addiction* 113: 220–37.

Petrakis IL, Poling J, Levinson C (2005) Naltrexone and disulfiram in patients with alcohol dependence and comorbid psychiatric disorders. *Biol Psychiatry* 57: 1128–37.

Pettinati HM, O'Brien CP, Rabinowitz AR (2006) The status of naltrexone in the treatment of alcohol dependence. Specific effects on heavy drinking. *J Clin Psychopharmacol* 26: 610–25.

Roozen HG, de Waart R, van der Windt DAW, et al. (2005) A systematic review of the effectiveness of naltrexone in the maintenance treatment of opioid and alcohol dependence. *Eur Neuropsychopharmacol* 16: 311–23.

Smith-Bernardin S, Rowe C, Behar E, et al. (2018) Low threshold extended release naltrexone for high utilizers of public services with severe alcohol use disorder: a pilot study. *J Subst Abuse Treat* 85: 109–15.

Soyka M (2014) Nalmefene for the treatment of alcohol dependence: a current update. *Int J Neuropsychopharmacol* 17: 675–84.

Van Amsterdam J, van den Brink W (2013) Reduced risk drinking as a viable treatment goal in problematic alcohol use and alcohol dependence. *J Psychopharmacol* 27: 987–97.

Wiers CE, Stelzel C, Gladwin TE, et al. (2015) Effects of cognitive bias modification training on neural alcohol cue reactivity in alcohol dependence. *Am J Psychiatry* 172: 334–43.

Substance Abuse: Cannabis

Black N, Stockings E, Campbell G, et al. (2019) Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta analysis. *Lancet Psychiatry* 6: 995–1010.

Haney M, Hill MN (2018) Cannabis and cannabinoids: from synapse to society. *Neuropsychopharm Rev* 43: 1–212.

Hindley G, Beck K, Borgan B (2020) Psychiatric symptoms caused by cannabis constituents: a systematic review and meta-analysis. *Lancet Psychiatry* 7: 344–53.

Hines LA, Freeman TP, Gage SH, et al. (2020) Association of high potency cannabis use with mental and substance use in adolescence. *JAMA Psychiatry* 77: 1044–51.

Hurd YL, Spriggs S, Alishayev J, et al. (2019) Cannabidiol for the reduction of cue-induced craving and anxiety in drug abstinent individuals with heroin use disorder: a double blind randomized placebo controlled trial. *Am J Psychiatry* 176: 911–22.

James S (2020) *A Clinician's Guide to Cannabinoid Science*. Cambridge: Cambridge University Press.

Kovacs FE, Knop T, Urbanski MJ, et al. (2012) Exogenous and endogenous cannabinoids suppress inhibitory neurotransmission in the human neocortex. *Neuropsychopharmacology* 37: 1104–14.

Mason BJ, Crean R, Goodell V, et al. (2012) A proof-of-concept randomized controlled study of gabapentin: effects on cannabis use, withdrawal and executive function deficits in cannabis-dependent adults. *Neuropsychopharmacology* 37: 1689–98.

Nugent SM, Morasco BJ, O'Neil ME, et al. (2017) The effects of cannabis among adults with chronic pain and an overview of general harms: a systematic review. *Ann Intern Med* 167: 319–31.

Substance Abuse: Nicotine

Akkus F, Ametamey SM, Treyer V, et al. (2013) Market global reduction in mGlutR5 receptor binding in smokers and ex smokers determined by ^{11}C-ABP688 positron emission tomography. *Proc Natl Acad Sci USA* 10: 737–42.

Akkus F, Treyer V, Johayem A, et al. (2016) Association of long-term nicotine abstinence with normal metabotropic glutamate receptor 5 binding. *Biol Psychiatry* 79: 474–80.

Crunelle CL, Miller ML, Booij J, van den Rink W (2010) The nicotinic acetylcholine receptor partial agonist varenicline and the treatment of drug dependence: a review. *Eur Neuropsychopharmacol* 20: 69–79.

Culbertson CS, Bramen J, Cohen MS (2011) Effect of bupropion treatment on brain activation induced by cigarette-related cues in smokers. *Arch Gen Psychiatry* 68: 505–15.

Evins AE, Culhane MA, Alpert JE, et al. (2008) A controlled trial of bupropion added to nicotine patch and behavioral therapy for smoking cessation in adults with unipolar depressive disorders. *J Clin Psychopharmacol* 28: 660–6.

Franklin T, Wang Z, Suh JJ, et al. (2011) Effects of varenicline on smoking cue-triggered neural and craving responses. *Arch Gen Psychiatry* 68: 516–26.

King DP, Paciga S, Pickering E, et al. (2012) Smoking cessation pharmacogenetics: analysis of varenicline and bupropion in placebo-controlled clinical trials. *Neuropsychopharmacology* 37: 641–50.

Lotipour S, Mandelkern M, Alvarez-Estrada M, Brody AL (2012) A single administration of low-dose varenicline saturates α4β2* nicotinic acetylcholine receptors in the human brain. *Neuropsychopharmacology* 37: 1738–48.

Steinberg MB, Greenhaus S, Schmelzer AC, et al. (2009) Triple-combination pharmacotherapy for medically ill smokers. A randomized trial. *Ann Intern Med* 150: 447–54.

Substance Abuse: Opioids

Bell J, Strang J (2020) Medication treatment of opioid use disorder. *Biol Psychiatry* 87: 82–8.

Chutuape MA, Jasinski DR, Finerhood MI, Stitzer ML (2001) One-, three-, and six-month outcomes after brief inpatient opioid detoxification. *Am J Drug Alcohol Abuse* 27: 19–44.

Davids E, Gastpar M (2004) Buprenorphine in the treatment of opioid dependence. *Eur Neuropsychopharmacol* 14: 209–16.

Elkader A, Sproule B (2005) Buprenorphine: clinical pharmacokinetics in the treatment of opioid dependence. *Clin Pharmacokinet* 44: 661–80.

Han B, Compton WM, Blanco C, et al. (2017) Prescription opioid use, misuse and use disorders in US adults: 2015 national survey on drug use and health. *Ann Intern Med* 167: 293–301.

Johansson J, Hirvonen J, Lovro Z, et al. (2019) Intranasal naloxone rapidly occupies brain mu opioid receptors in human subjects. *Neuropsychopharmacology* 44: 1667–73.

Kowalczyk WJ, Phillips KA, Jobes ML, et al. (2015) Clonidine maintenance prolongs opioid abstinence and decouples stress from craving in daily life: a randomized controlled trial with ecological momentary assessment. *Am J Psychiatry* 172: 760–7.

Krupitsky E, Nunes EV, Ling W, et al. (2011) Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicenter randomized trial. *Lancet* 377: 1506–13.

Lee JD, Nunes EV, Novo P, et al. (2018) Comparative effectiveness of extended-release naltrexone versus buprenorphine–naloxone for opioid relapse prevention (X:BOT): a multicentre, open label, randomized controlled trial. *Lancet* 391: 309–18.

Marquet P (2002) Pharmacology of high-dose buprenorphine. In *Buprenorphine Therapy of Opiate Addiction*, Kintz P and Marquet P (eds.), Totawa, NJ: Humana Press, 1–11.

National Institute on Drug Abuse. Drugs, brains, and behavior. www.drugabuse.gov/sites/default/files/soa_2014.pdf. Accessed January 2018.

Patel B, Koston TR (2019) Keeping up with clinical advances: opioid use disorder. *CNS Spectrums* 24: 17–23.

Saanijoki T, Tuominen L, Tuulari JJ et al. (2018) Opioid release after high intensity interval training in healthy human subjects. *Neuropsychopharmacology* 43: 246–54.

Smyth BP, Barry J, Keenan E, Ducray K (2010) Lapse and relapse following inpatient treatment of opiate dependence. *Ir Med J* 103: 176–9.

Spagnolo PA, Kimes A, Schwandt ML, et al. (2019) Striatal dopamine release in response to morphine: a ^{11}C-raclopride positron emission tomography study in healthy men. *Biol Psychiatry* 86: 356–64.

Stahl SM (2018) Antagonist treatment is just as effective as replacement therapy for opioid addition but neither is used often enough. *CNS Spectrums* 23: 113–16.

Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: results from the 2016 National Survey on Drug Use and Health. www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.htm#opioid1. Accessed January 2018.

Sullivan MA, Bisage A, Bavlicova M, et al. (2019) A randomized trial comparing extended release injectable suspension and oral naltrexone, both combined with behavioral therapy, for the treatment of opioid use disorder. *Am J Psychiatry* 176: 129–37.

Tanum L, Solli KK, Latif ZE, et al. (2017) Effectiveness of injectable extended-release naltrexone vs. daily buprenorphine–naloxone for opioid dependence: a randomized clinical noninferiority trial. *JAMA Psychiatry* 74: 1197–205.

Tiihonen J, Krupitsky E, Verbitskaya E, et al. (2012) Naltrexone implant for the treatment of polydrug dependence: a randomized controlled trial. *Am J Psychiatry* 169: 531–6.

Volkow ND (2014) America's addiction to opioids: Heroin and prescription drug abuse. Presented at the Senate Caucus on International Narcotics Control. https://archives.drugabuse.gov/testimonies/2014/americas-addiction-to-opioids-heroin-prescription-drug-abuse.

Volkow ND, Frieden TR, Hyde PS, Cha SS (2014) Medication-assisted therapies: tackling the opioid-overdose epidemic. *N Engl J Med* 370: 2063–6.

World Health Organization (2009) *Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence*. Geneva: World Health Organization.

Substance Abuse: Stimulants

Bauman MH, Ayestas MA Jr., Partilla JS, et al. (2012) The designer methcathinone analogs, mephedrone and methylone, are substrates for monoamine transporters in brain tissue. *Neuropsychopharmacology* 37, 1192–203.

Bradberry CW (2002) Dose-dependent effect of ethanol on extracellular dopamine in mesolimbic striatum of awake rhesus monkeys: comparison with cocaine across individuals. *Psychopharmacology* 165: 67–76.

Collins GT, Narasimhan D, Cunningham AR, et al. (2012) Long-lasting effects of a PEGylated mutant cocaine esterase (CocE) on the reinforcing and discriminative stimulus effects of cocaine in rats. *Neuropsychopharmacology* 37: 1092–103.

Dakwar E, Nunes EV, Hart CL, et al. (2019) A single ketamine infusion combined with mindfulness based behavioral modification to treat cocaine dependence: a randomized clinical trial. *Am J Psychiatry* 176: 923–30.

Ersche KD, Bullmore ET, Craig KJ, et al. (2010) Influence of compulsivity of drug abuse on dopaminergic modulation of attentional bias in stimulant dependence. *Arch Gen Psychiatry* 67: 632–44.

Ersche KD, Jones PS, Williams GB, et al. (2012) Abnormal brain structure implicated in stimulant drug addiction. *Science* 335: 601–4.

Ferris MJ, Calipari ES, Mateo Y, et al. (2012) Cocaine self-administration produces pharmacodynamic tolerance: differential effects on the potency of dopamine transporter blockers, releasers, and methylphenidate. *Neuropsychopharmacology* 37: 1708–16.

Hart CL, Marvin CB, Silver R, Smith EE (2012) Is cognitive functioning impaired in methamphetamine users? A critical review. *Neuropsychopharmacology* 37: 586–608.

Heinz A, Reimold M, Wrase J, et al. (2005) Stimulant actions in rodents: implications for attention-deficit/hyperactivity disorder treatment and potential substance abuse. *Biol Psychiatry* 57: 1391–6.

Leyton M, Boileau I, Benkelfat C, et al. (2002) Amphetamine-induced increases in extracellular dopamine, drug wanting, and novelty seeking: a PET/[^{11}C]raclopride study in healthy men. *Neuropsychopharmacology* 27: 1027–35.

Lindsey KP, Wilcox KM, Votaw JR, et al. (2004) Effect of dopamine transporter inhibitors on cocaine self-administration in rhesus monkeys: relationship to transporter occupancy determined by positron emission tomography neuroimaging. *J Pharmacol Exp Ther* 309: 959–69.

Little KY, Krolewski DM, Zhang L, Cassin BJ (2003) Loss of striatal vesicular monoamine transporter protein (VMAT2) in human cocaine users. *Am J Psychiatry* 160: 47–55.

Livni E, Parasrampuria DA, Fischman AJ (2006) PET study examining pharmacokinetics, detection and likeability, and dopamine transporter receptor occupancy of short- and long-acting oral methylphenidate. *Am J Psychiatry* 163: 387–95.

Martinez D, Narendran R, Foltin RW, et al. (2007) Amphetamine-induced dopamine release: markedly blunted in cocaine dependence and predictive of the choice to self-administer cocaine. *Am J Psychiatry* 164: 622–9.

Narendran R, Lopresti BJ, Martinez D, et al. (2012) In vivo evidence for low striatal vesicular monoamine transporter 2 (VMAT2) availability in cocaine abusers. *Am J Psychiatry* 169: 55–63.

Overtoom CCE, Bekker EM, van der Molen MW, et al. (2009) Methylphenidate restores link between stop-signal sensory impact and successful stopping in adults with attention deficit/hyperactivity disorder. *Biol Psychiatry* 65: 614–19.

Peng, XO, Xi ZX, Li X, et al. (2010) Is slow-onset long-acting monoamine transport blockade to cocaine as methadone is to heroin? Implication for anti-addiction medications. *Neuropsychopharmacology* 35: 2564–78.

Santos MD, Salery M, Forget B, et al. (2017) Rapid synaptogenesis in the nucleus accumbens is induced by a single cocaine administration and stabilized by mitogen-activated protein kinase interacting kinase-1 activity. *Biol Psychiatry* 82: 806–18.

Selzer J (2006) Buprenorphine: reflections of an addictions psychiatrist. *J Clin Psychiatry* 67: 1466–7.

Spencer TJ, Biederman J, Ciccone PE, et al. (2006) Stimulant medications: how to minimize their reinforcing effects? *Am J Psychiatry* 163: 359–61.

Wee S, Hicks MJ, De BP, et al. (2012) Novel cocaine vaccine linked to a disrupted adenovirus gene transfer vector blocks cocaine psychostimulant and reinforcing effects. *Neuropsychopharmacology* 37: 1083–91.

Substance Abuse: Hallucinogens, Entactogens, Dissociatives

Brawley P, Dufield JC (1972) The pharmacology of hallucinogens. *Pharmacol Rev* 34: 31–66.

Carhart-Harris RL, Goodwin GM (2017) The therapeutic potential of psychedelic drugs: past, present and future. *Neuropsychopharmacology* 42: 2105–13.

Carhart-Harris RL, Bolstridge M, Day CMG, et al. (2018) Psilocybin with psychological support for treatment-resistant depression: six month follow up. *Psychopharmacology* 235: 399–408.

Carhart-Harris RL, Bolstridge M, Rucker J, et al. (2016) Psilocybin with psychological support for treatment-resistant depression: an open label feasibility study. *Lancet Psychiatry* 3: 619–27.

Carhart-Harris RL, Erritzoe D, Williams T, et al. (2012) Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. *Proc Natl Acad Sci USA* 109: 2138–43.

Carhart-Harris RL, Leech R, Williams TM, et al. (2012) Implications for psychedelic assisted psychotherapy: a functional magnetic resonance imaging study with psilocybin. *Br J Psychiatry* 200: 238–44.

DiIorio CR, Watkins TJ, Dietrich MS (2012) Evidence for chronically altered serotonin function in the cerebral cortex of female 3,4-methylenedioxymethamphetamine polydrug users. *Arch Gen Psychiatry* 69: 399–409.

Erritzoe D, Frokjaer VG, Holst KK, et al. (2011) In vivo imaging of cerebral serotonin transporter and serotonin 2a receptor binding in 3,4-methylenedioxymethamphetamine (MDMA or "Ecstasy") and hallucinogen users. *Arch Gen Psychiatry* 68: 562–76.

Fantegrossi WE, Murnane KS, Reissig CJ (2008) The behavioral pharmacology of hallucinogens. *Biochem Pharmacol* 25: 17–33.

Feduccia AA, Mithoefer MC (2018) MDMA-assisted psychotherapy for PTSD: are memory reconsolidation and fear extinction underlying mechanisms. *Prog Neuropsychopharmacol Biol Psychiatry* 84: 221–8.

Liechti ME (2017) Modern clinical research on LSD. *Neuropsychopharmacology* 42: 2114–27.

Madsen MK, Fisher PM, Burmester D, et al. (2019) Psychedelic effects of psilocybin correlate with serotonin 2A receptor occupancy and plasma psilocin levels. *Neuropsychopharmacology* 44: 1328–34.

Mithoefer MC, Wagner MT, Mithoefer AT, et al. (2011) The safety and efficacy of {+/−} 3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. *J Psychopharmacol* 25: 439–52.

Passie T, Halpern JH, Stichtenoth DO, et al. (2008) The pharmacology of lysergic acid diethylamide: a review. *CNS Neurosci Ther* 14: 295–314.

Pitts EG, Minerva AR, Chandler EB, et al. (2017) 3,4-Methylenedioxymethamphetamine increases affiliative behaviors in squirrel moneys in a serotonin 2A receptor dependent manner. *Neuropsychopharmacology* 42: 1962–71.

Quednow BB, Komeer M, Geyer MA, et al. (2012) Psilocybin induced deficits in autonomic and controlled inhibition are attenuated by ketanserin in healthy human volunteers. *Neuropsychopharmacology* 37: 630–40.

Schmid Y, Enzler F, Gasser P, et al. (2015) Acute effects of lysergic acid diethylamine in healthy subjects. *Biol Psychiatry* 78: 544–53.

Titeler M, Lyon RA, Gleenon RA (1988) Radioligand binding evidence implicates the brain $5HT_2$ receptor as a site of action for LSD and phenylisopropylamine hallucinogens. *Psychopharmacology* 94: 213–16.

Urban NBL, Girgis RR, Talbot PS, et al. (2012) Sustained recreational use of Ecstasy is associated with altered pre and postsynaptic markers of serotonin transmission in neocortical areas: a PET study with [^{11}C]DASB and [^{11}C] MDL 100907. *Neuropsychopharmacology* 37: 1465–73.

Binge Eating/Gambling

Balodis IM, Kober H, Worhunsky PD, et al. (2012) Diminished frontostriatal activity during processing of monetary rewards and losses in pathological gambling. *Biol Psychiatry* 71: 749–57.

Gearhardt AN, Yokum S, Orr PT, et al. (2011) Neural correlates of food addiction. *Arch Gen Psychiatry* 68: 808–16.

Grant JE, Kim SW, Hartman BK (2008) A double-blind, placebo-controlled study of the opiate antagonist naltrexone in the treatment of pathological gambling urges. *J Clin Psychiatry* 69: 783–9.

Lawrence AJ, Luty J, Bogdan NA, Sahakian BJ, Clark L (2009) Impulsivity and response inhibition in alcohol dependence and problem gambling. *Psychopharmacology* 207: 163–72.

Lobo DSS, Kennedy JL (2006) The genetics of gambling and behavioral addictions. *CNS Spectrums* 11: 931–9.

McElroy SL, Hudson JI, Capece JA, et al. (2007) Topiramate for the treatment of binge eating disorder associated with obesity: a placebo-controlled study. *Biol Psychiatry* 61: 1039–48.

Miedl SF, Peters J, Buchel C (2012) Altered neural reward representations in pathological gamblers revealed by delay and probability discounting. *Arch Gen Psychiatry* 69: 177–86.

Salamone JD, Correa M, Mingote S, Weber SM (2002) Nucleus accumbens dopamine and the regulation of effort in food-seeking behavior: implications for studies of natural motivation, psychiatry, and drug abuse. *J Pharmacol Exp Ther* 305: 1–8.

Van Holst RJ, Veltman DJ, Buchel C, van den Brink W, Goudriaan AE. (2012) Distorted expectancy coding in problem gambling: is the addictive in the anticipation? *Biol Psychiatry* 71: 741–8.

Zack M, Poulos CX (2007) A D_1 antagonist enhances the rewarding and priming effects of a gambling episode in pathological gamblers. *Neuropsychopharmacology* 32: 1678–86.

Impulsivity/Compulsivity

Berlin HA, Rolls ET, Iversen SD (2005) Borderline personality disorder, impulsivity, and the orbitofrontal cortex. *Am J Psychiatry* 162: 2360–73.

Chamberlain SR, del Campo N, Dowson J, et al. (2007) Atomoxetine improved response inhibition in adults with attention deficit/hyperactivity disorder. *Biol Psychiatry* 62: 977–84.

Chamberlain SR, Muller U, Blackwell AD, et al. (2006) Neurochemical modulation of response inhibition and probabilistic learning in humans. *Science* 311: 861–3.

Chamberlain SR, Robbins TW, Winder-Rhodes S, et al. (2011) Translational approaches to frontostriatal dysfunction in attention-deficit/hyperactivity disorder using a computerized neuropsychological battery. *Biol Psychiatry* 69: 1192–203.

Dalley JW, Everitt BJ, Robbins TW (2011) Impulsivity, compulsivity, and top-down cognitive control. *Neuron* 69: 680–94.

Dalley JW, Mar AC, Economidou D, Robbins TW (2008) Neurobehavioral mechanisms of impulsivity: fronto-striatal systems and functional neurochemistry. *Pharmacol Biochem Behav* 90: 250–60.

Fineberg NA, Chamberlain SR, Goudriaan AR (2014) New developments in human neurocognition: clinical, genetic, and brain imaging correlates of impulsivity and compulsivity. *CNS Spectrums* 19: 69–89.

Lodge DJ, Grace AA (2006) The hippocampus modulates dopamine neuron responsivity by regulating the intensity of phasic neuron activation. *Neuropsychopharmacology* 31: 1356–61.

Robbins TW, Gillan CM, Smith DG, de Wit S, Ersche KD (2012) Neurocognitive endophenotypes of impulsivity and compulsivity: towards dimensional psychiatry. *Trends Cogn Sci* 16: 81–91.

Shaw P, Gilliam M, Liverpool M, et al. (2011) Cortical development in typically developing children with symptoms of hyperactivity and impulsivity: support for a dimensional view of attention deficit hyperactivity disorder. *Am J Psychiatry* 168: 143–51.

Sugam JA, Day JJ, Wightman RM, Carelki RM (2012) Phasic nucleus accumbens dopamine encodes risk-based decision-making behavior. *Biol Psychiatry* 71: 199–205.

Weathers JD, Stringaris AR, Deveney CM, et al. (2012) A development study of the neural circuitry mediating motor inhibition in bipolar disorder. *Am J Psychiatry* 16: 633–41.

Index

5HT. *See* serotonin

ABC model of apathy, 536
abstinence, 571–4
acamprosate, 556
acetyl coenzyme A, 505
acetylcholine, 5, 505–10
  dopamine and, 166
acetylcholinesterase, 505
acetylcholinesterase inhibition, 509–18
action potential, 67, 73
active site, 45, 46
acute pain, 379, 380
addiction, 476, 539
  behavioral, 575
  dopamine theory of, 542–3
  substance addictions, 544–75
adenosine, 440
ADHD (attention deficit hyperactivity disorder), 34, 449, 485, 539
  comorbidities, 466, 480
  neurodevelopment, 463–5
  oppositional symptoms, 484
  prefrontal cortex tuning, 454–63
  symptoms and circuits, 449–53
  treatments, future, 484
  treatments, NET inhibitors, 480–4
  treatments, stimulants, 467–79
  treatments, symptoms and, 466–7
advanced sleep phase disorder, 435, 437
affective blunting, 142
affective disorders, 244
affective symptoms, 95
  positive and negative, 278, 280, 306
  schizophrenia, 145
aggression, 145–7, 521, 577–8
agitation, 145, 521–3
  dementia, 145, 157, 197
  glutamate target, 533
  neuronal networks of, 528–30
  treatment, 523–4
  treatment, multimodal monoamine, 530–2
agomelatine, 306–8
agonist spectrum, 37, 43, 45, 56–62, 184, 192
agonists, 57, 58
  full, 37–41, 56, 192
  inverse, 42, 44–5, 61, 62, 240
  no agonist, 37
  partial. *See* partial agonists
AIMS (Abnormal Involuntary Movement scale), 174
akathisia, 166, 169
alcohol, 377, 553–6
  abstinence, 573
  co-addictions, 553
  treatment of alcoholism, 556
alcohol abuse, 378
allodynia, 380
allopregnanolone, 320, 322
allosteric modulation, 64–6, 261, 262
alogia, 142
alpha-1 antagonism, 216, 225, 236, 327–8
alpha-2 adrenergic agonists, 481–4
alpha-2 antagonism, 309
alpha-2 autoreceptors, 254, 256, 258
alpha-2-delta ligands, 366, 377, 380
  pain alleviation, 398
  SNRI combinations, 399
alpha pore, 69, 70
alpha-synuclein, 493, 494
alternative splicing, 26
Alzheimer disease, 487–90, *See also* dementia
  agitation in, 521–4, 528–33
  delusions in, 157
  dementia stage 3, 502
  early detection, importance of, 497
  impulsivity, 539
  MCI stage 2, 500–2
  memory and cognition treatment, 509–18
  Parkinson's disease comorbidity, 494
  pathology, 488
  presymptomatic stage, 499–501
  psychosis in, 521–4
  targeting amyloid, 496–9
  vascular dementia comorbidity, 492
amantadine, 169
amisulpride, 205
amotivational syndrome, 563
AMPA receptors, 101, 104, 330, 331
amphetamine, 337, 356, 441–2, 472–6, 569
  ADHD, 484
  formulations, 475
  isomers, 472
amygdala, fear and, 364–5, 372, 374
amyloid cascade hypothesis, 496–9
amyloid plaques. *See* beta-amyloid
amyloid precursor protein, 497–8
amyotrophic lateral sclerosis, 353
analgesia, 380
anatomical basis of neurotransmission, 1–5
anesthesia, dissociative, 570
anhedonia, 142, 162
antagonists, 41–3, 57, 58, 60, 62
  alpha-1, 216, 225, 236, 327–8
  alpha-2, 309
  silent, 41, 42, 45, 192
anticholinergics, 166, 168, 215, 294
anticonvulsants
  doubtful efficacy in bipolar disorder, 352–3
  insomnia treatment, 426
  mood stabilizers, 346
  proven efficacy in bipolar disorder, 347–51
antidepressant actions, 195–234, 267, 283
antihistamines, 161, 215, 295, 425–6
antipsychotic actions, 161–2, 242
antipsychotics. *See* drugs targeting serotonin receptors, drugs targeting dopamine D_2 receptors
anxiety, 78, 145, 359
  OCD and, 576
anxiety disorders, 196, 378
  ADHD and, 468
  comorbidity, 360
  core symptoms, 360
  definition, 360
  major depression and, 360–2
  MAOIs, 336
  noradrenergic hyperactivity in, 370–2
  overlapping symptoms of different, 362–3
  pain disorders and, 387
  psychotherapy, 359
  serotonin and, 368–70
  treatment of, 377–8, 421
anxiety phenotype, 363
anxiolytic actions, 196, 366
apathy, 78, 536–7
APOE4 gene, 497
aripiprazole, 192, 229, 239, 326
armodafinil, 442–4
arousal, 457, 459
arousal spectrum, 402
asenapine, 220, 232
asociality, 142
asymptomatic amyloidosis, 499–501

atomoxetine, 480–1
auditory hallucinations, 113
autoreceptors
  alpha-2, 254, 256, 258
  monoamine, 8
avolition, 142
axoaxonic synapses, 1, 3
axodendritic synapses, 1, 3
axosomatic synapses, 1, 3

barbiturates, 556
bath salts, 546
BDNF (brain-derived neurotrophic factor), 266, 268, 329
behavioral addictions, 575
behavioral variant FTD, 494
benzodiazepine-insensitive $GABA_A$ receptors, 263–4
benzodiazepines, 321, 366, 377
  caution with, 378
  insomnia treatment, 421–2
benzodiazepine-sensitive $GABA_A$ receptors, 259–62
beta-amyloid, 488, 496–8, 502
  detection, 499, 501
beta blockers, 375, 376
beta subunits, 68
bifeprunox, 192
binge-eating disorder, 575
bipolar depression, 244
  drug treatment, 236, 240
  family history of, 250
  first-line treatment, 342
  identifying, 250
  missed or delayed diagnosis, 250
  schizophrenia and, 249
  suicide rates, 251
  versus unipolar, 249–51
bipolar disorder
  anticonvulsants with proven efficacy, 347–51
  anticonvulsants with uncertain efficacy, 352–3
  bipolar I, 247
  bipolar II, 244, 247
  combination treatments, 353
  drug treatment, 338–58
blocking fear conditioning, 375–7
blonanserin, 234, 241
brexanolone, 320
brexpiprazole, 192, 197, 230, 239, 327–8, 378, 530–2
bright light therapy, 438, 440, 444
buprenorphine, 560, 561, 562
bupropion, 306–8, 353–4, 480, 533
  nicotine addiction, 551
  sertraline combination, 294
buspirone, 333, 370
butyrylcholinesterase, 505, 510

caffeine, 440–1
calcium channel blockers (L-type), 352
cannabidiol (CBD), 563, 565, 567
cannabis, 150, 563–7
  benefits and risks, 564
  side effects, 563
  therapeutic uses, 564
carbamazepine, 350, 530
cardiometabolic risk, 196, 224
cardiometabolism, 198–201, 415
cardiovascular disease, 156, 415, 432, 492, 524
carfentanil, 560
cariprazine, 192, 231, 240, 328, 343–5
cataplexy, 434, 435, 446
catechol-*O*-methyltransferase, 253
central disorders of hypersomnolence, 432
central pain, 379
central sensitization, 395
chemical neurotransmission, 1, 28
  anatomical versus, 1–5
  epigenetics, 23–6
  ion channels and, 73–6
  mood disorders, 252–64
  principles of, 5–9
  signal transduction cascades, 9–23, 28, 53
  triggering gene expression, 18
  ultradian sleep cycle, 414–16
chemotherapy, side effects, 309
child abuse, 370
chlorpromazine, 161, 181, 201, 202
choline, 505
cholinergic agonists, 242
cholinergic pathways, 509
chromatin, 23
chronic back pain, 388
chronic pain, 379–400
  decreased gray matter, 387–90
  duloxetine treatment, 302–3
  milnacipran treatment, 303
  targeting sensitized circuits, 395–9
  treatment, 390–400
circadian rhythm disorders, 430, 435–8
  depression, 271–5
circadian rhythms, 307, 308
  setting of, 275
circadian treatments, 438–40
circadian wake drive, 409, 412
citalopram, 295–6
classic neurotransmission, 6
clock genes, 271
clomipramine, 335
clonidine, 390, 482–3, 561

closed state, 63
clozapine, 217, 222–5
cocaine, 544, 545
codeine, 559
cognition, Fab Four of, 317
cognitive behavioral therapy, 374, 377, 576
cognitive dysfunction
  ADHD, 455, 456, 458
  Alzheimer disease, 509–18
  chronic pain, 388
  depression, 273
  fibromyalgia, 390, 400
  Parkinson's disease, 493
  sleep disorders, 402
  sleep disturbance and, 414, 417
  vortioxetine treatment, 315–17
cognitive symptoms, schizophrenia, 95, 144, 157
competitive elimination, 151, 154
compulsivity, 538–9, 571, 578
  impulsive–compulsive disorders, 539–43, 575
  OCD, 295, 360, 576–7
conceptual disorganization, 78
conditioned responses, 539
conditioned stimuli, 539, 544
consolidation, 375
constitutive activity, 37, 57
continuous positive airway pressure, 443
controlled substance, 447
cortico-brainstem glutamate pathways, 102
cortico-cortical glutamate pathways, 105
cortico-striatal glutamate pathways, 104
cortico-striato-thalamo-cortical (CSTC) loops, 87, 362, 365–9
cortico-thalamic glutamate pathway, 105
CREB system, 15
criminogenic behavior, 146, 147
cytochrome P450 (CYP450), 49–50, 323

daridorexant, 424
DAT transporter. *See* dopamine transporters (DATs)
date rape drugs, 447, 559
delayed sleep phase disorder, 435, 437
delirium, 569
delusions, 77, 141, 524
  Alzheimer disease, 157
  dementia, 521
  Parkinson's disease psychosis, 157
dementia, 486, 537, *See also* Alzheimer disease
  agitation in, 145, 157, 197
  apathy in, 536–7
  behavioral symptoms of, 521, 537
  definition, 487
  depression in, 534–5

major causes of, 488–96
psychosis in, 110, 134, 157, 521–3
psychosis in, treatment, 523–7
symptomatic treatments, 503–5
dendrites, 2
depression, 145, *See also* bipolar depression, unipolar depression
affective symptoms, 278, 280
circadian rhythm disorder in, 271–5
clinical effects of treatment, 284–5
dementia and, 534–5
drug side effects, 200
drug treatment, 229, 239
insomnia and, 418
major depressive disorder. *See* major depressive disorder
major depressive episode. *See* major depressive episode
mixed features of, 251
monoamine hypothesis of, 264–5, 290
monoamine receptor hypothesis of, 264–6, 267, 290
mood stabilizer treatment, 288
neuroplasticity and neuroprogression hypothesis of, 266–76
serotonin or dopamine blockers in, 342
symptom-based algorithm treatment, 280
time course of effects of drugs, 266
depression with mixed features, 248, 342
depressive psychosis, 78, 157
descending spinal norepinephrine pathway, 390, 392
descending spinal serotonergic pathway, 390, 394
desensitization, 63, 64
desvenlafaxine, 299, 302
deuteration, 175, 177, 354
dextromethadone, 355–8
dextromethorphan, 306, 353–4, 533, 536
diabetes, 198, 199, 415
diabetic ketoacidosis, 199, 200
Diagnostic and Statistical Manual of Mental Disorders (DSM-5)
ADHD, 463
insomnia, 420
major depressive episode, 245
manic episode, 245
mixed features, 248
dietary tyramine interaction, 338
diphenhydramine, 426
direct (go) dopamine pathway, 89, 90
disorganized/excited psychosis, 78
disorientation, 78
dissociation-assisted psychotherapy, 574
dissociative anesthesia, 570
dissociatives, 569–71
disulfiram, 556
DNA methylation, 24
donepezil, 510
DOPA decarboxylase, 253
dopamine, 5
acetylcholine and, 166
conversion to norepinephrine, 253
increase in prefrontal cortex, 299–302
inefficient tuning of PFC by, 454–63
projections, 279
release, $5HT_{2A}$ regulation, 184–8
synthesis, 79, 80
volume neurotransmission, 8
dopamine β-hydroxylase, 253
dopamine blockers, 468
adverse effects, 524
bipolar disorder spectrum, 338–45
dopamine D_1 receptors
drugs targeting, 204–41
dopamine D_2 receptors. *See also* drugs targeting dopamine D_2 receptors
pre- and postsynaptic, 228
dopamine D_3 receptors, 343–5
drugs targeting, 210, 240, 241
dopamine deficiency syndrome, 306
dopamine hypothesis of psychosis, 79–95, 110–14, 141
dopamine neurotransmitter network, 79–91
classic pathways and key brain regions, 84
mesolimbic pathway, 89, 542–3
nigrostriatal pathway, 87–9
thalamic pathway, 85
tuberoinfundibular pathway, 85
dopamine receptors, 81–5
dopamine theory of addiction, 542–3
dopamine transporters (DATs), 31, 80
ADHD treatment, 473–9
inhibition, 294, 333
dopaminergic neurons, 79
dorsal anterior cingulate cortex (dACC), 450, 451
dorsal horn neurons, 382–4
dorsal horn, descending spinal synapses in, 390–5
dorsal root ganglia, 380, 381
dorsolateral prefrontal cortex, 387, 400, 449
doxepin, 425, 427
drug abuse, 447, 539
DAT occupancy and, 476, 479
reversal of habit, 571–4
stimulants, 544–7
drug-induced dystonia, 166, 169
drug-induced parkinsonism, 165, 166–9, 181
drugs targeting dopamine D_1 receptors, 204–41
drugs targeting dopamine D_2 receptors, 159, 242
agitation in dementia, 197
antidepressant actions, 195–234
anxiolytic actions, 196
cardiometabolic actions, 198–201
first generation, 179–82, 201–3
individual properties, 204–41
mesocortical, 163
mesolimbic/mesostriatal, 161–3
nigrostriatal, 165–81
partial agonists, 189–92, 204–41
serotonin 2A and, 182–8
tuberoinfundibular, 164
drugs targeting dopamine D_3 receptors, 210, 240, 241
drugs targeting serotonin receptors, 159, 243
1A receptors, 192–5, 207
1B and 1D receptors, 214
2A receptors, 182–8
2C receptor, 211
3 receptor, 212
6 and 7 receptors, 213
agitation in dementia, 197
antidepressant actions, 195–234
anxiolytic actions, 196
cardiometabolic actions, 198–201
individual properties, 204–41
DSST (digital symbol substitution test), 317
dual orexin receptor antagonists (DORAs), 423–4, 430
duloxetine, 299, 302–3, 535
dynorphins, 390
dyslipidemia, 198
dystonia, drug-induced, 166, 169

eating disorders, 293, 575
Ecstasy, 358, 569
empathogens, 569
endocannabinoids, 6, 563, 564
enkephalins, 390
entactogens, 569
enzyme inhibitors, 45
irreversible, 46
reversible, 47
enzymes, 45–50
activity, 45
epigenetics, 23–6
Epworth Sleepiness Scale, 430
escitalopram, 296
esketamine, 331, 353, 571
eslicarbazepine, 352
euphoria, 560
excessive daytime sleepiness. *See* hypersomnia
excitation–secretion coupling, 6, 8–9, 73, 75

excitatory amino acid transporter, 96, 99
excitement, 78
executive dysfunction, 144, 449–50
exposure therapy, 374, 378, 574, 576, 577
extinction
  fear, 373, 374–5, 574
  pharmacological, 573
extrapyramidal symptoms, 166

F17464, 241
FDG PET, 490, 492, 502
fear, 363–6
  neurobiology of, 364–5
  noradrenergic hyperactivity, 371
fear conditioning, 370–4
  blocking, 375–7
fear extinction, 373, 374–5, 574
fentanyl, 559
fibro-fog, 390, 400
fibromyalgia, 303, 387–9
  cognitive dysfunction, 388, 400
  targeting ancillary symptoms, 399–400
  treatment, 448
fight or flight response, 359, 364
first messengers, 11, 13
flashbacks, 568
flumazenil, 263
fluoxetine, 293–4
  olanzapine combination, 293, 326, 343
fluphenazine, 202, 203
fluvoxamine, 295
forensic hospitals, 146, 147, 156
frontotemporal dementias, 494–6
frontotemporal lobar degeneration, 494
full agonists, 37–41, 56, 192

G protein, 14
G-protein-linked receptors, 36–45, 50
  agonist spectrum, 37, 43, 45
  agonists, 37–41
  antagonists, 41–3
  inverse agonists, 42, 44–5
  no agonist, 37
  partial agonists, 41, 43–4
  structure and function, 36
G-protein-linked systems, 11, 12, 13
GABA (γ-aminobutyric acid), 5, 257–64, 349
  action termination, 258
  synthesis, 255
GABA interneurons
  5HT receptors on, 121, 125, 130
  prefrontal cortex, 105–10
GABA receptors, 258–64
  $GABA_A$, 321, 366, 421–3
  $GABA_A$ receptor subtypes, 258–61
  $GABA_A$, benzodiazepine-insensitive, 263–4
  $GABA_A$, benzodiazepine-sensitive, 259–62
GABA transaminase (GABA-T), 258
GABA transporter (GAT), 34, 258
GABAergic drugs, 276
gabapentin, 352, 366, 395, 426
galanthamine, 514
gambling disorder, 575
gamma-hydroxybutyrate (GHB), 400, 446–8, 559
gene activation, 18, 19, 24, 25
gene expression
  epigenetics, 23–6
  molecular mechanism, 18–23
  neurotransmission triggering, 18
  phosphoprotein triggering cascades, 15–18
gene silencing, 24, 25
generalized anxiety disorder, 361, 377
genetic testing, 323–5
genetics
  ADHD, 463
  schizophrenia, 148–50
genotyping, 50
ghrelin, 415
glucose metabolism, 490
glutamate, 5, 96
  agitation in Alzheimer disease, 533
  Alzheimer disease target, 515–18
  key pathways in the brain, 102
  synthesis, 96–7
  synthesis of GABA from, 255
glutamate hypothesis of psychosis, 95–114
glutamate neurotransmitter network, 96–106
glutamate receptors, 99–105
  ionotropic, 54
  metabotropic, 100, 103
  NMDA. *See* NMDA glutamate receptors
glutamate transporters, 34
glutamic acid decarboxylase, 255
glycine transporters, 34
glycine, synthesis, 97–9
Goldilocks solution, 43, 60, 191, 227, 428
grandiose expansiveness, 78
gray matter, chronic pain, 387–90
GSK-3 (glycogen synthase kinase), 48
guanfacine, 482–3

habit circuit, 544, 561, 571, 572
habits, 538, 539, 576
hallucinations, 77, 113, 141, 435, 568
  dementia, 521
  Parkinson's disease psychosis, 157
  visual, 113, 524
hallucinogen-assisted psychotherapy, 355–8, 376
hallucinogens, 135, 138, 567–9
haloperidol, 181, 202, 204
heroin, 559, 561, 573
heteroreceptors, 125
hippocampal-accumbens glutamate pathway, 104
hippocampus, 372, 374
histamine, 35, 402–6, 409
histamine 1 antagonism, 425–6, 427
histamine receptors, 406
histones, methylation, 23
homeostatic sleep drive, 408, 412
hormone-linked systems, 11, 12
hostile belligerence, 78
HPA (hypothalamic-pituitary-adrenal) axis, 266, 270
human genome, 18
Huntington's disease, 28, 175
hydrocodone (Vicodin), 559
hyperactivity, 452, 454, 463
hyperalgesia, 380
hyperarousal, 418
hyperdopaminergia, 90, 92, 93
hyperglycemic hyperosmolar syndrome, 199, 200
hyperprolactinemia, 165, 187, 192
hypersomnia, 402, 430–40
  causes of, 431–5
  treatment of, 440–8
hypervigilance, 402
hypnotic actions, 311
  insomnia treatment, 421–30
hypnotics, sedative, 556
hypocretins, 406–11
hypodopaminergia, 95
hypomania, 248
hypothalamic neurons, 407

idiopathic hypersomnia, 432, 433
illusions, 568
iloperidone, 225, 236
immediate early genes, 19, 20
impulse control disorders, 577–8
impulsive–compulsive disorders, 539
  binge eating, 575
  neurocircuitry of, 539–43
impulsive violence, 147, 577
impulsivity, 452, 454, 463, 538–9, 571, 578
inactivation state, 61, 63
inattention, 449, 450, 451, 463
indirect (stop) dopamine pathway, 89, 90
inhalants, 547
inherited disease, classic theory of, 148
insomnia, 311, 402, 418–20

behavioral treatments, 430
diagnosis and comorbidities, 418–20
treatment, 421–31
insulin resistance, 197, 198, 200
internet addiction, 575
interneurons, 380
inverse agonists, 42, 44–5, 61, 62, 240
ion-channel-linked systems, 11, 12
ion channels, 76
ligand-gated. *See* ligand-gated ion channels
neurotransmission and, 73–6
voltage-sensitive. *See* voltage-sensitive ion channels
ionotropic glutamate receptors, 54
iproniazid, 336
irreversible enzyme inhibitors, 46

kainate receptors, 101, 104
ketamine, 106, 328–32, 353, 376, 569–71
ketamine-assisted psychotherapy, 574
kinase, third messenger, 14, 16

lamotrigine, 350–1
late genes, 20, 22
lemborexant, 423
leptin, 415
leucine zippers, 19, 20, 21
levodopa, 170
levomilnacipran, 300, 303
Lewy bodies, 157
Lewy body dementias, 492–5
licarbazepine, 352
ligand-gated ion channels, 51–66, 76
agonist spectrum, 56–62
allosteric modulation, 64–6
different states of, 61–4
gatekeeper, 52
pentameric subtypes, 53
structure and function, 53
tetrameric subtypes, 54–5
lisdexamfetamine, 473, 575
lithium, 48, 332, 345–6
local anesthesia, 380
lofexidine, 561
long-term potentiation, 151
LSD, 358, 568
lumateperone, 227, 237–9
lurasidone, 226, 236, 343

magic mushrooms, 358
magnesium, 104
magnetic resonance imaging, 491
major depressive disorder, 246, 252
anxiety disorder and, 360–2
core symptoms, 360
major depressive episode, 248, 277
symptoms and circuits, 277
mania
anticonvulsant treatment, 346
carbamazepine treatment, 350
drug treatment, 195
lithium treatment, 345
mixed features of, 248, 251
mood stabilizer treatment, 288
serotonin and dopamine blockers in, 338, 342
valproate treatment, 349
manic episodes, 245, 277, 278
MAOIs. *See* monoamine oxidase inhibitors
mazindol, 485
MDMA, 356, 376, 378, 569–71
assisted psychotherapy, 574
MDPV, 546
medication-assisted therapy, 561
melatonergic agents, 439, 440
melatonin, 275, 439, 440
melatonin receptors, 306
memantine, 520, 521–4, 533
memory difficulties, 316
Alzheimer disease, 509–18
memory, traumatic, 356, 366, 375, 574
mesocortical dopamine pathway, 95
mesocortical hypodopaminergia, 95
mesolimbic dopamine pathway, 89, 542–3
mesolimbic hyperdopaminergia, 90
mesostriatal hyperdopaminergia, 93
messenger RNA (mRNA), 26
metabolic highway, 198, 199, 201
metabolic monitoring, 196, 199
metabolic toolkit, 201
metabotropic glutamate receptors, 100, 103
metformin, 201
methadone, 355, 559, 560, 561, 562
methylation, 23, 24
methylphenidate, 441–2, 469–72, 484
formulations, 470
mianserin, 309
microRNA (miRNA), 27
migrants, 150
mild cognitive impairment, 487, 490, 493, 500–2
milnacipran, 300, 303
mirtazapine, 232, 308–13, 333
mixed dementia, 495
mixed features, 248, 251–2
modafinil, 333, 442–4
Molly, 358, 569
monoamine autoreceptors, 8
monoamine hypothesis of depression, 264–5, 290
monoamine oxidase (MAO), 253
monoamine oxidase inhibitors (MAOIs), 336–7, 377
bipolar depression, 342
dietary tyramine interaction, 338
drug–drug interactions, 338
subtypes, 337–41
monoamine projections, 279
monoamine receptor hypothesis of depression, 264–6, 267, 290
monoamine transporters, 30, 31–4, 208
unipolar depression, 285–8
mood disorders, 244, 282, *See also* mania, depression
description of, 244–52
future treatments for, 353–8
mixed features of, 248, 251–2
neurobiology of, 252–76
pain disorders and, 387
symptom-based treatments, 279–82
symptoms and circuits in, 277–82
mood episodes, 246
mood related psychosis, 157
mood spectrum, 244–9
mood-stabilizers, 288, 345–6
mood-stabilizing action, 283
morphine, 559, 561
motivation, lack of, 536
motor disturbances, 78
motor side effects, 165–81
partial agonists, 192
mu-opioid receptors, 390, 556
multimodal monoamines, 530–2
Multiple Sleep Latency Test, 431
muscarinic receptors, 506–7

nalmefene, 556, 573
naloxone, 560
naltrexone, 306, 556, 561, 563, 573, 575
NAMs (negative allosteric modulators), 64–6
narcolepsy, 407, 430, 433, 435, 443, 444, 446
nausea and vomiting, 309
n-back test, 449, 451
nefazodone, 311
negative affect, 278, 280
negative feedback regulatory signal, 255
negative symptoms, 95, 142–4, 156
secondary, 162–3
NET transporters. *See* norepinephrine transporters (NETs)
neuroactive steroids, 320–5
neurobiology
mood disorders, 252–76
sleep and wakefulness, 402–15
neurodevelopment, 151, 152
ADHD, 463–5
schizophrenia, 151–3

neurofibrillary tangles, 488, 502, 503
neuroinflammation, 270
neuroleptic-induced deficit syndrome, 162
neuroleptic malignant syndrome, 169
neuroleptics, 162
neuronal cell loss, 488, 490, 491
neurons, 1, 2
  general structure, 2
neuropathic pain, 380, 382–90, *See also* fibromyalgia
  central mechanisms, 382–6
  peripheral mechanisms, 382
neuropathic pain syndromes, 380
neuropeptides, 35
neuroplasticity and neuroprogression hypothesis of depression, 266–76
neurotransmission, 1, *See also* chemical neurotransmission
  anatomical basis of, 1–5
neurotransmitters, 5–6
  enzymes as. *See* enzymes
  psychosis pathways, 79
  transporters. *See* transporters
neurotrophic factors, loss of, 266, 268
neurotrophin-linked systems, 11, 12
neutropenia, 224
NGF (nerve growth factor), 6
nicotine, 63, 466, 547–53
  alternative forms of delivery, 551
  treatment of addiction, 548–53
nicotinic receptors, 506, 507–9, 548
nigrostriatal dopamine pathway, 87–9
nitric oxide, 6
nitric oxide synthase, 295
NMDA antagonism, 328, 330, 355
NMDA glutamate hypofunction hypothesis of psychosis, 105–14
NMDA glutamate receptors, 97–101, 104
  histamine at, 406
  hypofunction, 111, 114
NMDA receptor activation, 375
nociception, 380, 381
  pain pathways, 396
nociceptive nerve fibers, activation, 381
nociceptive pathway, 381
  from the spinal cord to the brain, 382–4
  to the spinal cord, 381–2
non-24-hour sleep–wake disorder, 437, 438
non-REM sleep, 413, 414
noradrenaline. *See* norepinephrine
noradrenergic hyperactivity, 370–2
norepinephrine, 5, 252–6, 370
  action termination, 253
  inefficient tuning of prefrontal cortex by, 454–63
  projections, 279
  synthesis, 252
norepinephrine–dopamine reuptake inhibitors (NDRIs), 303–6, 333
norepinephrine receptors, 254–6, 258
norepinephrine transporters (NETs), 31, 254
norepinephrine transporter (NET) inhibition, 294, 298–303, 370
  ADHD, 480–4
norquetiapine, 227
NRX101, 237
NSAIDs (nonsteroidal anti-inflammatory drugs), 382
nucleosomes, 23
nucleus accumbens, 162

obesity, 198, 415, 575
obsessive–compulsive disorder (OCD), 295, 360, 576–7
obstructive sleep apnea, 430, 431, 434, 443
olanzapine, 218, 225
  fluoxetine combination, 293, 326, 343
ondansetron, 556
OPC4392, 193
open state, 63
opiates, 559
opioid use disorder, 355
opioids, 375, 390, 556, 559
  abstinence, 573
  addiction, 559–60
  addiction, treatment of, 560–2
  endogenous neurotransmitter system, 559
orbital frontal cortex, 454
orexin, 409, 435
  dual orexin receptor antagonists, 423–4, 430
orexin receptors, 407
orexins, 406–11
oxcarbazepine, 352
oxycodone (OxyContin), 559

pain, 379–84, *See also* chronic pain
  definition, 380
  in dementia, 537
  mood and anxiety disorders and, 387
paliperidone, 223, 235
PAMs (positive allosteric modulators), 64–6, 421–3
panic attacks, 361, 377, 569
panic disorder, 361, 372, 377
paralytic ileus, 167, 183
paranoid psychosis, 78
parkinsonism, drug-induced, 165, 166–9, 181
Parkinson's disease, 338
  Alzheimer disease comorbidity, 494
  cognitive dysfunction, 493
Parkinson's disease dementia, 492–5
Parkinson's disease psychosis, 78, 133, 136, 139, 157, 524
paroxetine, 294, 295
partial agonists, 41, 43–4, 57–61, 189–95, 204–41
Pavlov's dogs, 370
pentameric ligand-gated ion channels, 53
perceptual distortions, 78
periaqueductal gray, 390
peripheral pain, 379
perospirone, 233, 241
PET scans
  beta-amyloid, 499, 501
  FDG PET, 490, 492, 502
pharmacodynamics, 49
pharmacokinetics, 49
  hypnotic actions, 426–30
pharmacological extinction, 573
phasic dopamine system, 455
phasic inhibition, 259
phencyclidine, 106, 569–71
phosphatase, third messenger, 15, 16
phosphoprotein cascades, 15–18
phosphoprotein messenger, 13–15
pimavanserin, 231, 240, 526
pitolisant, 444
plasma membrane transporters, 30
polygenic risk score, 150
polysomnography, 420, 431
positive affect, 278, 280, 306
positive symptoms, 90, 141, 156
  psychosis, 92–3
postsynaptic dopamine receptors, 81
posttraumatic stress disorder (PTSD), 360, 362
  drug treatment, 196
  fear conditioning, 372
  treatments for, 377, 568, 574
prazocin, 370
predementia AD, 500–2
prefrontal cortex
  disorder of the, 449–53, 463
  dopamine neurotransmission, 8
  dorsolateral, 387, 400, 449
  GABA interneurons, 105–10
  increased dopamine in, 299–302
  inefficient tuning of, 454–63
  ventromedial, 372, 374
pregabalin, 352, 366, 395, 426
presymptomatic stage of Alzheimer disease, 499–501
presynaptic dopamine receptors, 81, 82
primary afferent neurons, 380, 381
primary transcript, 26
prisons, 146, 156

processing speed, 317
prodromal negative symptoms, 143
proinflammatory molecules, 270
projection neurons, 380
prolactin levels, 164, 187, 193
pseudobulbar affect, 535
psilocin, 568
psilocybin, 358, 376, 568, 569
  assisted psychotherapy,
psychedelic experience, 568
psychiatric vital sign, 381, 399, 401
psychic pain, 302
psychomotor retardation, 78
psychopathic violence, 147, 577
psychosis, 77, 158, *See also* schizophrenia
  cannabis and, 563
  dementia, prevalence in, 521
  dementia-related, 110, 134, 157, 521–3
  dementia-related, treatment of, 523–7
  depressive, 78, 157
  dopamine hypothesis of, 79–95, 110–14, 141
  drug treatment. *See* drugs targeting serotonin receptors, drugs targeting dopamine D_2 receptors
  glutamate hypothesis of, 95–114
  mood-related, 157
  neurotransmitter pathways, 79
  other psychotic disorders, 156–8
  paranoid, 78
  Parkinson's disease. *See* Parkinson's disease psychosis
  positive symptoms of, 90, 92–3
  serotonin hyperfunction hypothesis of, 131–41
  serotonin hypothesis of, 111–41
  symptoms of, 77–8
psychotherapy
  anxiety disorders, 359
  cognitive behavioral therapy, 374, 377, 576
  dissociation-assisted, 574
  hallucinogen-assisted, 355–8, 376
  ketamine-assisted, 574
  MDMA-assisted, 574
  psilocybin-assisted, 574
  PTSD, 378
psychotic violence, 146, 577
psychotomimetic experience, 569
psychotropic drugs
  enzymes as targets of, 45–50
  G-protein-linked receptors as targets, 36–45, 50
  ion channels as targets of, 51–76
  molecular targets, 29
  nomenclature, 29
  transporters as targets, 29–35, 50
PTSD. *See* posttraumatic stress disorder (PTSD)

quetiapine, 219, 220, 227–32, 326, 343
quinidine, 353–4, 534, 536

radafaxine, 304
ramelteon, 439
rasagiline, 338
rashes, 352
receptor tyrosine kinases, 48
reconsolidation, 374, 375, 376, 574
recurrence in depression, 284
reduced positive affect, 280, 306
relapse, 571
  in depression, 284, 286
REM sleep, 413, 414, 435
remission in depression, 284, 286
repetitive transcranial magnetic stimulation (rTMS), 577
reserpine, 174
response in depression, 284
resting state, 57, 61, 63
retrograde neurotransmission, 6–7
reuptake pumps, 174, *See also* transporters
reversible enzyme inhibitors, 47
reward, 542, 544
reward conditioning, 545
reward pathway, 572
rheostat analogy, 43
ribosomal RNA (rRNA), 27
riluzole, 352
risperidone, 222, 234, 235
rivastigmine, 510–16
RNA, 26–7
RNA interference, 26
roluperidone, 235, 241

safinamide, 338
SAGE-217, 322
salivation, excessive, 224
samidorphan, 201
schizoaffective disorder, 249
schizophrenia, 141, 156, *See also* psychosis
  affective symptoms, 95, 145
  aggressive symptoms, 145–7
  bipolar disorder and, 249
  cognitive symptoms, 95, 144, 157
  dopamine hypothesis of psychosis in, 92–5
  drug treatment. *See* drugs targeting serotonin receptors, drugs targeting dopamine D_2 receptors
  future drug treatment, 241–2
  genetics and, 148–50
  life expectancy, 156
  nature and nurture of, 149
  negative symptoms, 95, 142–4, 156
  neurodegeneration and, 154–6
  neurodevelopment and, 151–3
  NMDA receptor hypofunction, 111, 114
  positive symptoms, 141, 156
  positive symptoms of psychosis in, 92–3
second messenger
  forming, 11–14
  to phosphoprotein cascades, 15–18
  to phosphoprotein messenger, 13–15
secondary negative symptoms, 162–3
sedation, 197, 202
sedative hypnotics, 556
segmental central sensitization, 384
selegiline, 337, 338
SEP-363856, 242
serine, synthesis, 97–9
serious mental illness (SMI), 156
serotonergic hypnotics, 424–5
serotonin, 5, 113
  anxiety and, 368–70
  dementia-related psychosis, 524–7
  neuronal network, 121
  projections, 279
  synthesis and termination of action, 114–15
serotonin antagonist/reuptake inhibitors (SARIs), 311–16
serotonin blockers
  bipolar disorder spectrum, 338–45
serotonin hyperfunction hypothesis of psychosis, 131–41
serotonin hypothesis of psychosis, 111–41
serotonin network, 113–33
  constructing, 119–21
serotonin partial agonist reuptake inhibitor (SPARI), 296–9
serotonin receptors. *See also* drugs targeting serotonin receptors
  $5HT_{1A}$, 116, 118, 121, 296–9, 317
  $5HT_{1B}$, 125, 318
  $5HT_{1B/D}$, 118, 119, 318
  $5HT_{2A}$, 125
  $5HT_{2A}$, dopamine release regulation, 184–8
  $5HT_{2A}$, hyperactivity/imbalance, 111–41
  $5HT_{2B}$, 117, 119
  $5HT_{2C}$, 125, 293–4
  $5HT_3$, 125–9, 309–13, 318
  $5HT_6$, 130
  $5HT_7$, 130–3, 318–24
  overview, 114
serotonin transporters (SERTs), 31, 33
  inhibition of, 289, 296, 317, 318–24
sertindole, 232, 240

sertraline, 294, 378
setiptiline, 309
shift work disorder, 435, 436, 444
sigma-1 binding, 294, 295
signal propagation, 74
signal transduction cascades, 9–23, 28, 53
  four important types of, 11, 12
  second messenger, forming, 11–14
  second messenger, to phosphoprotein cascades, 15–18
  second messenger, to phosphoprotein messenger, 13–15
  time course, 11
silent antagonists, 41, 42, 45, 192
Sinclair method, 573
SLC1 gene family, 31, 35
SLC17 gene family, 31, 35
SLC18 gene family, 31, 35
SLC32 gene family, 31, 35
SLC6 gene family, 30, 31–5
sleep
  neurobiology of, 402–15
  purpose of, 414–15
  REM and non-REM, 413, 414, 435
sleepiness, 430–4
sleep/wake cycle, 412–13
  disturbance of, 414, 416
small interfering RNA (siRNA), 27
small nuclear RNA (snRNA), 27
smoking, 476, *See also* nicotine
  cessation, 306, 573
snare proteins, 73
SNRIs (serotonin–norepinephrine reuptake inhibitors), 298–303
  $\alpha_2\delta$ ligand combinations, 399
  anxiety disorders, 368
  arousal combo, 333
  mirtazapine combination, 333
  pain treatment, 380
  triple action combo, 333
social anxiety disorder, 362, 372, 377
sodium oxybate, 446–8
sodium potassium ATPase (sodium pump), 32, 33
sodium valproate, 347–50
solriamfetol, 444
soma, 2
somatic pain, 302
somatosensory cortex, 380
specific neutral amino acid transporters (SNATs), 96
spinobulbar tracts, 380
spinothalamic tract, 380
SSRIs (selective serotonin reuptake inhibitors), 289–96
  anxiety disorders, 368
  clinical uses of, 289
  common features of six drugs, 289–92
  depression in dementia, 534
  OCD, 577
  triple-action combo, 333
  unique properties of six drugs, 292–3
stabilizers. *See* partial agonists
steroids, neuroactive, 320–5
Stevens Johnson syndrome, 352
stigma, 145
stimulants, 467–79, 544–7
  atypical, 546
  slow release vs. fast release, 478–9
  targeting DATs, 473–8
  treatment of addiction, 547
stimulus-response conditioning, 571
strengthening, synapse, 151, 154
stress, ADHD, 467, 469, 480
stroke, 492, 524
Stroop test, 450, 451
subjective memory complaints, 487, 488
sublingual formulation, 232
substance addictions, 544–75
substrates, 45, 46
suicide, 145, 156
  clozapine treatment, 223
  depressed patients, 251
  mixed feature patients, 251
  prevention, 346
suicide inhibitors, 46
sulpiride, 202, 205
supersensitivity, 170, 171
suprachiasmatic nucleus, 275, 307
suprasegmental central sensitization, 384, 390
suvorexant, 423
synapses, 1, 3
  enlarged, 5
synaptic neurotransmission, 4
synaptogenesis, 151, 154

tardive dyskinesia (TD), 166
  pathophysiology, 170–4
  treatment, 174–81
tasimelteon, 439
tau protein, 488, 494, 502, 503
tetrabenazine, 175–6
tetrahydrocannabinol (THC), 563, 565, 567
tetrameric ligand-gated ion channels, 54–5
thalamic dopamine pathway, 85
thalamo-cortical glutamate pathway, 104
third-messenger kinase, 14, 16
third-messenger phosphatase, 15, 16
thyroid, 333
tonic inhibition, 259, 263
topiramate, 201, 352, 556, 575
trace amines, 241–38
tradozone, 311–15, 424–5
transduction, 381
transfer RNA (tRNA), 27
transporters, 29–35, 50
  classification and structure, 29–31
  histamine and neuropeptides, 35
  monoamine, 30, 31–4, 208
  SLC1 gene family, 31
  vesicular, 32, 35
tranylcypromine, 337
traumatic memories, 356, 366, 375, 574
trazodone, 535
treatment responsiveness, 155
tricyclic antidepressants (TCAs), 333–7
triglyceride levels, 197, 198, 199
tryptophan, 114
tuberoinfundibular dopamine pathway, 85
tuberomammillary nucleus, 406, 408
type 2 diabetes, 415
tyramine, 338
tyrosine, 80, 252
tyrosine hydroxylase, 253

ultradian sleep cycle, 413–16
unipolar depression, 34, 244
  augmenting strategies for, 325–35
  drugs for, 289–325
  monoamine reuptake blockers, 285–8
  or bipolar, 249–51
  second-line monotherapies, 333–8
  treatment resistance in, 323–38

valbenazine, 177
valproic acid (valproate), 347–50
varenicline, 551, 552, 573
vascular dementia, 491–2, 534
VEGF (vascular endothelial growth factor), 329
venlafaxine, 299, 302
ventromedial prefrontal cortex, 372, 374
vesicular transporter for glutamate, 99
vesicular transporters, 31, 32, 35
VIAATs (vesicular inhibitory amino acid transporters), 255
vilazodone, 296–9
viloxazine, 485
violence, 145–7, 575, 577–8
visual hallucinations, 113, 524
vital sign, 381, 399, 401
VMAT1, 174
VMAT2 inhibition, 174–81
VMAT2 transporter, 31, 81, 254
VMATs (vesicular monoamine transporters), 35

voltage-sensitive calcium channels (VSCCs), 70–3, 366, 395
voltage-sensitive ion channels, 66–73, 76
  structure and function, 66
voltage-sensitive sodium channels (VSSCs), 67–70, 347, 350, 351, 381
volume neurotransmission, 6–9
vortioxetine, 311, 315–20, 535

wake-promoting agents, 440–8
wakefulness, neurobiology of, 402–15
weight gain, 198, 224
widespread pain index (WPI), 387
withdrawal syndrome, 546, 560
worry, 362, 363
  neurobiology of, 365–9
  noradrenergic hyperactivity, 372

xanomeline, 242

Z drugs, 425–6
ziprasidone, 224, 236
zolpidem, 423
zopiclone, 423
zotepine, 221, 233