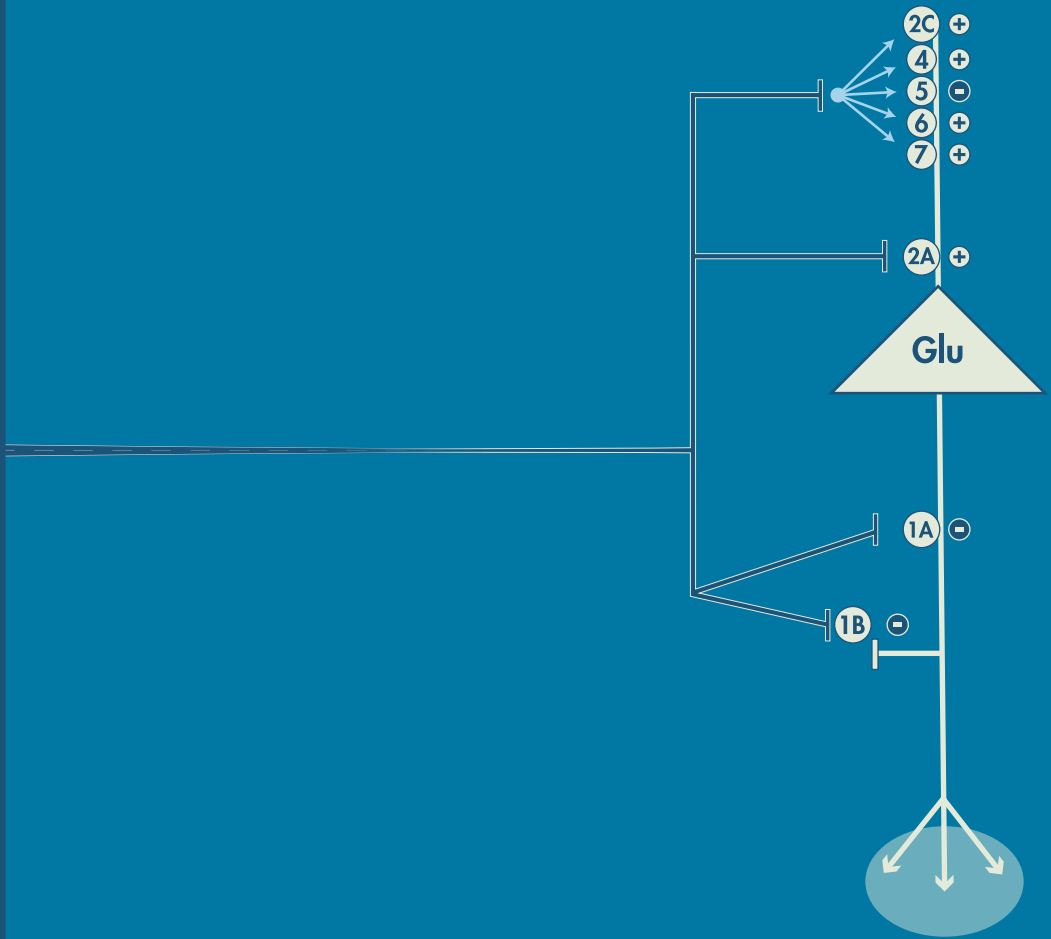
The Road to Remission:

Optimizing Pharmacological Treatment of Unipolar Depression

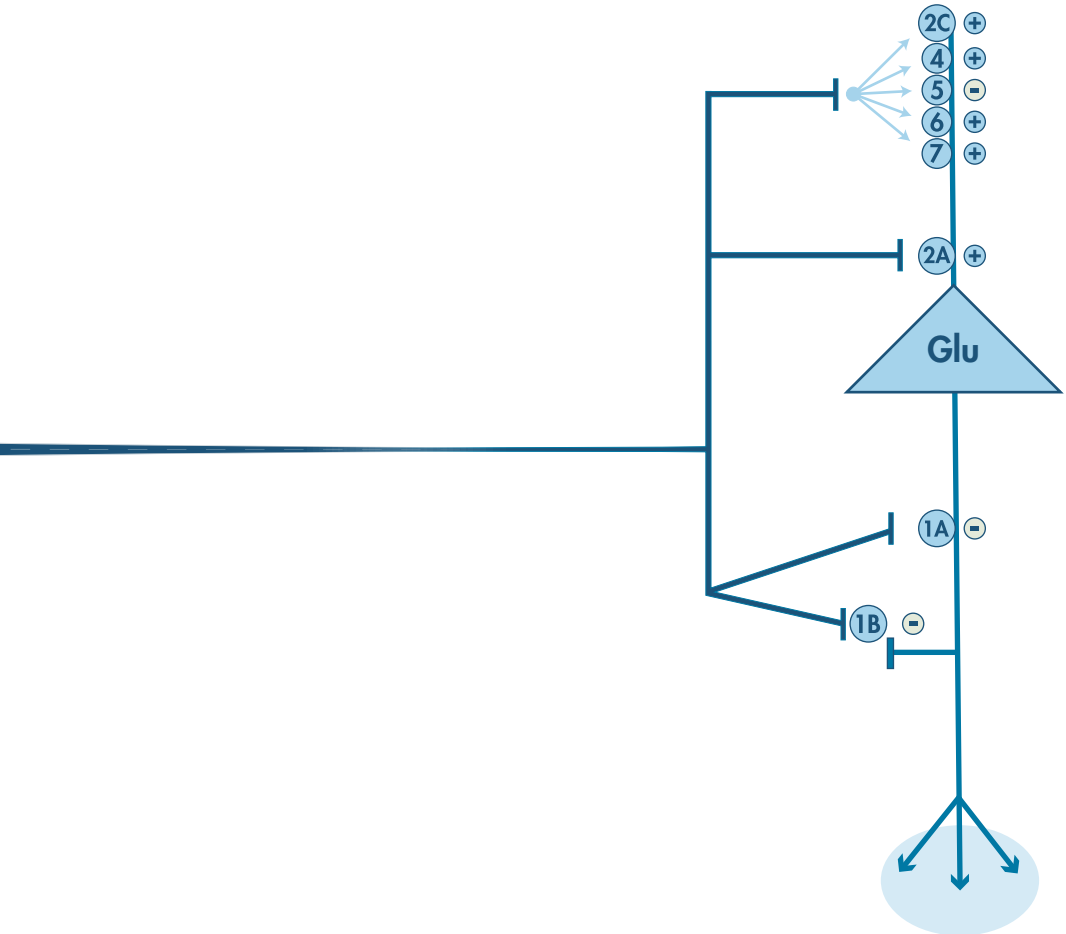


Supported by an unrestricted educational grant from
Takeda Pharmaceuticals International, Inc.

Released: August, 2015
CME Credit Expires: August, 2018

The Road to Remission:

Optimizing Pharmacological Treatment of Unipolar Depression



PUBLISHED BY NEI PRESS, an imprint of NEUROSCIENCE EDUCATION INSTITUTE
Carlsbad, California, United States of America

NEUROSCIENCE EDUCATION INSTITUTE
1930 Palomar Point Way, Suite 101
Carlsbad, California 92008

http://www.neiglobal.com

Printed in the United States of America
First Edition, August 2015
Electronic versions, December 2015

Typeset in Enzo OT

Library of Congress Cataloging-in-Publication Data
ISBN 978-1-4225-0089-6 Print
ISBN 978-1-4225-0050-0 Adobe® PDF
ISBN 978-1-4225-0052-7 EPUB

Table of Contents

CME Information

Overview

Patients with major depressive disorder are much more likely to achieve response than remission, yet true wellness is the ultimate goal. If one understands both the neurobiology behind the spectrum of symptoms that are associated with depressive disorders, and the mechanisms behind the spectrum of drugs characterized as antidepressants, then it is possible to apply informed strategies to the selection of first-line treatment as well as the management of residual symptoms and side effects, which ideally will lead to hastened remission and return to wellness.

Target Audience

This activity has been developed for nurse practitioners specializing in psychiatry. There are no prerequisites. All other health care providers interested in psychopharmacology are welcome for advanced study.

Statement of Need

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

- Documented gaps between established best practices and actual practice of monitoring patients with depression over time in order to track treatment adherence, response, and side effects
- Documented gaps between established best practices and actual practice of implementing evidence-based treatment adjustments, including adjunct treatment, switching, and nonpharmacological approaches, to address inadequate response

To help address clinician performance deficits with respect to depression, quality improvement efforts need to provide education regarding implementation of monitoring techniques and evidence-based treatment strategies to address inadequate response for patients with major depressive disorder.

Learning Objectives

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

- Identify risk factors for nonadherence to antidepressant treatment
- Employ strategies to assess treatment effectiveness and adherence over time
- Implement evidence-based treatment adjustments for patients with inadequate antidepressant response

Accreditation and Credit Designation Statements

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

The Neuroscience Education Institute designates this enduring material for a maximum of 2.5 *AMA PRA Category I Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

The American Society for the Advancement of Pharmacotherapy (ASAP), Division 55 of the American Psychological Association, is approved by the American Psychological Association to sponsor continuing education for psychologists. ASAP maintains responsibility for this program and its content.

The American Society for the Advancement of Pharmacotherapy designates this program for 2.5 CE credits for psychologists.

Nurses: for all of your CNE requirements for recertification, the ANCC will accept *AMA PRA Category I Credits*™ from organizations accredited by the ACCME. The content of this activity pertains to pharmacology and is worth 2.5 continuing education hours of pharmacotherapeutics.

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

A certificate of participation for completing this activity is available.

Note: the content of this electronic book activity also exists as a print monograph under the same title. If you received CME credit for the print monograph version, you will not be able to receive credit again for completing this electronic book version.

Instructions

The estimated time for completion of this activity is 2.5 hours. There is no posttest fee nor fee for CME credits.

1. Read the book in sequence, evaluating the content presented
2. Complete the posttest and activity evaluation, available only online at **www.neiglobal.com/CME** (under "Book")
3. Print your certificate (if a score of 70% or more is achieved)

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

Peer Review

This material has been peer-reviewed by an MD to ensure the scientific accuracy and medical relevance of information presented and its independence from commercial bias. The Neuroscience Education Institute takes responsibility for the content, quality, and scientific integrity of this CME activity.

Disclosures

It is the policy of NEI to ensure balance, independence, objectivity, and scientific rigor in all its educational activities. Therefore, all individuals in a position to influence or control content are required to disclose any 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.

Disclosed financial relationships with conflicts of interest have been reviewed by the NEI CME Advisory Board Chair and resolved.

Authors/Developers

Meghan Grady
Director, Content Development, Neuroscience Education Institute, Carlsbad, CA
No financial relationships to disclose.

Stephen M. Stahl, MD, PhD
Adjunct Professor, Department of Psychiatry, University of California, San Diego School of Medicine, San Diego, CA
Honorary Visiting Senior Fellow, University of Cambridge, UK
Director of Psychopharmacology, California Department of State Hospitals, CA
Grant/Research: Alkermes, Clintara, Forest, Forum, Genomind, JayMac, Jazz, Lilly, Merck, Novartis, Otsuka America, Pamlab, Pfizer, Servier, Shire, Sprout, Sunovion, Sunovion UK, Takeda, Teva, Tonix
Consultant/Advisor: Acadia, BioMarin, Forum/EnVivo, Jazz, Orexigen, Otsuka America, Pamlab, Servier, Shire, Sprout, Taisho, Takeda, Trius
Speakers Bureau: Forum, Servier, Sunovion UK, Takeda
Board Member: BioMarin, Forum/EnVivo, Genomind, Lundbeck, Otsuka America, RCT Logic, Shire

The **peer reviewer, design staff,** and **planning committee** 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.

Disclaimer

Participants have an implied responsibility to use the newly acquired information from this activity to enhance patient outcomes and their own professional development. The information presented in this educational activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this educational activity should not be used by clinicians without evaluation of their patients' conditions and possible contraindications or dangers in use,

review of any applicable manufacturer's product information, and comparison with recommendations of other authorities. Primary references and full prescribing information should be consulted.

Cultural and Linguistic Competency

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

Provider

This activity is provided by the Neuroscience Education Institute.

Additionally provided by the American Society for the Advancement of Pharmacotherapy.

Support

This activity is supported by an unrestricted educational grant from Takeda Pharmaceuticals International, Inc.

Date of Release/Expiration

Print Monograph Released: August, 2015

Electronic Books Released: December, 2015

CME Credit Expires: August, 2018

Chapter I:

Disease Models in Depression—An Overview

"Depression" is a Disorder of Brain Structure and Function

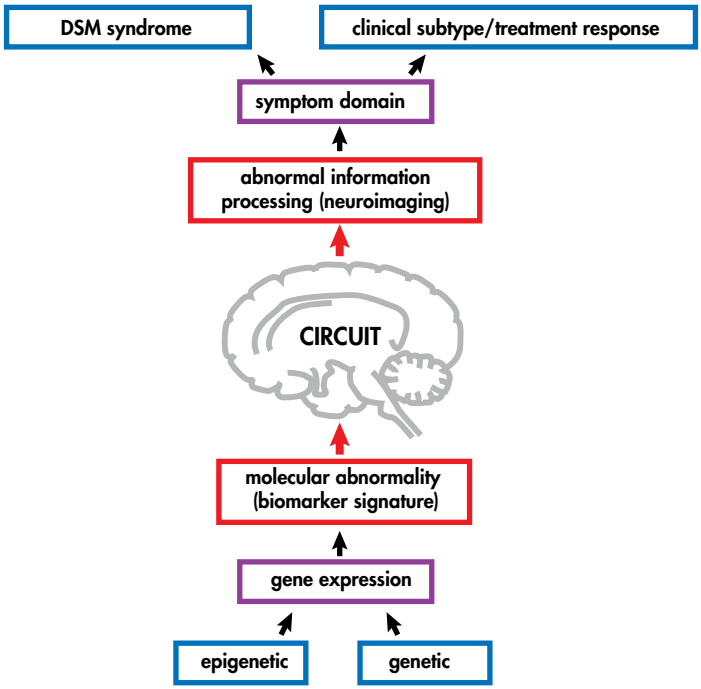


FIGURE I.I. As psychiatric research evolves, it is increasingly apparent that these are disorders of brain structure and function, and that the genetic and molecular factors underlying symptoms cut across traditional diagnostic categories. Correspondingly, treatment may be best applied not by thinking in terms of general drug classes, but rather by linking symptoms to malfunctioning circuits and malfunctioning circuits to potential drug targets.

If one understands both the neurobiology behind the spectrum of symptoms that are associated with depressive disorders, and the mechanisms behind the spectrum of drugs characterized as antidepressants, then it is possible to apply informed strategies to the selection of first-line treatment as well as the management of residual symptoms and side effects.

Early Disease Model in Depression: The Monoamine Hypothesis

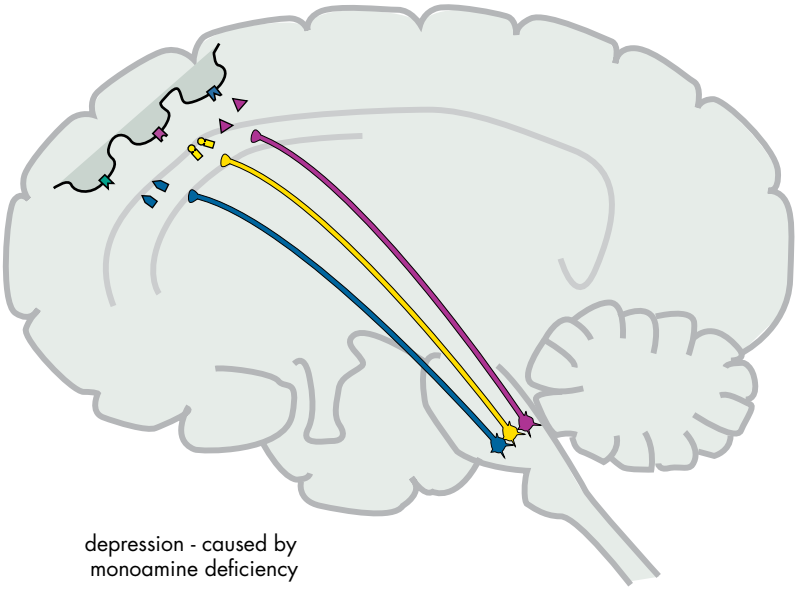
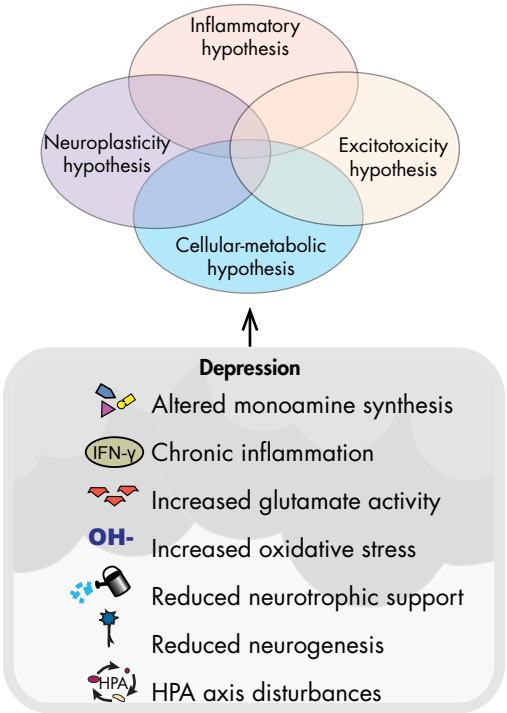


FIGURE I.2. For many decades, the focus of research on depression and its treatment revolved around three principal neurotransmitters: the monoamines serotonin (5HT), norepinephrine (NE), and dopamine (DA) (Stahl, 2013). Indeed, many of the symptoms of depression are hypothesized to involve dysfunction of various combinations of these three systems, and essentially all known treatments for mood disorders act upon one or more of these three systems. However, evolving research has shown that the classic monoamine hypothesis of depression—i.e., that depression is due to a deficiency of these neurotransmitters—is far too simplistic (Stahl, 2013).

Evolving Disease Models in Depression



Evolving Disease Models in Depression

FIGURE I.3. Today, the growing body of research on the pathogenesis of depression has led to several potential disease models that move far beyond monoamines to include inflammatory, excitotoxic, neurotrophic, endocrine, and metabolic factors (Miller et al., 2009; Dowlati et al., 2010; Howren et al., 2009; Pace et al., 2007; Pariante, 2009). These theories are not mutually exclusive; in fact, research has identified interactions between all of these systems. Furthermore, the heterogeneous presentation of depression is almost certainly a function of heterogeneous pathophysiology, and it may be that there is a subpopulation of patients who have underlying dysfunction related primarily to inflammation, another subpopulation for whom the pathophysiology is dominated by stress and endocrine factors, etc. In the future, we may be able to use collections of biomarkers to stratify patients based on their underlying pathogenesis and use that information to implement personalized treatment.

In this book, we focus on how to optimize treatment for patients now, and therefore on what is understood about the neurobiology of depression as it relates to the mechanisms of known and available treatments, with only brief mention of mechanisms under investigation.

Monoamines Have Downstream Effects on Neuroplasticity

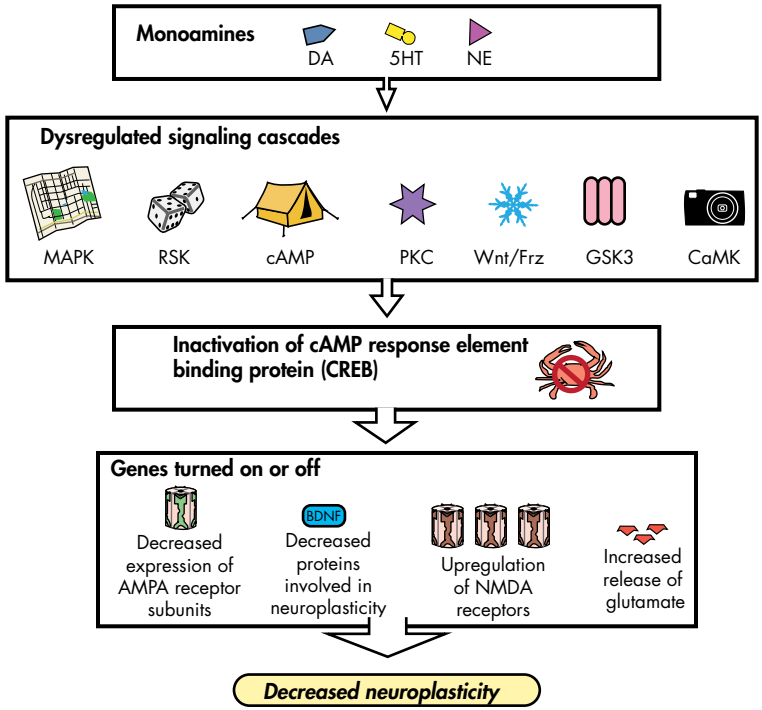


FIGURE I.4. Although direct evidence for the monoamine hypothesis of depression is lacking, it remains true that virtually all available antidepressants directly affect one or more of the monoamine neurotransmitter systems. The monoamines therefore remain of interest; however, the focus has now shifted from the neurotransmitters themselves to their receptors and the downstream molecular events that these receptors trigger, including the regulation of gene expression and the role of growth factors. That is, there may be a deficiency in downstream signal transduction of the monoamine neurotransmitters, leading to reduced synthesis of proteins involved in neurogenesis and synaptic plasticity and increased synthesis of those involved in excitotoxicity (Duman, 2004).

Downstream Effects of Monoamines: BDNF Production

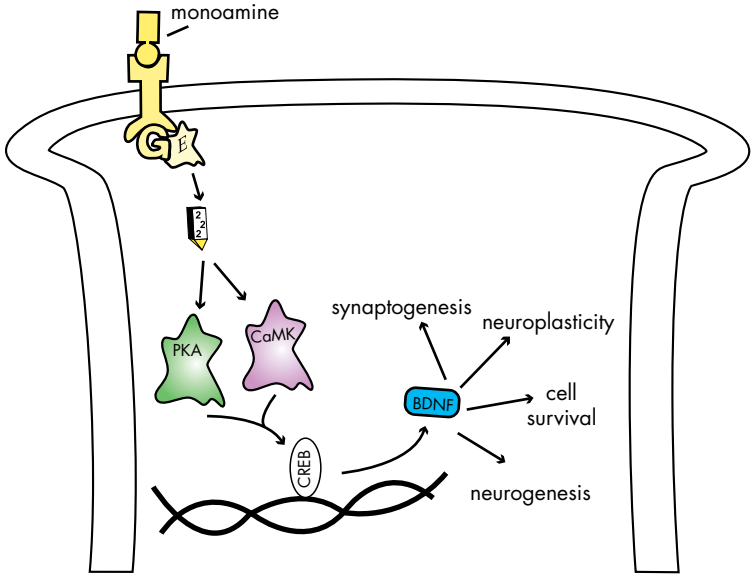
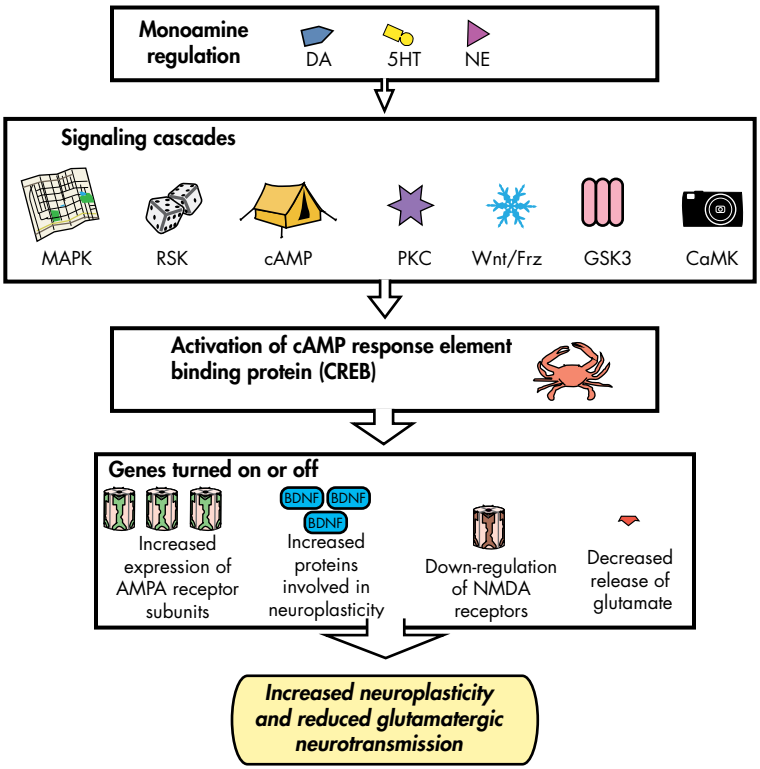


FIGURE I.5. For example, monoamines such as 5HT can trigger cascades that lead to the production of brain-derived neurotrophic factor (BDNF), which is important for synaptogenesis, neuroplasticity, cell survival, and neurogenesis. If monoamine levels are depleted, then BDNF levels may correspondingly go down; this could potentially contribute to cell atrophy or even cause cell loss.

In fact, there are brain imaging studies that show that BDNF levels in the hippocampus and prefrontal cortex are low in depressed patients (Brunoni et al., 2008; Sen et al., 2008). Correspondingly, patients with depression have reduced volume of the hippocampus and prefrontal cortex, atrophy of dendritic arborization, loss of dendritic spines, and reduction in the number of neurons and glia (Musazzi et al., 2011; Palazidou, 2012; Pittenger and Duman, 2008). Furthermore, there is a negative correlation between BDNF levels and severity of depression (Karege et al., 2002).

There is also evidence that antidepressant treatment may increase the synthesis of BDNF. Clinical studies have also shown that chronic antidepressant treatment can restore abnormally low BDNF levels, and that this can correlate with reduced scores on depression rating scales (Sen et al., 2008).

Downstream Effects of Antidepressants



Downstream Effects of Antidepressants

FIGURE I.6. Increasing evidence shows that various classes of antidepressants as well as brain stimulation techniques such as ECT are capable of correcting dysfunctional neuroplasticity and increasing neurogenesis (Crupi et al., 2011; Pittenger and Duman, 2008). Treatment with antidepressant agents stimulates a variety of signaling cascades, which are likely initiated by the increased binding of 5HT (5HT), norepinephrine (NE), and dopamine (DA) to various receptors. 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 brain-derived neurotrophic factor (BDNF).

Another form of synaptic plasticity, long-term potentiation (LTP), involves the strengthening of synapses through the modulation of glutamate receptors. Chronic antidepressant treatment has been shown to downregulate glutamatergic neurotransmission. The activation of CREB due to antidepressant treatment modulates the expression of glutamatergic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunits along a timeline that is consistent with the delayed therapeutic actions of antidepressants (Racagni and Popoli, 2008; Barbon et al., 2011). Unlike AMPA receptors, glutamatergic N-methyl-D-aspartate (NMDA) receptors are downregulated following antidepressant treatment (Racagni and Popoli, 2008; Crupi et al., 2011; Pittenger and Duman, 2008; Pittaluga et al., 2007). Although this may seem contradictory, it has been proposed that antidepressant treatments may modify the AMPA:NMDA receptor ratio, increasing AMPA while reducing NMDA input to restore glutamate homeostasis in the depressed brain (Barbon et al., 2011). The upregulation of AMPA receptors, the downregulation of NMDA receptors, and reduced glutamate release may rebalance glutamatergic neurotransmission and facilitate neuroplasticity in the depressed brain.

The hypothesis that the therapeutic effects of antidepressants are due to downstream changes in neuroplasticity is consistent with the fact that clinical improvement with antidepressants is typically delayed by several weeks. It also presents the possibility that agents with direct activity at these downstream targets may lead to faster treatment response.

Ketamine Directly Targets Glutamate Neurotransmission

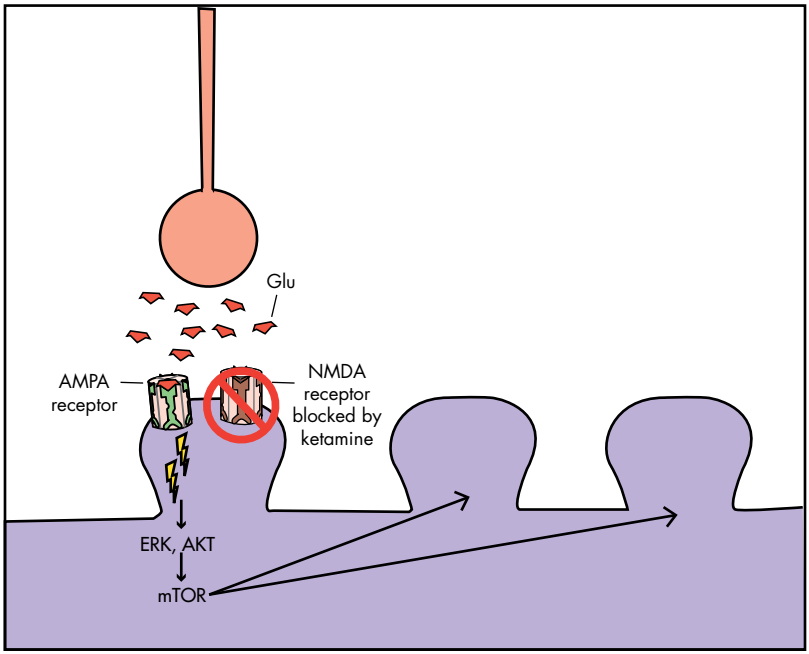
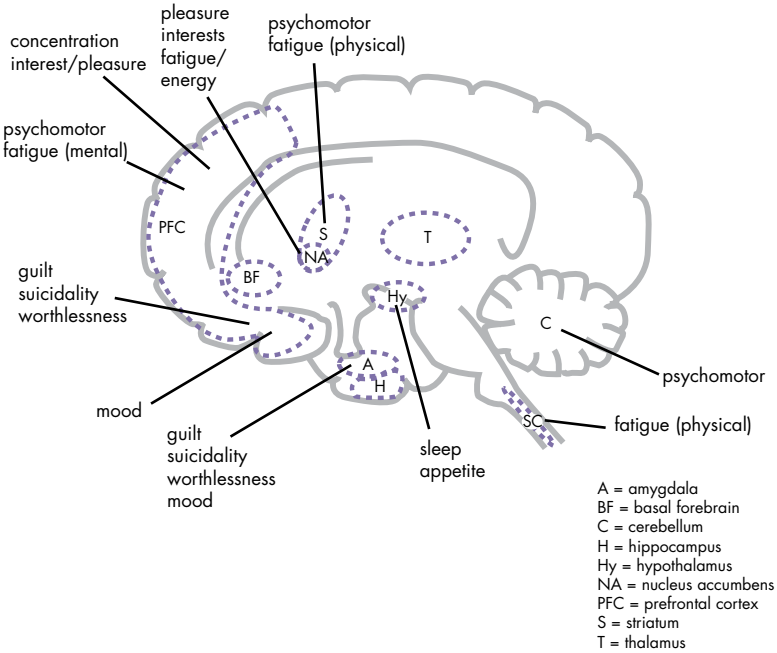


FIGURE I.7. As shown in Figure I.6, the downstream effects of monoaminergic antidepressants include increased AMPA receptor expression, decreased NMDA receptor expression, and decreased glutamate. Ketamine, as an NMDA receptor antagonist, directly targets glutamate neurotransmission and thus causes similar effects much faster (Bunney and Bunney, 2012). It is not yet known if ketamine's antidepressant effects are due directly to its NMDA antagonism or to its downstream stimulation of AMPA receptors. One hypothesis is that activation of AMPA receptors leads to activation of the ERK/AKT signal transduction cascade, which in turn triggers the mammalian target of rapamycin (mTOR) pathway (Duman and Voleti, 2012). This causes the expression of synaptic proteins and leads to an increased density of dendritic spines, which has been seen with ketamine administration in animals (Li et al., 2010; Li et al., 2011). Hypothetically, this increase in dendritic spines causes the rapid antidepressant effect that has been seen with injections of ketamine.

Chapter 2:

Linking Symptoms to Circuits to Mechanisms

Linking Depression Symptoms to Circuits

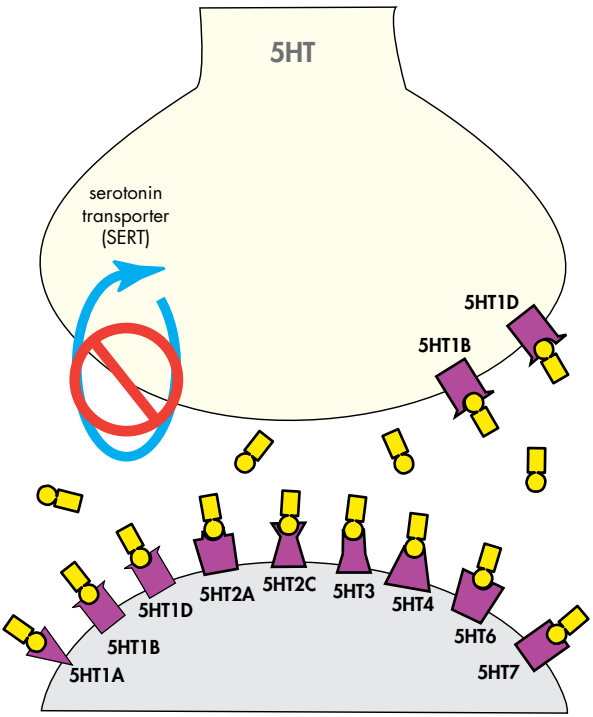


Linking Depression Symptoms to Circuits

FIGURE 2.I. The brain is a neuronal network in which many different types of neurons connect with each other. Since there is topographical localization of function within the brain, one network of brain circuits can regulate entirely different functions than another. Thus, different functions, such as mood, cognition, fear, reward, and arousal, each map to different brain circuits and brain regions (Stahl, 2013; Insel et al., 2010). Correspondingly, symptoms of psychiatric disorders are hypothetically associated with inefficient information processing within various brain circuits, with different symptoms topographically localized to specific brain regions.

Changes in neurotransmitter release within the brain can theoretically alter the "strength" of connectivity of one brain area to the next. Thus, drugs that alter the release of neurotransmitters can modify the connectivity of the brain and thereby potentially reduce symptoms by changing the efficiency of information processing in specific brain circuits. There are numerous symptoms associated with major depression, each of which can be mapped onto brain regions with theoretically inefficient information processing; thus, it is likely that there are numerous networks with altered connectivity involved in the disorder (Stahl, 2013). Theoretically, then, treatment strategies that can change more than one neurotransmitter's release in more than one site have the possibility of changing multiple symptoms linked to multiple circuits (Stahl, 2013; Pehrson and Sanchez, 2014).

Antidepressant Effects: Not Just About Synaptic 5HT



Antidepressant Effects: Not Just About Synaptic 5HT

FIGURE 2.2. Although we can to some extent associate changes in the synaptic amount of a particular neurotransmitter with clinical effects, in reality, each neurotransmitter can bind to multiple receptors, with potentially divergent downstream effects at those different receptors (Ohno et al., 2013). What matters, therefore, is not just the level of a particular neurotransmitter in the brain, but rather in what region and at what receptors the neurotransmitter is binding.

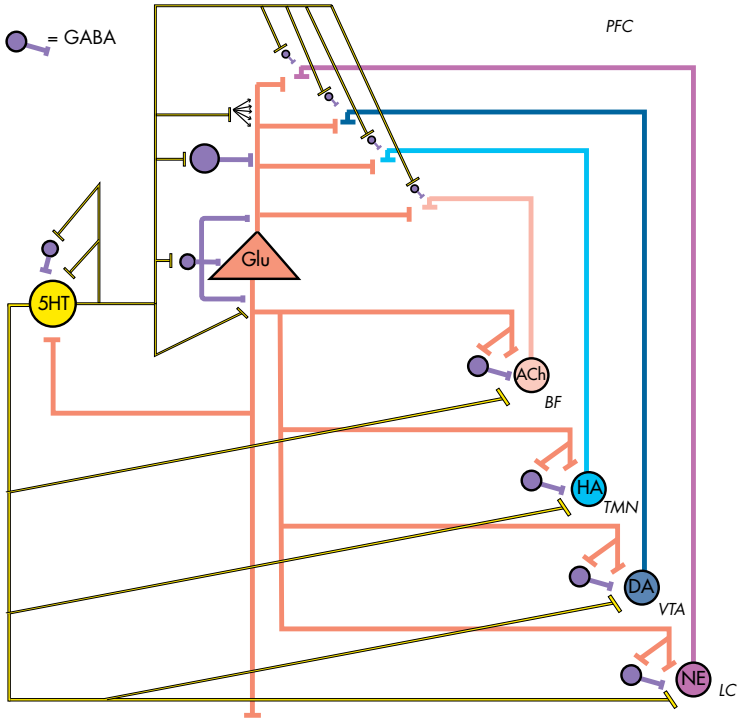
For example, most—though not all—antidepressants are primarily serotonergic in mechanism and in particular block the 5HT transporter, thus increasing synaptic 5HT throughout the brain (and, in fact, the body).

However, there are 7 families of 5HT receptors, with at least 14 subtypes, some that are presynaptic and directly influence the release of 5HT itself, and others that are postsynaptic and may influence the release of any number of different neurotransmitters (Stahl, 2013; Ohno et al., 2013). Furthermore, some serotonin receptor subtypes are inhibitory, while others are stimulatory.

Because blocking the 5HT transporter increases synaptic 5HT, which can then bind at all 14 receptor subtypes, it can be difficult to predict exactly what the net effects linked to the therapeutic actions of a 5HT reuptake inhibitor may be. It may in fact be quite individualized, depending on the unique receptor profile in a particular patient's brain, which itself may be influenced not only by genetics but also by epigenetic processes resulting from stress, psychotropic medications, or many other factors.

A better understanding of the functions of the different receptors and how stimulating or inhibiting them can modulate neurotransmission could theoretically help us better understand the potential effects of antidepressant agents. In this chapter, we focus on the receptors for which the most data are available with respect to potential therapeutic effects in depression: 5HTIA, 5HTIB, 5HT2A, 5HT3, and 5HT7. We also discuss the alpha 2 receptors, which is a known target of mirtazapine. Tables summarizing the actions of antidepressants at these receptors are included at the end of the chapter.

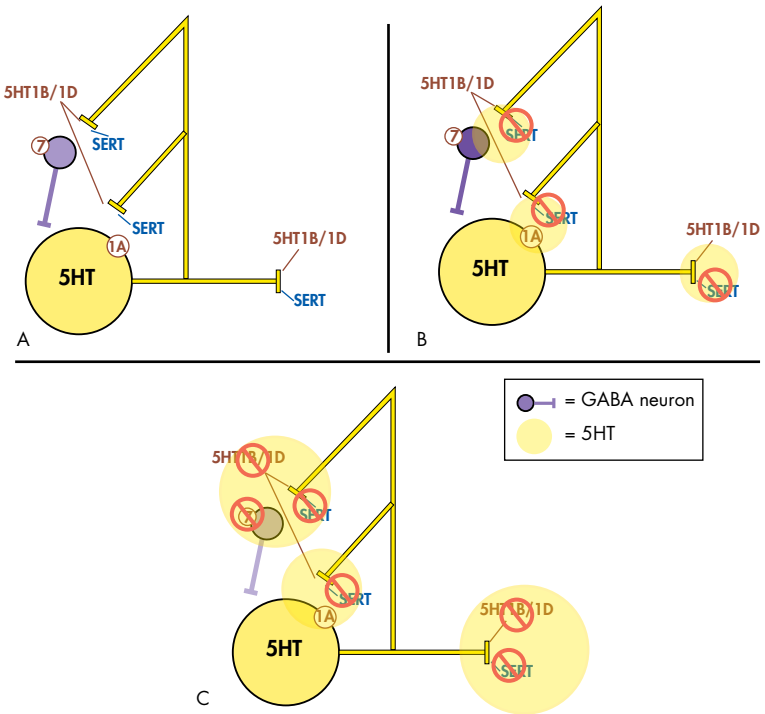
5HT Interacts in a Neuronal Network



5HT Interacts in a Neuronal Network

FIGURE 2.3. 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 as well as the loci for the cell bodies of neurons of other neurotransmitters, such as the locus coeruleus for norepinephrine,the ventral tegmental area for dopamine, the tuberomammilary nucleus of the hypothalamus for histamine, and the basal forebrain for acetylcholine (Mann, 2013; Stahl, 2013). 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, including major depressive disorder (Mann, 2013).

5HT Receptors Regulate 5HT Release: IA, IB, ID, and 7



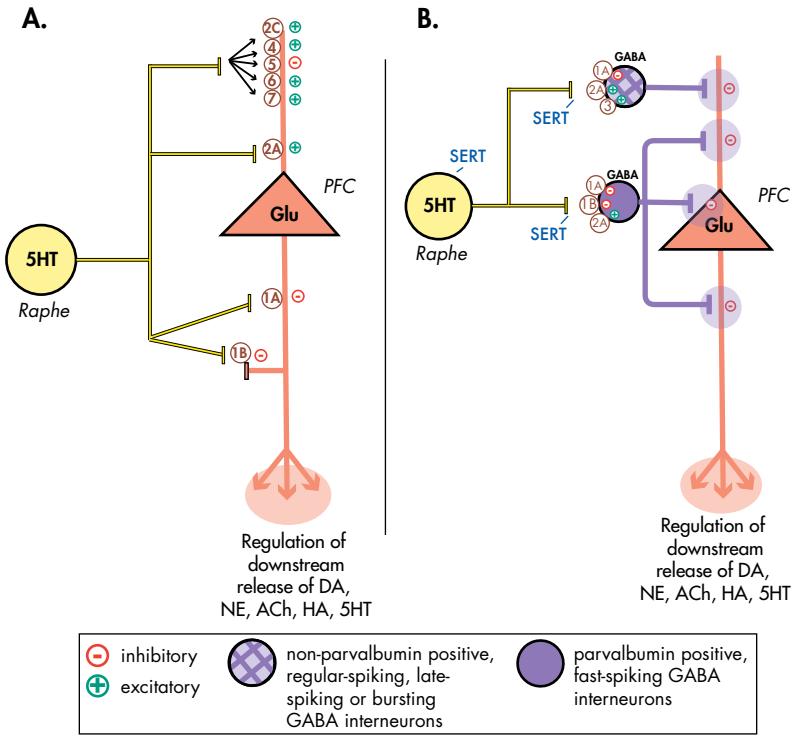
5HT Receptors Regulate 5HT Release: IA, IB, ID, and 7

FIGURE 2.4. (A) 5HT regulates synaptic serotonin levels mainly through the 5HT transporter, which clears 5HT out of the synapse. Serotonin also regulates its own release through presynaptic autoreceptors (Fink and Gothert, 2007). 5HTIA presynaptic autoreceptors are located on the cell body and dendrites and are therefore called somatodendritic autoreceptors. When 5HT binds to these receptors, it causes a shutdown of 5HT neuronal impulse flow and a resultant decrease in 5HT release from the axon terminal (Gardier et al., 1996). Presynaptic 5HTIB and ID receptors are located at the other end of the neuron, on axon terminals, and are therefore called terminal autoreceptors. These receptors detect the presence of 5HT in the synapse, and when stimulated by 5HT, shut down its further release (Adell et al., 2001). 5HT also inhibit its own release by stimulating 5HT7 receptors that innervate GABA neurons in the raphe nucleus. This causes the release of inhibitory GABA, which then turns off further 5HT release (Sarkisyan et al., 2010; Harshing et al., 2004). Yet another mechanism for 5HT self-regulation is through 5HT3 receptors on GABA interneurons (see Figures 2.7 and 2.8).

(B) The benefit of this self-regulating system is clear. Without it, there could be too much buildup of 5HT. This can lead to 5HT toxicity, which can cause side effects and even be fatal. However, this self-regulating system for 5HT also has treatment implications. For example, a 5HT reuptake inhibitor causes accumulation of 5HT in synapses, which then stimulates the autoreceptors to shut down 5HT release. In theory, then the actions of SSRIs are blunted by 5HT autoreceptors. Thus, these autoreceptors must be desensitized in order for the increase in 5HT to be maximized and lead to maximum downstream effects. This is in fact part of the theory behind why 5HT reuptake inhibitors have delayed therapeutic effects (Stahl, 2013).

(C) Theoretically, simultaneous stimulation of 5HTIA presynaptic autoreceptors and blockade of the 5HT transporter may lead to more rapid desensitization of the 5HTIA receptors and therefore hasten the enhanced release of 5HT (Stahl, 2015a); this is supported by preclinical data (Assie et al., 2006; Gardier et al., 1996; Romero et al., 1996). Adding blockade or partial blockade of presynaptic 5HTIB and ID receptors and postsynaptic 5HT7 receptors to 5HT reuptake inhibition may also enhance 5HT release.

5HT Receptors Regulate Glutamate Release Both Directly and Indirectly



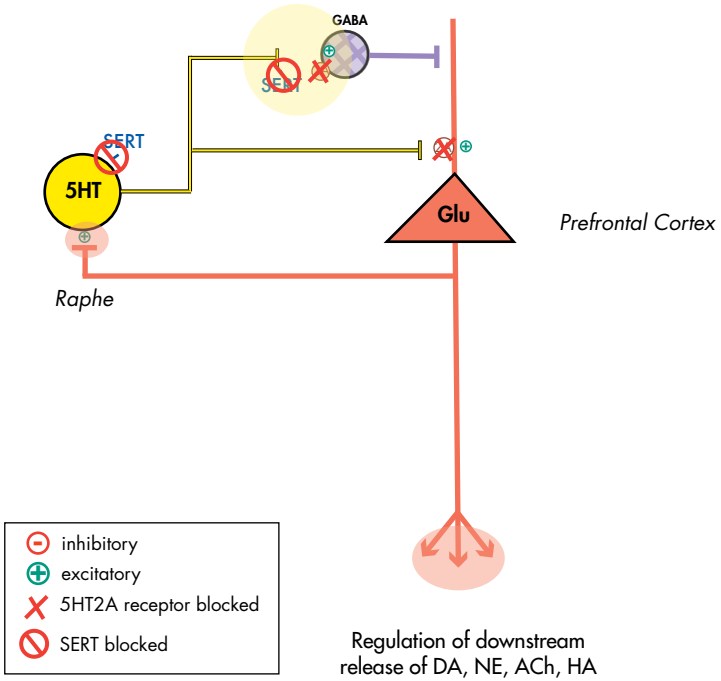
5HT Receptors Regulate Glutamate Release Both Directly and Indirectly

FIGURE 2.5. Most 5HT receptor subtypes are postsynaptic heteroreceptors and reside on the neurons that release any of a number of neurotransmitters. Perhaps one of the most important connections of 5HT neurons to other neurons is in the prefrontal cortex, where 5HT projections synapse with glutamate pyramidal neurons both directly (A) and indirectly via GABA interneurons that in turn terminate upon glutamate neurons (B) (Ciranna, 2006). 5HT's direct influence on glutamate pyramidal neurons can be both excitatory (e.g., at 5HT2A, 5HT2C, 5HT4, 5HT6, and 5HT7 receptors) and inhibitory (at 5HTIA, 5HT5, and possibly postsynaptic 5HTIB heteroreceptors) (Stahl, 2015b). Glutamate neurons, in turn, synapse with the neurons of most other neurotransmitters to regulate their downstream release. Thus, 5HT—or drugs—binding at 5HT receptors can indirectly influence DA, NE, ACh, HA, and 5HT release.

Glutamate output can also be controlled by 5HT receptors on inhibitory GABAergic interneurons. "Fast spiking" GABA interneurons that stain for the calcium-binding protein parvalbumin contain inhibitory 5HTIA receptors and excitatory 5HT2A and 5HT3 receptors (Stahl, 2015b; Puig et al., 2010). A second major population of GABAergic interneurons stains for different neurochemical markers and fires with electrical activity that is regular spiking, late spiking, or bursting in character; these neurons contain inhibitory 5HTIA receptors, possibly inhibitory 5HTIB heteroreceptors, and excitatory 5HT2A receptors (Celada et al., 2013; Kubota, 2014).

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., 5HT2A), 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. For example, 5HT affinity is several times higher for 5HTIA receptors than for 5HT2A or 5HT3 receptors (Stahl, 2015b). Thus, when 5HT concentrations are low, the inhibitory effects of 5HTIA receptors may supercede the excitatory effects of 5HT2A and 5HT3 receptors. As 5HT concentrations rise, the excitatory effects of 5HT2A and 5HT3 receptors may become more prominent.

5HT2A Receptors Regulate Glutamate Release



5HT2A Receptors Regulate Glutamate Release

FIGURE 2.6. Excitatory 5HT2A receptors are present on GABA interneurons and when stimulated cause GABAergic inhibition of glutamate (Artigas, 2013). However, 5HT2A receptors are also located on glutamate pyramidal neurons, and through the stimulation of these receptors can increase glutamate release (Artigas, 2013). Thus, the net effects of 5HT2A stimulation—or of 5HT2A antagonism—on glutamate neurotransmission will depend on multiple factors, including the density of the receptors and the local concentration of 5HT.

There is evidence that 5HT2A receptors are upregulated in patients with depression and that treatment with 5HT2A antagonists results in downregulation of the receptors in conjunction with antidepressant effects (Carr and Lucki, 2011). Knowing exactly which receptors are downregulated with antidepressant treatment—i.e., those on GABA interneurons, glutamate neurons, or both—could help determine the role of these receptors in antidepressant effects.

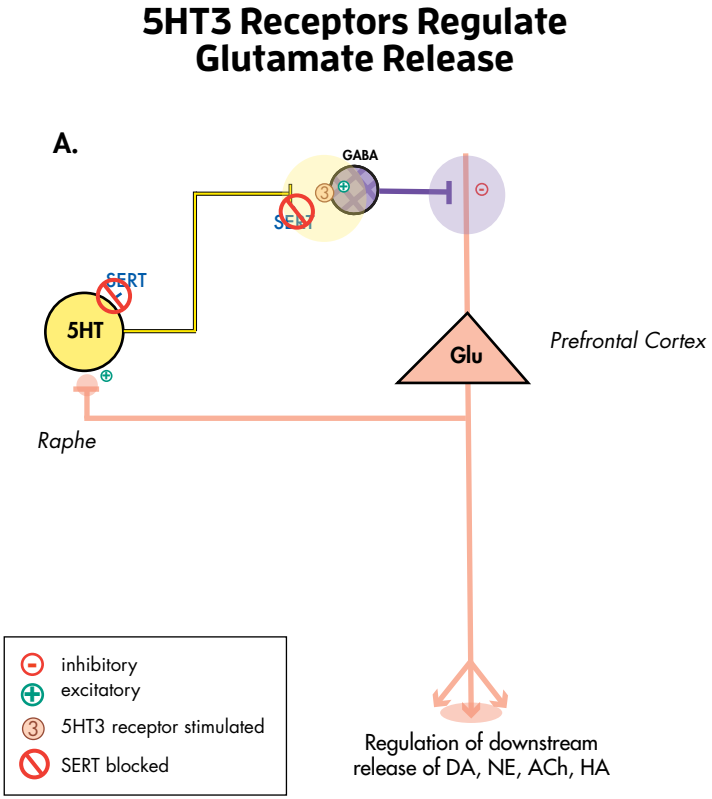
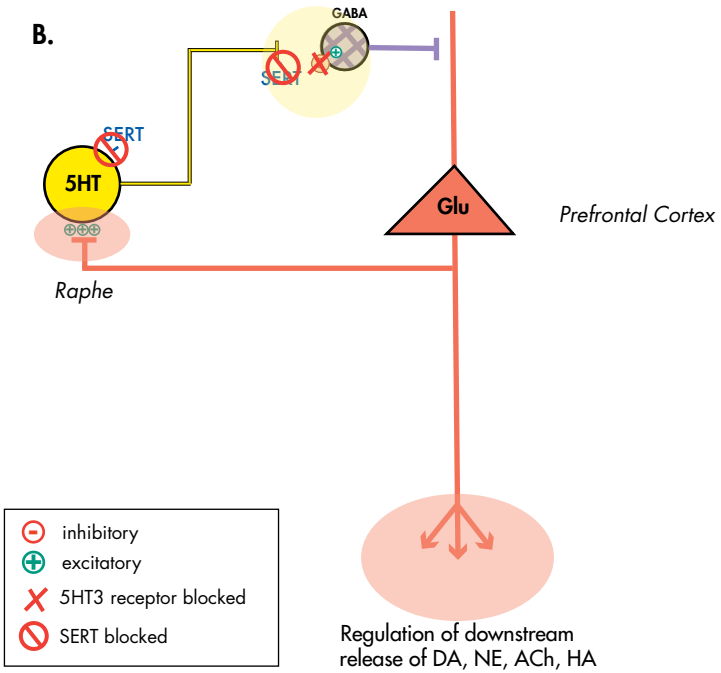


FIGURE 2.7. (A) 5HT binding at 5HT3 receptors on GABA interneurons is stimulatory; thus, it increases GABA release. GABA, in turn, inhibits glutamate pyramidal neurons, reducing glutamate output (Zhou and Hablitz, 1999; Ciranna, 2006). Decreased release of excitatory glutamate means that there may be a resultant decrease in downstream release of neurotransmitters, since pyramidal neurons synapse with the neurons of most other neurotransmitters. These neurotransmitters include DA, ACh, NE, HA, and even 5HT (note the glutamatergic projection to the midbrain raphe). In the presence of a 5HT reuptake inhibitor, the resultant increase in 5HT3 receptor stimulation may further reduce glutamate neurotransmission and downstream release of these neurotransmitters.

5HT3 Receptors Regulate Glutamate Release



(B) Adding antagonism at the 5HT3 receptor removes GABA inhibition and thus disinhibits pyramidal neurons. The increase in glutamate neurotransmission may in turn increase the downstream release of 5HT as well as of the other neurotransmitters. Because DA, ACh, NE, and HA are pro-cognitive, 5HT3 antagonism may theoretically have pro-cognitive effects.

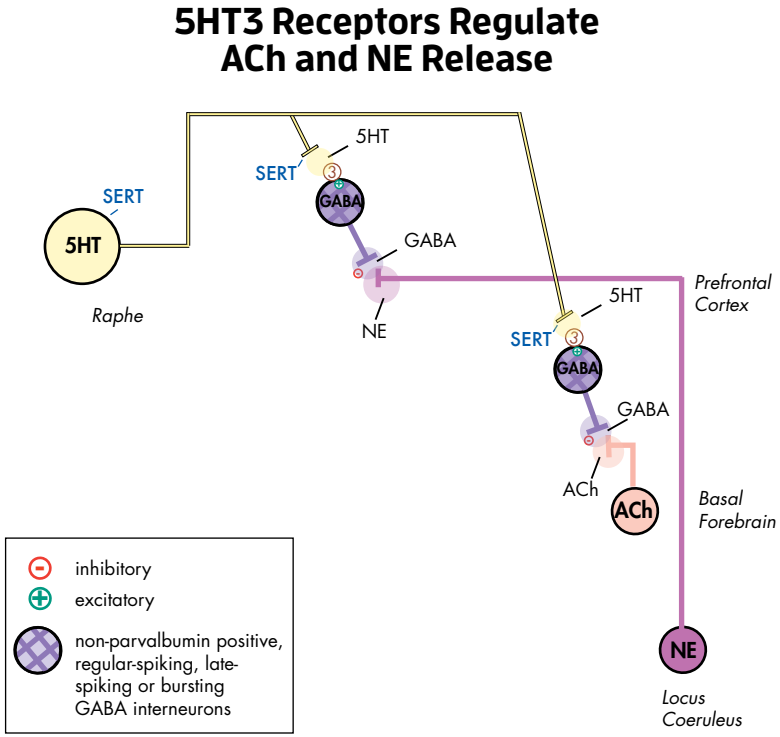


FIGURE 2.8. 5HT3 heteroreceptors located directly on the terminals of neuronal projections in the prefrontal cortex can regulate the release of pro-cognitive neurotransmitters via GABA interneurons (Giovannini et al., 1998; Artigas, 2013). When 5HT is released, it binds to 5HT3 receptors on GABAergic neurons, causing them to release GABA onto noradrenergic and cholinergic neurons, thus reducing the release of NE and ACh, respectively. This may theoretically contribute to symptoms of depressed mood and impaired cognition.

5HT reuptake inhibition may further reduce ACh and NE. In contrast, a 5HT3 antagonist binding at GABAergic neurons inhibits GABA release, which in turn disinhibits, or turns on, noradrenergic and cholinergic neurons, leading to the release of norepinephrine and acetylcholine (Artigas, 2013; Stahl 2015c). The increase in noradrenergic and cholinergic activity may contribute to both antidepressant and pro-cognitive effects.

5HTIA Heteroreceptors May Regulate the Release of Pro-cognitive Neurotransmitters

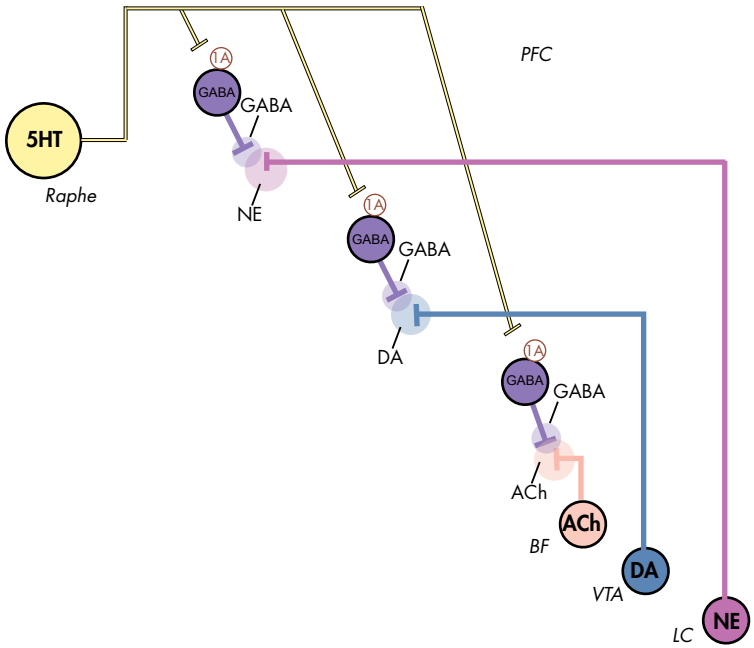


FIGURE 2.9. 5HTIA heteroreceptors on GABA interneurons in the prefrontal cortex can theoretically regulate the release of ACh, DA, and NE (Carr and Lucki, 2011; Artigas, 2013). Stimulation of these receptors is inhibitory; thus, 5HTIA agonism or partial agonism could theoretically reduce GABA output and thus disinhibit ACh, DA, and NE release (Stahl, 2015d). Studies with antidepressants suggest that, unlike 5HTIA presynaptic autoreceptors, 5HTIA postsynaptic heteroreceptors do not desensitize over time; thus, the potential effects on ACh, DA, and NE may sustain throughout treatment (Stahl, 2015d).

This explanation of how 5HTIA agonism modulates ACh, NE, and DA is still theoretical. Preliminary data have also led to the theory that stimulation of 5HTIB heteroreceptors on ACh, HA, DA, and NE neurons may inhibit the release of these neurotransmitters (not shown); thus, partial agonism or antagonism at these receptors could potentially increase the release of these neurotransmitters (Stahl, 2015d). There is also very preliminary evidence that 5HT4 receptor stimulation may regulate ACh and HA release (not shown) (Johnson et al., 2012).

Alpha 2 Receptors Regulate 5HT and NE Release

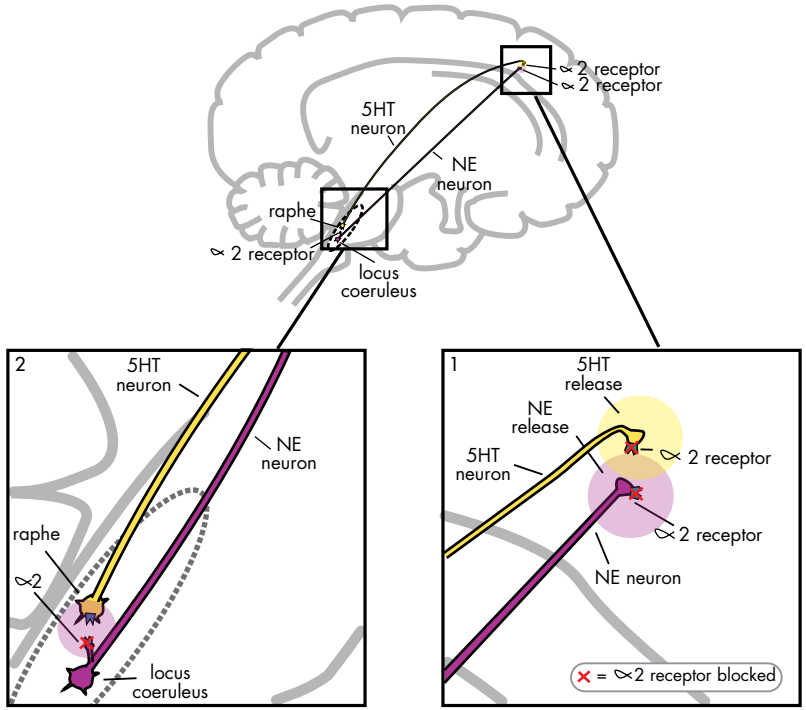


FIGURE 2.10. Alpha 2 adrenergic receptors are presynaptic autoreceptors and thus are the "brakes" on noradrenergic neurons (Stahl, 2013). An alpha 2 antagonist can therefore increase norepinephrine release by binding to these receptors in the locus coeruleus (2) and in the cortex (1). In addition, alpha 2 heteroreceptors are located at the axon terminals of 5HT neurons in the prefrontal cortex (Stahl, 2013). When norepinephrine binds to these receptors, this shuts off 5HT release. An alpha 2 antagonist binding at these receptors blocks this effect and thus can increase 5HT in the prefrontal cortex (1).

Alpha 2 Receptors Regulate 5HT and NE Release

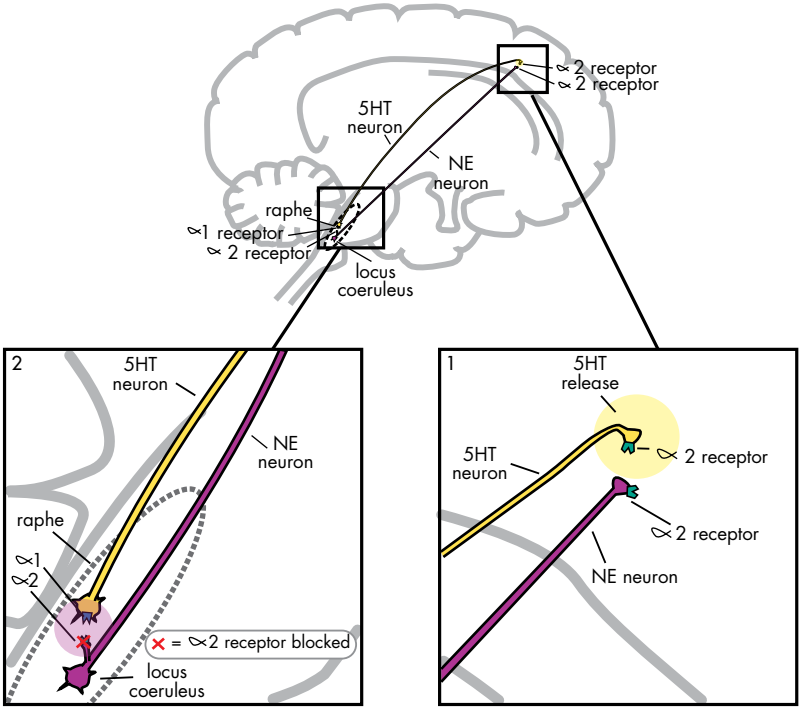
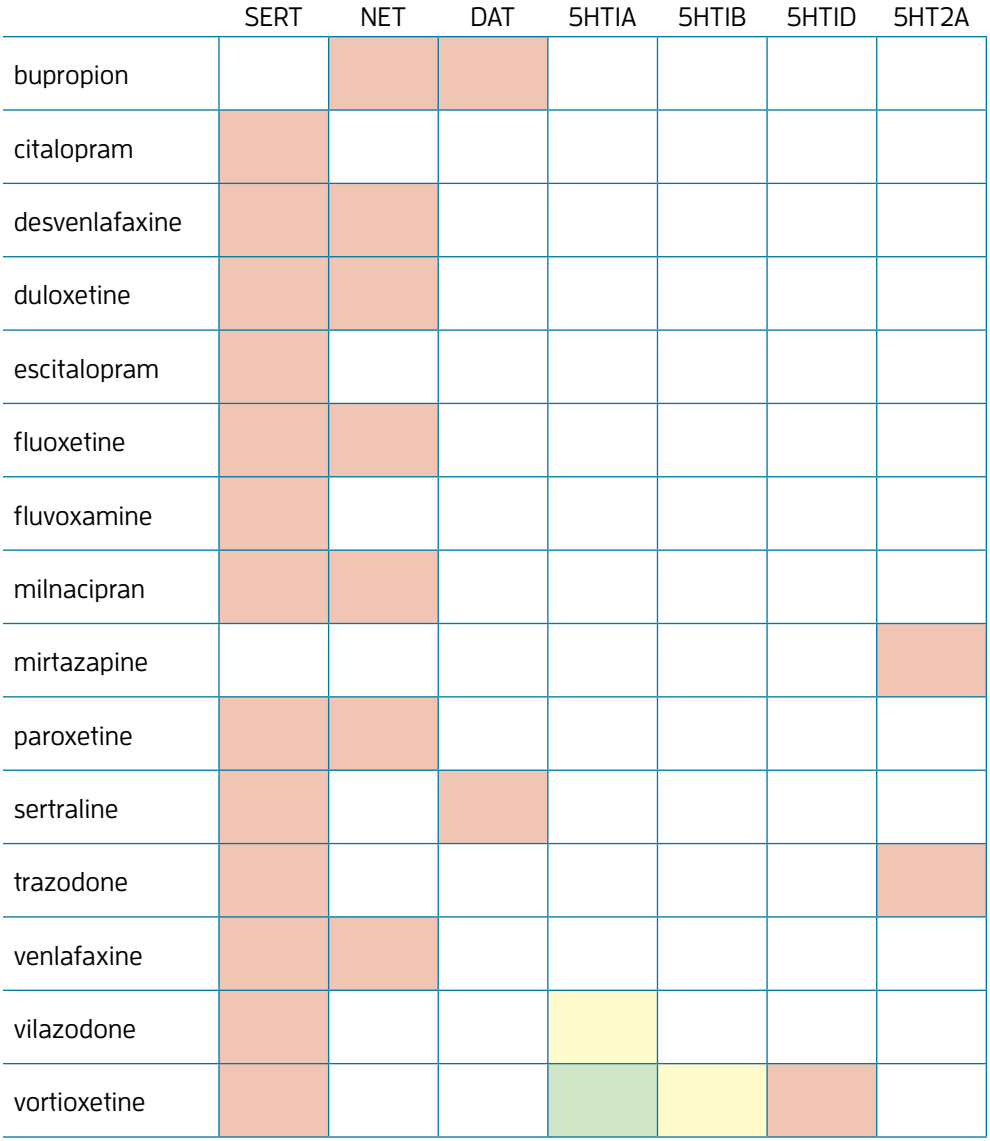


FIGURE 2.II. Furthermore, norepinephrine neurons from the locus coeruleus innervate the cell bodies of serotonergic neurons in the midbrain raphe and stimulate 5HT release from 5HT axon terminals via a postsynaptic alpha I receptor on the 5HT cell body (2) (Stahl, 2013). Thus, when alpha 2 antagonists cause norepinephrine release in the raphe, this also causes stimulation of postsynaptic alpha I receptors on 5HT neuronal cell bodies in the raphe (2), thereby provoking more 5HT release from the downstream axon terminals, such as those in the cortex (1). This is like stepping on the 5HT accelerator. Thus, $\alpha 2$ antagonists both "cut the brake cable" (Figure 2.10) and "step on the accelerator" to facilitate 5HT release.

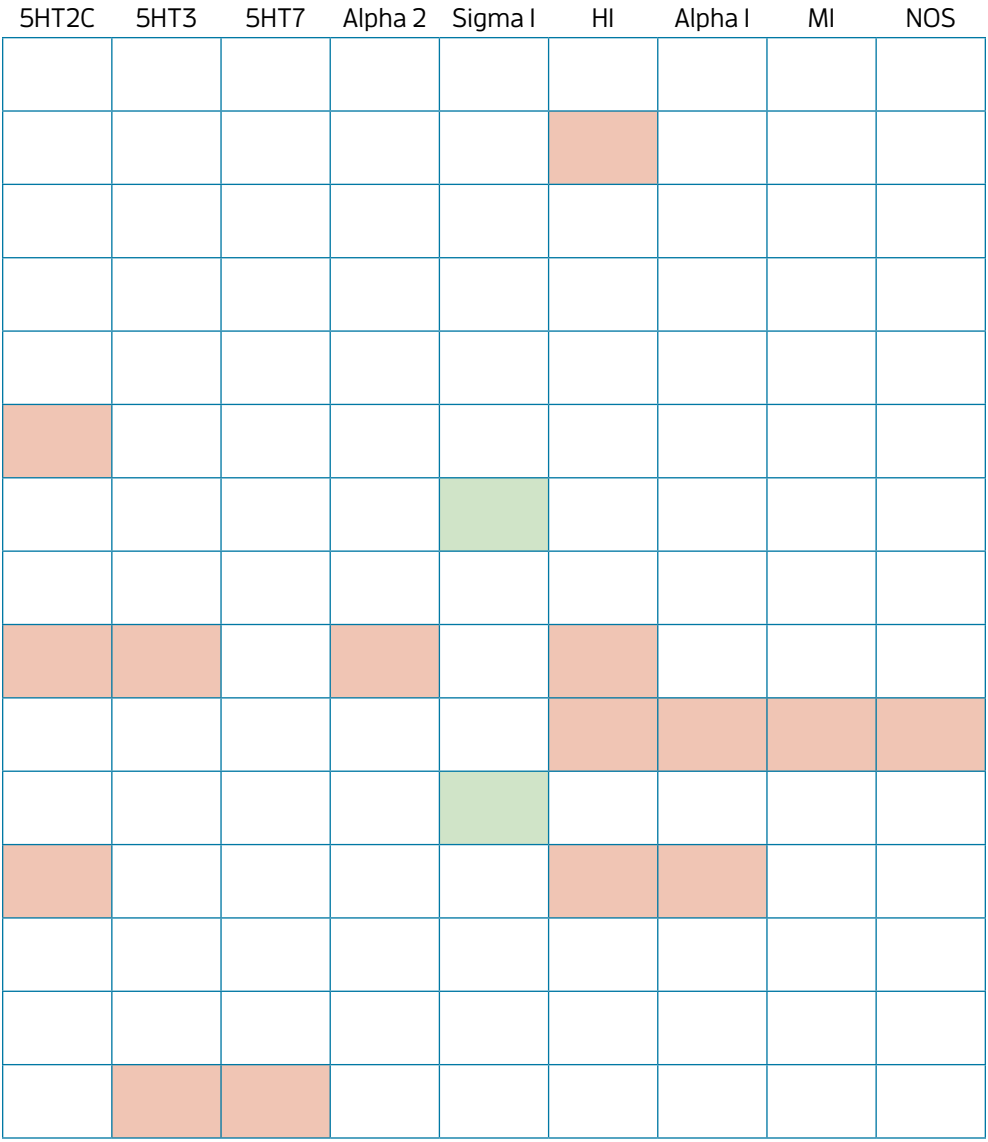
Mechanisms of First-Line Antidepressant Monotherapies



Red: inhibition or antagonism. Yellow: partial agonism. Green: agonism.

FIGURE 2.12. Binding of monoamines to each of their different receptor subtypes can have unique downstream effects. From a pharmacologic perspective, therefore, it may be that moving beyond the modulation of synaptic monoamines in general, and understanding the actions of these neurotransmitters at specific receptors or even combinations of receptors, can potentially be used to more deliberately influence

Mechanisms of First-Line Antidepressant Monotherapies



neurotransmission of many neurotransmitters in the brain and, theoretically, to achieve more targeted therapeutic effects. This could be achieved through monotherapies that target multiple receptors or by combining treatments with different receptor binding profiles. Histamine I antagonism, alpha I antagonism, muscarinic I antagonism, and inhibition of nitric oxide synthase (NOS) are associated with side effects (see Chapter 4).

Mechanisms of Second-Line Antidepressant Monotherapies

	SERT	NET	5HT2A	5HT2C	MAO-A	MAO-B	HI	Alpha I	MI
amitriptyline	■	■	■	■			■	■	■
amoxapine*	■	■	■	■			■	■	■
clomipramine	■	■	■	■			■	■	■
desipramine		■					■	■	■
doxepin	■	■	■	■			■	■	■
imipramine	■	■					■	■	■
isocarboxazid					■	■			
lofepramine		■					■	■	■
maprotiline		■					■	■	■
moclobemide					■				
nortriptyline*	■	■	■	■			■	■	■
phenelzine					■	■			
protriptyline		■					■	■	■
selegiline**					■	■			
tranylcypromine					■	■			
trimipramine	■	■					■	■	■

*Minimal SERT inhibition.
**At 6 mg or lower, MAO-A inhibition occurs only in the brain. At doses above 6 mg, MAO-A inhibition occurs in the gut as well.
Red: inhibition or antagonism.

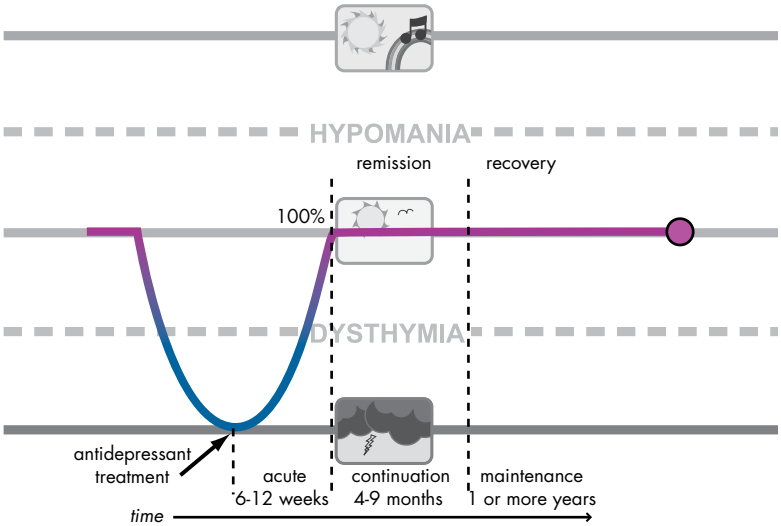
FIGURE 2.13. This table depicts the binding profiles of tricyclic antidepressants and monoamine oxidase inhibitors. Histamine I, alpha I, and muscarinic I antagonism are associated with side effects (see Chapter 4).

Chapter 3:

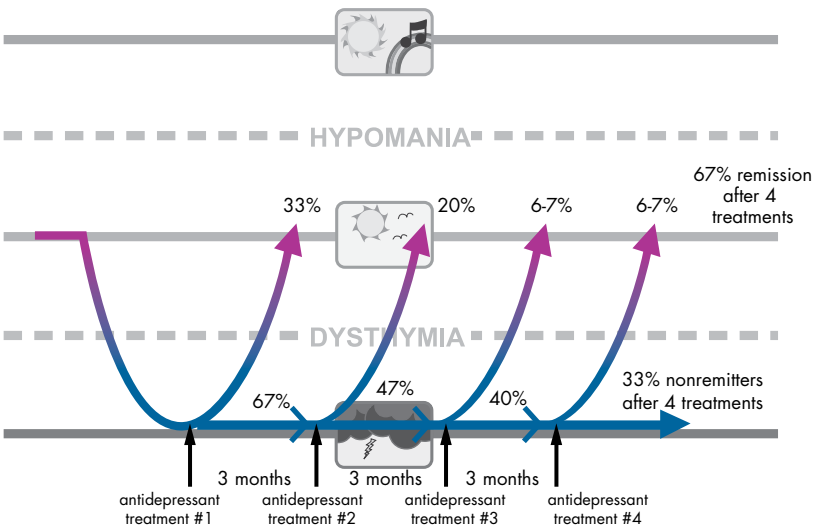
What Is Preventing Remission?

The Faster a Patient With Depression Achieves Remission, the Better the Outcomes

What is Remission?



What Proportion of Major Depressive Disorders Remit?



The Faster a Patient With Depression Achieves Remission, the Better the Outcomes

FIGURE 3.I. Remission—the resolution of essentially all symptoms (often defined in clinical trials as a score of 7 or less on the Hamilton Rating Scale for Depression)—is the initial goal when treating patients with depression. Approximately one-third to one-half of depressed patients will remit during the first trial with any antidepressant (Little, 2009; Saveanu, 2015). Unfortunately, for those who fail to remit, the likelihood of remission with another antidepressant monotherapy goes down with each successive trial. For example, in STAR*D, after a year of treatment with 4 sequential antidepressants taken for 12 weeks each, only two-thirds of patients achieved remission (Rush et al., 2006).

Patients who do not achieve remission not only experience ongoing impairment despite treatment, but are also at increased risk for full relapse compared to those who do remit (Judd et al., 1998; Rush et al., 2006). For example, the relapse rate at one year for patients who remit following their first antidepressant treatment is 33%, while the relapse rate for those who fail to remit is 60% (Rush et al., 2006).

Among individuals who do remit, the likelihood of relapse increases with the number of treatments it takes to get the patient to remission. Thus, for those who remit, the relapse rate ranges from 33% at 12 months after one treatment all the way up to 70% at 6 months after four treatments (Rush et al., 2006). In other words, the protective effect of remission virtually disappears once it takes four treatments to achieve remission.

It is clearly very important to help patients achieve remission as early in the treatment course as possible. Strategies to optimize outcomes for patients potentially include combining mechanisms earlier in the course of treatment (see Chapter 2 for the theoretical effects of binding at specific receptors), prompt and targeted attention to specific residual symptoms (see Chapter 5), communication about and strategies to address side effects (see Chapter 4), and consideration of "wellness" factors beyond mere symptom resolution.

Impediments to Remission: Anxiety and Residual Symptoms

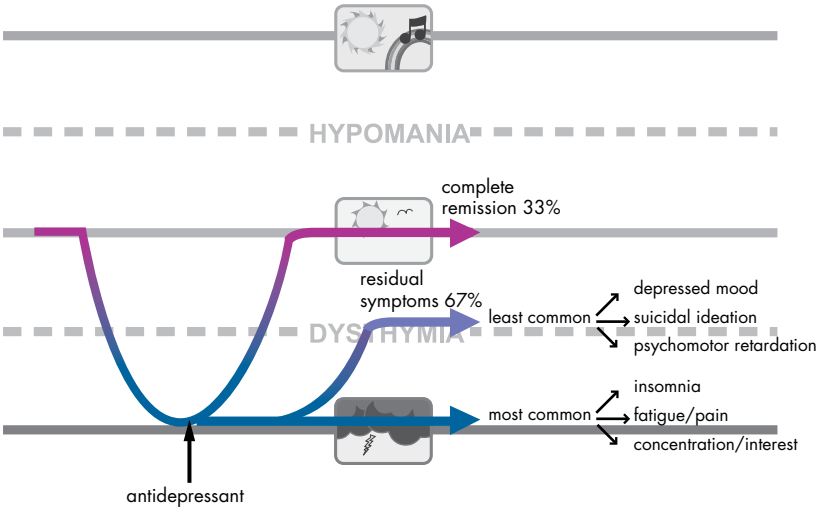


FIGURE 3.2. Residual symptoms are often predictive of poor long-term outcomes, including increased disability, more frequent relapses, relationship and work difficulties, and suicide (Iovieno et al., 2011; Fekadu et al., 2011; Conradi et al., 2010; Kennedy and Paykel, 2004; McClintock et al., 2011; Roca et al., 2011; ten Doesschate et al., 2010). The most common symptoms that persist after antidepressant treatment, thus preventing remission, are insomnia, fatigue and painful physical complaints (even though pain is not part of the formal diagnostic criteria for depression), problems concentrating, and lack of interest or motivation (Stahl, 2013). These particular symptoms present 94% of the time during a depressive episode and persist 44% of the time between depressive episodes (Conradi et al., 2010). In contrast, antidepressants appear to work fairly well in improving depressed mood, suicidal ideation, and psychomotor retardation (Stahl, 2013).

More severe anxiety at baseline is also associated with lower remission rates, independent of depression severity or diagnostic comorbidity (Saveanu et al., 2015).

Impediments to Remission: Antidepressants Don't Work If You Don't Take Them

FIGURE 3.3. Up to a third of patients in a real clinical practice setting never fill their first antidepressant prescription (Stahl et al., 2013). For those who do, many may discontinue their medication without the clinician even knowing: new data from the Collaborative Psychiatric Epidemiology Surveys show that 22% of participants discontinued their antidepressant without the advice or approval of their clinician (Samples and Mojtabai, 2015). Thus, the clinical effectiveness of antidepressants in clinical practice settings may be reduced by this failure of "persistency" of treatment for a long enough period of time to give the drug a chance to work.

The reasons that an individual patient may choose not to adhere to treatment may vary; however, side effects such as sleep disturbance and sexual dysfunction, unaddressed residual symptoms, and lack of information from the treating clinician (i.e., what to expect) have all been shown to predict nonadherence (Masand, 2003; Rush et al., 2006; Warden et al., 2009). Addressing nonadherence is particularly important since antidepressant discontinuation or lack of antidepressant use remains among the highest risks for suicide attempts (Valuck et al., 2009). However, studies suggest that clinicians tend to overestimate adherence rates (Bull et al., 2002; Kobak et al., 2002). Good communication with patients about treatment expectations is key to treatment persistence, as is the prompt implementation of strategies to address residual symptoms and/or side effects (discussed in subsequent chapters).

Monitoring Patients for Response, Side Effects, and Wellness

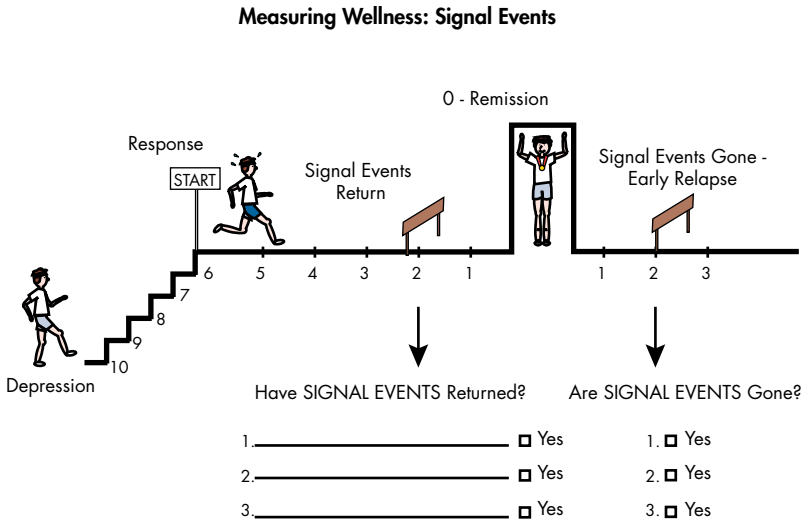


FIGURE 3.4. Monitoring patients by using brief, standardized tools can help to identify patients at risk for relapse or nonadherence (Rost, 2009), and studies suggest that these tools can be integrated fairly easily into clinical practice (Duffy et al., 2008). It is also now possible to use apps that track mood; this can be beneficial in that it can save time, engage the patient, and allow one to monitor mood between visits. Examples of useful apps include T2 Mood Tracker, MoodTracker.com, and MyMoodTracker.com.

Additionally, defining and assessing therapeutic endpoints specific to the individual patient provides a good measure of treatment effects (Trivedi, 2009). Wellness is unique to each individual and encompasses much more than just the elimination of symptoms. Thus, in addition to clinical interview and standardized rating scales, the use of "signal events" can be very useful for tracking response to antidepressant treatment. Using signal events involves asking the patient to define three things in life that he/she normally likes to do but is not doing or not enjoying while depressed, and then tracking whether or not he/she returns to doing those things. The loss of signal events may be the earliest sign of relapse after remission.

Chapter 4:

Common and Troubling Side Effects

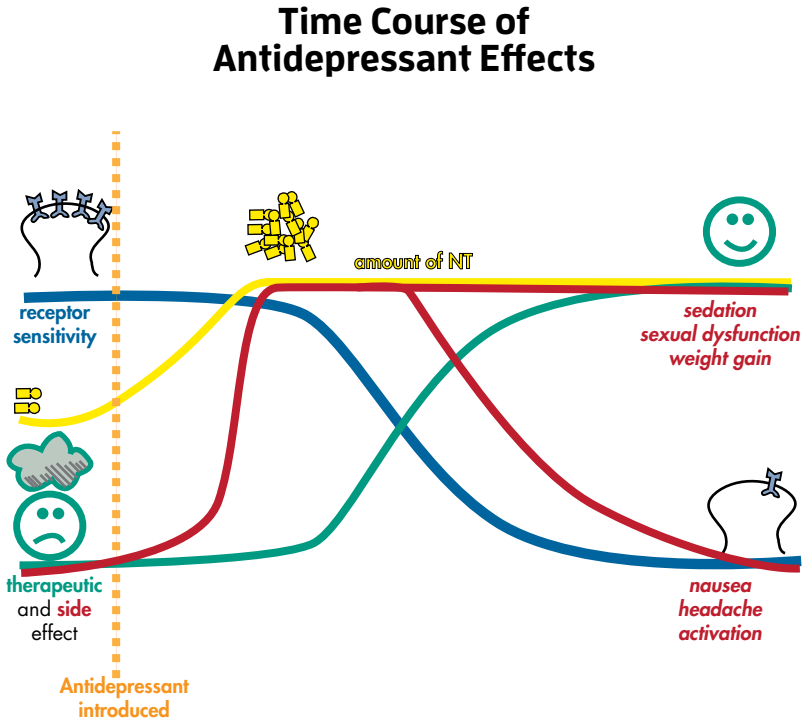


FIGURE 4.1. Do your patients ever ask why clinical improvement with antidepressants is typically delayed by several weeks, whereas side effects are often immediate? Theoretically, as described in Chapter 1, the therapeutic effects of antidepressants may occur because the initial rise in monoamines leads to downstream changes in gene expression.

In contrast, the acute onset of common side effects such as nausea and headache may be directly linked to the relatively rapid change in neurotransmitter levels following antidepressant introduction (Bostwick, 2010; Stahl, 2013; Cascade et al., 2009). These side effects are also typically short lived, however, which may be explained by downstream changes in receptor sensitivity (Stahl, 2013).

Adequate management of side effects is essential in order to improve adherence and maximize the chances of successful treatment. In this chapter, we briefly review the mechanisms associated with common, troubling side effects and discuss treatment and management strategies to address them.

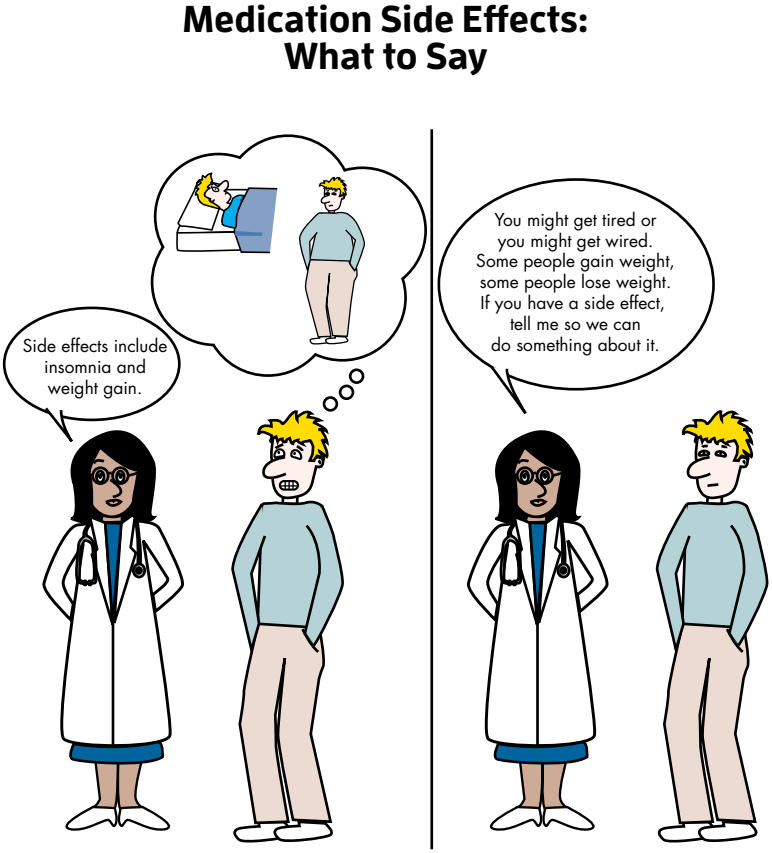


FIGURE 4.2. Side effects with antidepressant treatment are common and are associated with high rates of treatment discontinuation (Gartlehner et al., 2005; Goethe et al., 2007; Bull et al., 2002). It's important to discuss the possibility of side effects with patients; not doing so increases the risk that patients will discontinue medication if side effects develop. That said, there is also risk in telling patients about potential side effects. The nocebo effect—adverse events related to negative expectations about a medical treatment—has been documented in patients receiving placebo in randomized controlled trials of antidepressant effects (Mitsikostas et al., 2014; Mora et al., 2011). In fact, patients receiving placebo not only frequently report side effects, but also specifically report side effects typical of the active medication used in the study (Mora et al., 2011). Thus, when discussing the potential for side effects, it is important to frame the conversation in such a way that one does not create expectations of any particular side effect.

Ultimately, what matters most is for patients to understand that if they do experience a side effect that is bothersome, they should alert their clinician so that strategies can be implemented to address it.

Mechanisms Associated With Troubling Short-Term Side Effects

	Nausea 	Headache 	Activation 
5HT reuptake inhibition 	X	X	X
NE reuptake inhibition 	X		X
DA reuptake inhibition 			Psychomotor
5HT2C antagonism 			X

Adjusting and Augmenting for Tolerability: Nausea and Headache

FIGURE 4.3. In the short term, some of the most troubling side effects related to treatment discontinuation are nausea, headache, and activation (Bostwick, 2010; Cascade et al., 2009; Kelly et al., 2008). Nausea may occur with 5HT reuptake inhibitors because the increase in synaptic 5HT leads to stimulation of 5HT3 receptors. 5HT3 receptors that are localized in the chemoreceptor trigger zone of the brainstem mediate nausea and vomiting, while 5HT3 receptors in the gastrointestinal tract mediate nausea, vomiting, and bowel motility (Stahl, 2013).

Management strategies to alleviate nausea include slower titration, divided dosing, taking the dose with food, and consuming ginger. In addition, blocking 5HT3 receptors can reduce the short-term nausea and vomiting that often occur with 5HT reuptake inhibitors (Stahl, 2013). Selective 5HT3 antagonists that are used to relieve treatment-induced nausea and vomiting include ondansetron, tropisetron, and granisetron. Other adjunct medications that have been used to alleviate nausea include histamine antagonists (e.g., promethazine or prochlorperazine) and proton pump inhibitors (e.g., omeprazole) (Kelly et al., 2008). If nausea is truly intolerable, one can consider switching to an agent that does not increase synaptic 5HT, such as bupropion, or one that blocks 5HT3 receptors, such as mirtazapine or vortioxetine (Kelly et al., 2008; Stahl, 2013).

Headache is also a common side effect of serotonergic antidepressants and may be related to downstream actions at 5HT2A receptors (Srikiatkhachorn, 2001). Headache is generally best managed with the use of over-the-counter pain relievers, although one must be cognizant of the warning regarding the possible increased risk of bleeding when serotonergic antidepressants are combined with anticoagulants (e.g., nonsteroidal anti-inflammatory drugs, or NSAIDs) (Stahl, 2014). Slower titration can also be beneficial. If headache is intolerable for a particular patient, it may be preferable to consider a non-serotonergic antidepressant.

Adjusting and Augmenting for Tolerability: Activation

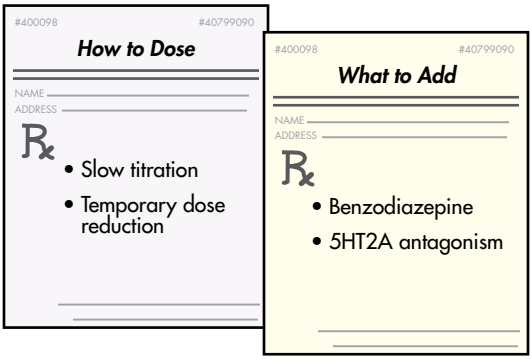


FIGURE 4.4. Activation—ie., anxiety, jitteriness, insomnia—may be related to reuptake inhibition of monoamines by selective 5HT reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs), and the corresponding stimulation of various receptors. However, not all antidepressants are as activating as others, and it may be that secondary properties contribute to activation. In particular, antagonism of 5HT2C receptors may contribute to unwanted activation (Stahl, 2013).,. This usually subsides within the first few weeks of treatment but can be very troubling to patients and is a risk factor for suicidality (McDowell et al., 2011). In fact, anxiety, panic attacks, agitation, and insomnia often precede suicide within hours/days/weeks (McDowell et al., 2011).

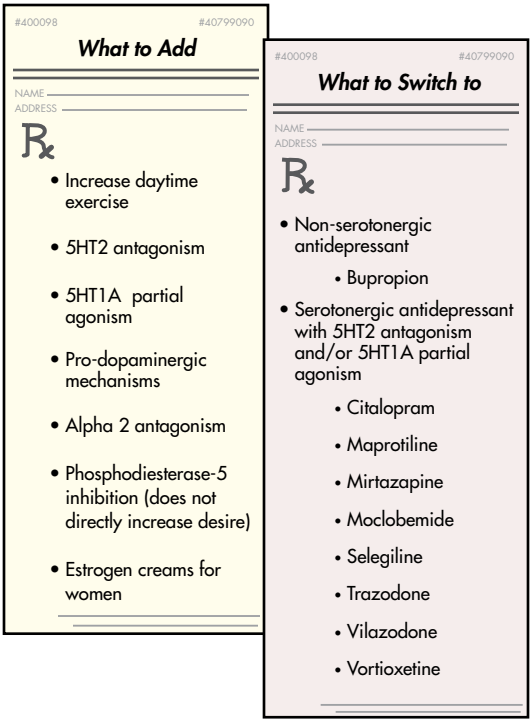
Patients experiencing antidepressant-induced activation should not discontinue their medication; however, some patients may benefit from a temporary reduction in dose or a more gradual uptitration (Kelly et al., 2008). Adding a benzodiazepine or a 5HT2A antagonist in the short term can also be beneficial (Stahl, 2014). Of the SSRIs, fluoxetine, which has 5HT2C antagonism, is the most likely to cause activation, followed by sertraline, which has dopamine reuptake inhibition (Stahl, 2013). These agents may be 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. On the other hand, they may be beneficial for patients with "atypical depression"—i.e., hypersomnia, low energy, and mood reactivity.

Mechanisms Associated With Troubling Long-Term Side Effects

	Sexual Dysfunction 	Weight Gain 	Sedation 
5HT reuptake inhibition	X	X	
5HT2 antagonism	Indirect	X	
Alpha1 antagonism	X	X	X
Histamine 1 antagonism		X	X
Anti-cholinergic	X	X	
NOS inhibition	X		

FIGURE 4.5. In the long term, the most troubling side effects are sexual dysfunction, weight gain, and sedation (Bostwick, 2010; Cascade et al., 2009; Kelly et al., 2008).

Adjusting and Augmenting for Tolerability: Sexual Dysfunction



Adjusting and Augmenting for Tolerability: Sexual Dysfunction

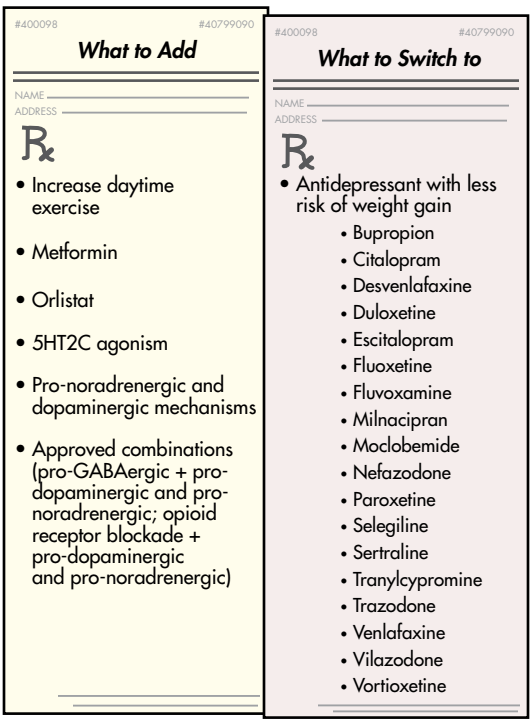
FIGURE 4.6. Sexual dysfunction is a common side effect of antidepressants; however, it can also be a symptom of depression. Thus, before starting any medication, it is important to assess sexual function. Assessment tools include the Arizona Sexual Experiences Scale (ASEX), the Changes in Sexual Functioning Questionnaire (CSFQ), the Psychotropic-Related Sexual Dysfunction Questionnaire (SALSEX or PRESexDQ), and the Sex Effects Scale (SexFX) (Rizvi et al., 2011).

Problems with sexual function can be related to any stage of the human sexual response, including desire, arousal, and orgasm or ejaculation. Common to all stages of the human sexual response is an inhibitory influence of 5HT. Presumably, 5HT has a negative influence on sexual function because it can reduce DA neurotransmission downstream by stimulating 5HT2A and 5HT2C receptors (Morehouse et al., 2011). This is supported by the fact that 5HT2A antagonists do not induce sexual dysfunction. There may be other mechanisms involved in antidepressant-induced sexual dysfunction as well. For example, some antidepressants have anticholinergic effects, some block alpha I adrenergic receptors, and paroxetine inhibits the synthesis of nitric oxide (Stahl, 2013).

Although it may be difficult to motivate depressed patients to exercise, exercise immediately prior to sexual activity may improve sexual desire and global sexual function in women with antidepressant-induced sexual dysfunction (Lorenz et al., 2014). In the same study, simply scheduling regular sexual activity improved orgasm function.

Because antidepressant-induced sexual dysfunction is hypothesized to be largely due to 5HT stimulation of 5HT2 receptors and the associated downstream decrease in DA, agents that lack or counteract this property may be least likely to cause sexual dysfunction (Morehouse et al., 2011). These include 5HT2 antagonists such as trazodone, mirtazapine, and vortioxetine; norepinephrine and dopamine reuptake inhibitors such as bupropion; and monoamine oxidase inhibitors. Antidepressants with secondary properties of alpha 2 antagonism (mirtazapine) or 5HTIA agonism (vilazodone, vortioxetine) may also be less likely to cause sexual dysfunction.

Adjusting and Augmenting for Tolerability: Weight Gain



Adjusting and Augmenting for Tolerability: Weight Gain

FIGURE 4.7. Not surprisingly, weight gain is an intolerable side effect for many patients. From a mechanistic perspective, antagonism of 5HT2C receptors is associated with increased risk for weight gain, especially in combination with histamine I antagonism. This is perhaps due in part to the presence of 5HT2C receptors in the hypothalamus, where appetite is largely regulated.

Meta-analyses have shown that although weight gain is a common side effect of antidepressants, the average weight gain per patient is small (Serretti and Mandelli, 2010). For those patients who experience significant weight gain, it is likely that multiple factors in addition to drug mechanism are contributatory, including genetic predisposition. If significant weight gain occurs, it is typically gradual over the course of many months, and does not appear to be dose-dependent.

Initial assessment may help to identify patients at risk of weight gain due to medical history and lifestyle. All patients prescribed an antidepressant should be monitored for weight, appetite, and metabolic changes, and of course supportive guidance on proper diet and exercise should be offered. For patients with significant weight gain, it may be best to consider switching to an agent with less risk of weight gain, such as bupropion. One could also consider augmentation with metformin, orlistat, bupropion, topiramate, zonisamide, lorcaserin (FDA-approved 5HT2C agonist), or one of the recently approved combination medications (phentermine-topiramate or naltrexone-bupropion).

Adjusting and Augmenting for Tolerability: Sedation

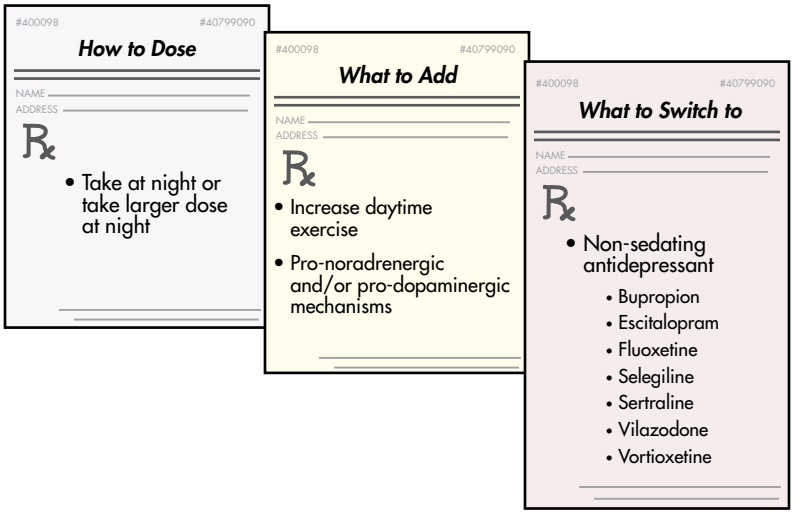


FIGURE 4.8. Sedation is most common with agents that have secondary properties of alpha I antagonism and/or histamine I antagonism, such as many of the tricyclic antidepressants (Morehouse et al., 2011; Stahl, 2013).

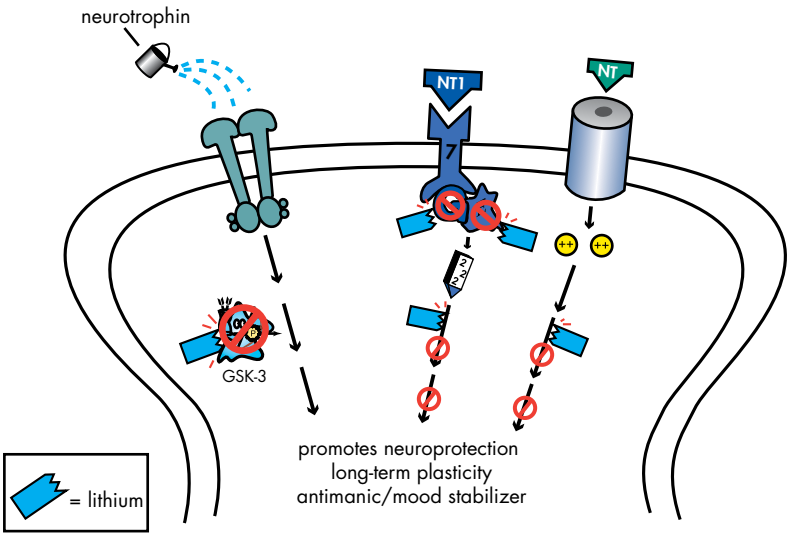
If possible, sedation may best be managed by adjusting the timing of dosing to correspond with sleep time. Increasing daytime exercise can also be beneficial. Otherwise, sedation can be successfully ameliorated through the use of adjunct medications with pro-dopaminergic and/or pro-noradrenergic properties, such as modafinil/armodafinil, bupropion, atomoxetine, or stimulants (Zajecka, 2007; Morehouse et al., 2011). If dosing adjustments and augmentation are not beneficial, one may consider switching to a non-sedating antidepressant.

Chapter 5:

Augmentation and Switching Strategies for Inadequate Response

Lithium

Possible Mechanism of Lithium Action on Downstream Signal Transduction Cascades

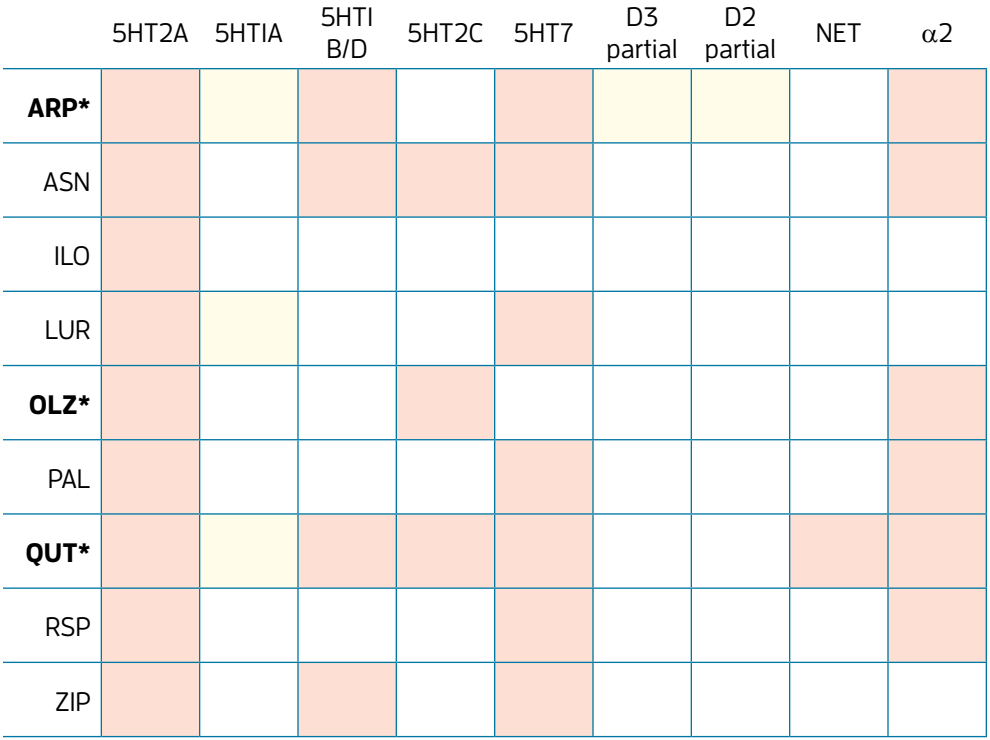


Lithium

FIGURE 5.I. The majority of the studies assessing the efficacy of lithium augmentation in treatment-resistant depression involve tricyclic antidepressants. In a meta-analysis of 10 studies, a significant benefit of lithium vs. placebo was seen; 7 of the studies involved tricyclic antidepressants, and 3 involved SSRIs (Crossley et al., 2007). The authors also conducted a meta-analysis of lithium augmentation for accelerating response to antidepressant treatment. All 5 of the included studies involved tricyclic antidepressants; there was a trend towards accelerated response, but this was not significant (Crossley et al., 2007). The largest study assessing lithium augmentation of newer antidepressants, STAR*D, was not able to confirm a beneficial effect (Nierenberg et al., 2006).

Lithium has been a first-line treatment for bipolar disorder for over 50 years, yet its mechanism of action is still not clear. There is, however, substantial evidence that lithium exerts neuroprotective effects that are likely downstream from its primary mode of action. That is, lithium seems to promote gene expression for growth factors, regulate neuronal plasticity, and induce autophagy, or the clearing of nonfunctional organelles and misfolded proteins that might otherwise contribute to cell death (Chui and Chuang, 2010). These effects most likely occur through the actions of lithium at various potential sites within signal transduction cascades. Candidates for the direct mechanisms of lithium are the inhibition of glycogen synthase kinase 3β (GSK- 3β) (left), the modulation of G proteins (middle), and the inhibition of second messenger enzymes such as inositol monophosphatase (IMPase, right) (Chui and Chang, 2010; Stahl, 2013). GSK-3β is involved in the regulation of inflammation and is, in general, pro-apoptotic. Specifically, it inhibits transcription factors that would otherwise induce the production of cytoprotective proteins such as brain-derived neurotrophic factor (BDNF); thus, its inhibition may be neuroprotective. IMPase indirectly leads to an increase in protein kinase C, which is overactive in mania. Thus, inhibition of IMPase by lithium could potentially reduce manic symptoms.

Atypical Antipsychotics



***Approved.** Red: inhibition/antagonism. Yellow: partial agonism.

ARP: aripiprazole. ASN: asenapine. ILO: lloperidone. LUR: lurasidone. OLZ: olanzapine. PAL: paliperidone. QUT: quetiapine. RSP: risperidone. ZIP: ziprasidone.

FIGURE 5.2. Atypical antipsychotics have been studied as adjuncts to SSRIs and SNRIs, with approvals for aripiprazole, quetiapine XR, and olanzapine (in combination with fluoxetine). Overall, most studies of atypical antipsychotics show a benefit of combination treatment over monotherapy, although effect sizes have been modest, and there is little head-to-head data with other strategies (Citrome, 2010). A recent meta-analysis of 11 randomized controlled trials involving augmentation with aripiprazole, olanzapine-fluoxetine, quetiapine, or risperidone showed that effect sizes were greater in patients with a higher degree of treatment resistance (Wang et al., 2015). Although atypical antipsychotics have the best evidence of efficacy for augmenting antidepressants in patients with inadequate response, their adverse event profiles may still put them later in the treatment algorithm. If used, there may be a higher risk of discontinuation due to adverse effects than with other options (Al-Ruthia et al., 2015).

Triiodothyronine (T3)

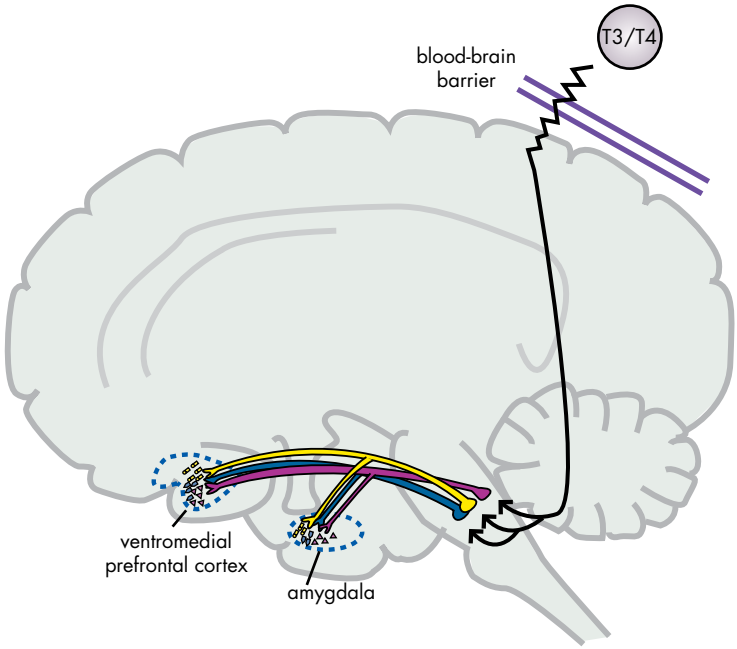
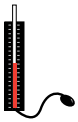


FIGURE 5.3. Thyroid hormones act by binding to nuclear ligand receptors to form a nuclear ligand-activated transcription factor (Stahl, 2013). Abnormalities in thyroid hormone levels have long been associated with depression, and various forms and doses of thyroid hormones have long been utilized as augmenting agents for antidepressants, either to boost their efficacy in patients with inadequate response or to speed up their onset of action. Thyroid hormones have many complex cellular actions, including actions that may boost monoamine neurotransmitters as downstream consequences of the thyroid's known abilities to regulate neuronal organization, arborization, and synapse formation. This may account for how thyroid hormones can enhance antidepressant action in some patients (Stahl, 2013).

There are some data in support of using triiodothyronine (T3) augmentation. T3 was included in the STAR*D study, in which there was a trend favoring it over lithium, although this may have been due to methodological factors (Joffe et al., 2006). A meta-analysis of 8 studies, all of which involved T3 augmentation of tricyclic antidepressants, demonstrated a significantly increased response rate over placebo and a number needed to treat of 4.3 (Aronson et al., 1996). There are mixed results for augmenting SSRIs with T3, with placebo-controlled studies showing no benefit (Connolly and Thase 2011).

Side Effects for Evidence-Based Augmentation Strategies




	Move-ment	Prolactin	Weight Gain	Sedation	Blood Pressure	Musca-rinic	Other
LI	0	0	++	++	0	0	tremor, GI, acne, thyroid, renal
T3	0	0	0	0	0	0	hyper-thyroidism
ARP	+	0	0	0	0	0	nausea, activation at low dose
OLZ	+	+	+++	++	+	++	
QUT	0	0	++	+++	++	++	

FIGURE 5.4. Unfortunately, some of the best evidenced augmenting options share some of the most troubling side effects of antidepressants, such as weight gain and sedation. In addition, these agents can also have some troubling side effects not common with antidepressants, as shown here (Stahl, 2014).

Dosing and Monitoring Guidelines for Evidence-Based Augmentation Strategies

Dosing Guidelines	
Drug	Daily Dose
lithium	0.6–1.0 mEq/L (bipolar depression)
T3	25–50 mcg
aripiprazole	2–10 mg
olanzapine	5–20 mg
olanzapine-fluoxetine combination	3/25 mg–12/50 mg
quetiapine	150–300 mg

Monitoring Guidelines (Mahli et al., 2012; Grandjean and Aubry, 2009)					
Parameter	Baseline	Monthly	3 Months	6 Months	12 Months
Renal	Lithium		Lithium		
Thyroid*				Lithium	Lithium
Calcium				Lithium	Lithium
Serum Levels				Lithium**	
Weight	Atypical	Atypical†	Atypical	Lithium	Atypical, Lithium
BP	Atypical		Atypical‡		Atypical
Fasting Lipids	Atypical		Atypical		Atypical
Fasting Glucose	Atypical		Atypical		Atypical

*Periodic for T3.

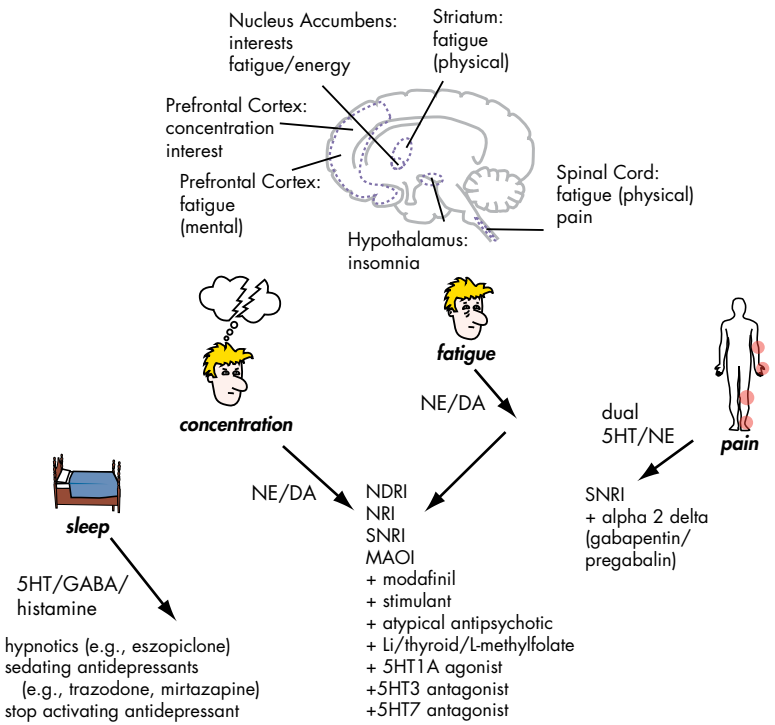
**Every 1–2 weeks until the desired serum concentration is achieved, then every 2–3 months for the first 6 months. Once the patient is stabilized, monitor every 6–12 months.

†For the first 3 months of treatment.

‡For the first year of treatment.

FIGURE 5.5.

Specific Strategies for Common Residual Symptoms



Specific Strategies for Common Residual Symptoms

FIGURE 5.6. It's not surprising that so many patients with depression also have disturbed sleep patterns. Physiological measurements of circadian rhythms, which are key to the regulation of sleep/wake cycles, show multiple alterations, including less fluctuation in body temperature over 24 hours, the same pattern but elevated cortisol levels over 24 hours, and the absence of a spike in melatonin levels at night (Dallaspezia and Benedetti, 2011; Pail et al., 2011). For many patients with depression, residual sleep disturbances can be successfully ameliorated through the use of sedative hypnotics or sedating antidepressants or through the discontinuation of antidepressants with activating properties. In addition to pharmacological measures, psychosocial and/or chronobiological strategies (e.g., cognitive behavioral therapy), such as sleep hygiene education and bright light therapy, respectively, may provide relief from insomnia (Thase et al., 2010; Dallaspezia and Benedetti, 2011; Watanabe et al., 2011).

Fatigue may be the most common symptom of depression, affecting as many as 97% of patients with MDD (Papakostas et al., 2006). For patients who are experiencing fatigue, antidepressant agents that can increase norepinephrine and dopamine systems are recommended. These agents include norepinephrine and dopamine reuptake inhibitors (NDRIs), norepinephrine reuptake inhibitors (NRIs), 5HT and norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAOIs). Adjunctive medications, including modafinil, stimulants, and certain atypical antipsychotics, may also provide relief from fatigue (Stahl, 2013).

Difficulty concentrating may also be alleviated by increasing norepinephrine and dopamine; this can be achieved through the same medication options as for fatigue. In addition, 5HT3 antagonists and 5HT7 antagonists may improve cognition (Stahl, 2013).

Painful physical symptoms are present in many patients with depression and are associated with worse clinical outcomes and increased healthcare costs (Gerrits et al., 2012). Strategies for treating pain in patients with MDD include both SNRIs and alpha-2 delta ligands such as gabapentin and pregabalin (Stahl, 2013).

Summary of Other Potential Augmenting Options

Option	Notes	References
Buspirone	Makes sense mechanistically but data are mixed/weak	Connolly and Thase 2011; Trivedi et al., 2006; Appelberg et al., 2001
Stimulants	Limited data show trend of benefit	Trivedi et al., 2013
DA agonists	Best evidence for modafinil/armodafinil; some evidence for pramipexole and ropinirole	Goss et al., 2013; Aiken, 2007; Cassano et al., 2005; Calabrese et al., 2010; Fava et al., 2005
Bright light therapy	Positive data in seasonal affective disorder; meta-analysis in non-seasonal suggests possible efficacy; 30 min at 10,000 lux or 2 hrs at 2,500 lux; administer light 7.5–9.5 hrs after evening melatonin secretion; patient should be 60–80 cm from the light source	Golden et al., 2005; Pail et al., 2011
SAMe	Positive controlled study; dosed 800–1600 mg/d oral or 200–400 mg/d IM; best absorbed if taken 20 min before a meal; not recommended in first trimester	Papakostas et al., 2010
Omega-3	Multiple meta-analyses suggest modest efficacy; 60% EPA (of total EPA+DHA) needed; 1–3 g/d is generally safe (including dietary intake)	Lin et al., 2012; Martins et al., 2012; Freeman et al., 2006; McNamara and Shawn, 2013
Folate	Positive controlled studies for l-methylfolate; dose depends on formulation	Bottiglieri, 2013
Exercise	5 times/week, 45–59 minutes/session was best in studies	Rethorst et al., 2009; Rimer et al., 2012
NAC	Positive data in bipolar depression; dosed 1,000 mg twice per day	Berk et al., 2013
Melatonin	Insufficient data; do not use in pregnancy	Dolberg et al., 1998; Serfaty et al., 2010
Vitamin D	Mixed data	Khoraminya et al., 2013; Kjaergaard et al., 2012

FIGURE 5.7.

Second-Line Agent: Tricyclic Antidepressant

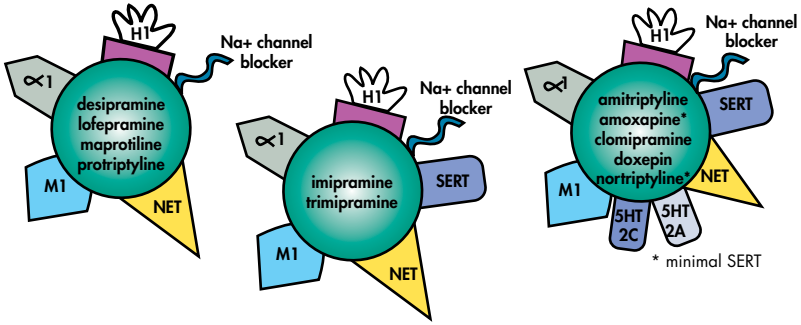


FIGURE 5.8. Tricyclic antidepressants (TCAs) are one of the oldest classes of antidepressants and are quite efficacious. In terms of therapeutic effects, all TCAs block the reuptake of norepinephrine. Some are also potent inhibitors of the 5HT reuptake pump. In addition, some are antagonists at 5HT2A and 2C receptors (Stahl, 2013). As explained in Chapter 2, the blockade of these receptors is associated with a possible improvement of sleep and a potential antidepressant action in its own right, possibly linked to a consequent increase in norepinephrine and dopamine release (Stahl, 2013). The blockade of these receptors may also reduce the likelihood of sexual dysfunction as a side effect of 5HT reuptake inhibition (Morehouse et al., 2011).

As a class, TCAs may not be as tolerable as some newer antidepressants because they are all antagonists at histamine I receptors (causing sedation and weight gain), alpha I adrenergic receptors (causing orthostatic hypotension), and muscarinic cholinergic receptors (causing constipation, dry mouth, and blurred vision) (Stahl, 2013). In addition, TCAs block voltage-sensitive sodium channels in the heart and the brain. The most important of these secondary actions (at least in the event of overdose) may be the blockade of voltage-sensitive sodium channels because it has the potential to cause coma and seizures as well as cardiac arrhythmias, cardiac arrest, and even death. Nonetheless, these agents are efficacious, and they are important treatment options for patients who do not respond to first-line agents, perhaps particularly so for patients with melancholic depression.

Second-Line Agent: Monoamine Oxidase Inhibitors (MAOIs)

Drugs that boost norepinephrine should be used with caution with MAOIs			
Decongestants	**Stimulants**	**Antidepressants with norepinephrine reuptake inhibition**	**Others**
Phenylephrine	Amphetamine	Most TCAs*	Phentermine
Pseudoephedrine	Methylphenidate	NRIs	Local anesthetics containing vasoconstrictors
	Modafinil	SNRIs	Cocaine, methamphetamine
	Armodafinil	NDRIs	Do not use: tramadol, tapentadol

Foods to AVOID*	**Foods ALLOWED**
Dried, aged, smoked, fermented, spoiled, or improperly stored meat, poultry, and fish	Fresh or processed meat, poultry, and fish
Broad bean pods	All other vegetables
Aged cheese	Processed cheese slices, cottage cheese, ricotta cheese, cream cheese, yogurt
Tap and unpasteurized beer	Bottled or canned beer and alcohol
Marmite	Brewer's and baker's yeast
Soy products/tofu	Peanuts
Banana peel	Bananas, avocados, raspberries
Sauerkraut, kimchee	
Tyramine-containing nutritional supplements	
*Not necessary for 6-mg transdermal or low-dose oral selegiline	

Second-Line Agent: Monoamine Oxidase Inhibitors (MAOIs)

FIGURE 5.9. MAOIs are one of the oldest and most effective treatment options for depression, but dietary and drug interactions have restricted their use, especially as newer agents with fewer interactions have become available. In short, there are 2 general types of potentially dangerous interactions with MAOIs that a practitioner must understand: those that can raise blood pressure by sympathomimetic actions and those that can cause a potentially fatal 5HT syndrome by 5HT reuptake inhibition.

Drugs and foods (i.e., those that contain tyramine) that cause an increase in norepinephrine have the potential to increase blood pressure (Wimbiscus et al., 2010). Normally, MAO-A (a subtype of MAO) destroys norepinephrine, keeping it in balance. When MAO-A inhibition takes place in the presence of a noradrenergic drug or tyramine, the consequent increase in norepinephrine is not countered by its destruction via MAO-A. This can lead to a very large accumulation of norepinephrine and cause dangerous vasoconstriction and elevated blood pressure. Some blood pressure elevations can be very large, sudden, and dramatic, causing a condition known as a hypertensive crisis, which can rarely cause intracerebral hemorrhage or even death (Stahl, 2013).

Because of the risk of hypertensive crisis, drugs that can increase noradrenergic activity should only be combined cautiously with MAOIs, while monitoring blood pressure, in patients for whom the benefits are greater than the risks. Cold medications with other mechanisms (e.g., antihistamines) are safe unless they also inhibit 5HT reuptake.

Tyramine content in food can instigate a hypertensive crisis in patients taking MAOIs. The average person can ingest approximately 400 mg of tyramine before their blood pressure is elevated (Stahl, 2013). However, as little as 10 mg of dietary tyramine may increase blood pressure when MAO-A is essentially knocked out by high doses of an MAOI (Da Prada et al., 1988); thus, 40 mg is considered a high-tyramine meal. Every prescriber should counsel patients taking the classic MAOIs about diet and keep current with the tyramine content of the foods their patients wish to eat.

Second-Line Agent: Monoamine Oxidase Inhibitors (MAOIs)

Drugs to avoid due to risk of 5HT toxicity (Gillman, 2005; Hartrick and Rozek, 2011)

Antidepressants	Drugs of abuse	Opioids	Others
SSRIs	MDMA (ecstasy)	meperidine	non-subcutaneous sumatriptan
SNRIs	cocaine	tramadol	chlorpheniramine
clomipramine	methamphetamine	methadone	brompheniramine
St. John's wort	high-dose or injected amphetamine	fentanyl	procarbazine?
			dextromethorphan

FIGURE 5.10. A potentially much more dangerous combination than that of adrenergic stimulants and MAOIs is the combination of agents that inhibit 5HT reuptake and those that inhibit MAO. The inhibition of the 5HT transporter (SERT) leads to the increased synaptic availability of 5HT (Dvir and Smallwood, 2008). Similarly, the inhibition of MAO leads to increased 5HT levels. In combination, these 2 mechanisms can cause excessive stimulation of postsynaptic 5HT receptors; this has the potential to cause fatal 5HT toxicity (Gillman, 2007).

Switching to and From an MAOI

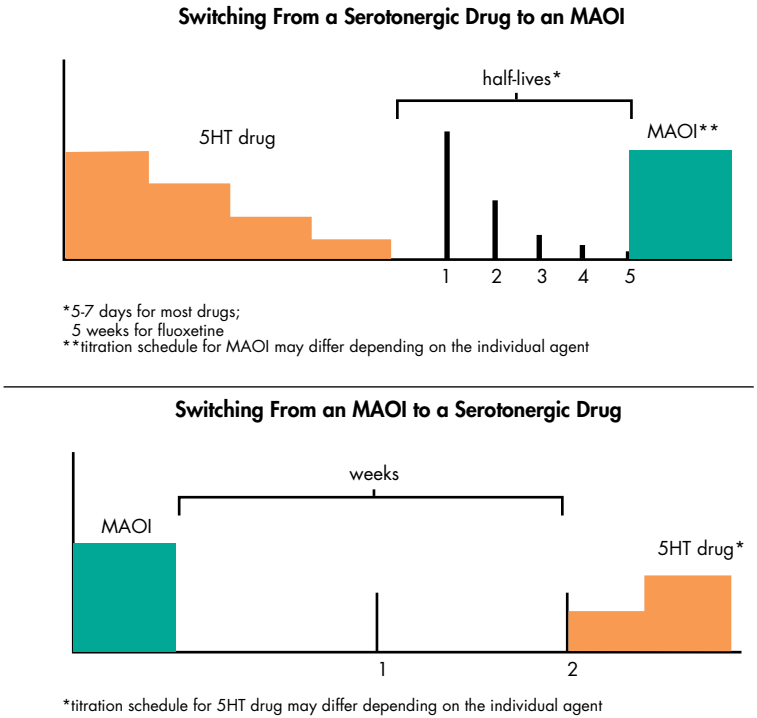
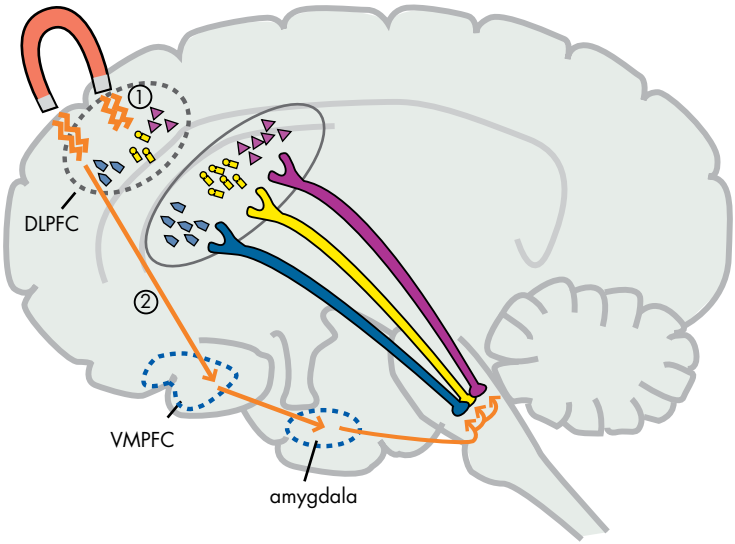


FIGURE 5.II. Because of the risk of 5HT toxicity, complete washout of a 5HT reuptake inhibitor is necessary before starting an MAOI (Stahl, 2013). The 5HT reuptake inhibitor must be down-titrated as tolerated, after which one must wait 5 half-lives (5–7 days for most drugs) of the serotonergic medication before starting the MAOI. If one is switching from an MAOI to a 5HT reuptake inhibitor, one must wait at least 14 days following the discontinuation of the MAOI before starting the serotonergic drug.

Because there is a required gap in antidepressant treatment when switching to or from an MAOI, clinicians may be concerned about managing symptoms during that time period. Depending on the individual patient's situation, there are many medication options, including benzodiazepines, Z drug sedative hypnotics, trazodone, lamotrigine, valproate, several other anticonvulsants, stimulants, and atypical antipsychotics.

Transcranial Magnetic Stimulation (TMS)



Transcranial Magnetic Stimulation (TMS)

FIGURE 5.12. Transcranial magnetic stimulation (TMS) is another brain stimulation treatment approved for treatment-resistant depression, defined as having failed at least 1 (not 2) pharmacological trials in the current episode. TMS involves an electromagnetic coil placed on the scalp, creating a magnetic field that penetrates the skull by a few centimeters. This depolarizes neurons in the superficial cortex; through neural pathways, this local stimulation causes functional changes in other brain regions. Its approval is based on a study of high-frequency TMS over the left dorsolateral prefrontal cortex (DLPFC) (O'Reardon et al., 2007); however, low-frequency right-sided stimulation has also shown efficacy (Blumberger et al., 2013).

Presumably, daily stimulation of this brain area for up to an hour over several weeks causes activation of various brain circuits, leading to an antidepressant effect (Stahl, 2013). If this activates a brain circuit beginning in the DLPFC and connecting to other brain areas such as the ventromedial prefrontal cortex (VMPFC) and the amygdala, with connections to the brainstem centers of the monoamine neurotransmitter system, the net result would be monoamine modulation (2). In this way, TMS would act through a mechanism unlike the known chemical antidepressants. However, TMS also releases neurotransmitters locally, in the area of the magnet, depolarizing the neurons and releasing neurotransmitters from their axon terminals in the DLPFC (1). This is a second mechanism unlike chemical antidepressants, and it may explain why TMS can be effective in patients who do not respond to chemical antidepressants. Finally, since all the effects of TMS are in the brain, there are no peripheral side effects such as nausea, weight gain, blood pressure changes, or sexual dysfunction. In fact, there are few if any side effects except headache (Berlim et al., 2013; Kalu et al., 2012).

TMS is generally done on an outpatient basis, requires no anesthesia, and does not involve loss of consciousness. The only contraindication is for patients with ferromagnetic metal within 30 cm of where the electromagnetic coil is placed. Caution should be exercised for patients with an implantable device controlled by physiological signs.

Electroconvulsive Therapy (ECT)

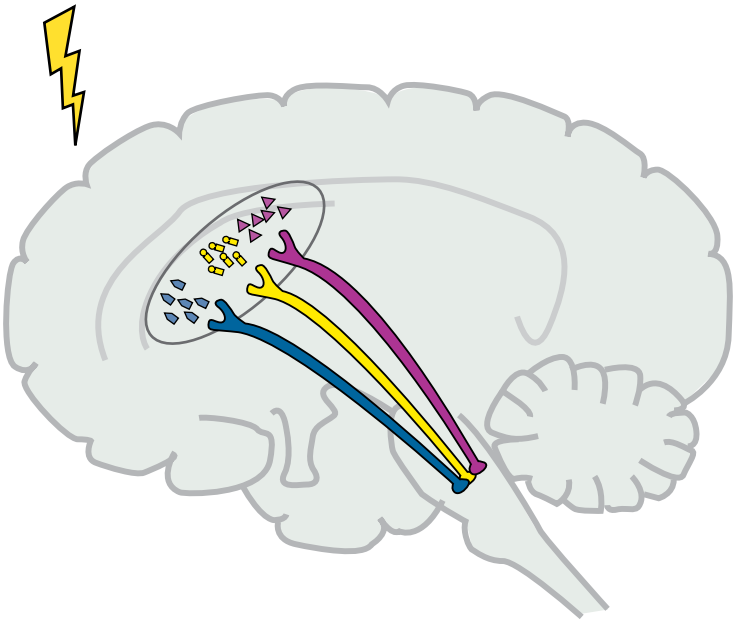


FIGURE 5.13. Electroconvulsive therapy (ECT) is the classic therapeutic form of brain stimulation for depression. The mechanism is unknown but may be related to increased neuroplasticity following the probable mobilization of neurotransmitters caused by the seizure (Stahl, 2013; Pittenger and Duman, 2008). ECT has the highest rates of response and remission of any antidepressant treatment and should be considered for patients with severe major depressive disorder that is not responsive to pharmacotherapy or psychotherapy (Gelenberg et al., 2010). The best data are for acute treatment; the data for maintenance treatment are not as clear cut. Existing data and expert clinical opinion support the idea that ECT response can be relatively rapid, often occurring after a few sessions. Consistent with this, the acute course of ECT treatment is typically 6–12 treatments and does not generally exceed 20 treatments (Gelenberg et al., 2010; Husain et al., 2004). However, treatment should continue until symptoms remit or plateau, as relapse rates are higher if ECT is discontinued prematurely. The most common side effect with ECT is memory loss. The frequency of sessions can affect memory side effects, as patients may not have sufficient time to recover from memory effects prior to the next session (Gelenberg et al., 2010; Husain et al., 2004). Right unilateral ECT is reported to have fewer memory effects than bilateral ECT (Gelenberg et al., 2010). There is no evidence to support any particular medication for maintaining response after ECT, although the best research is in the older literature and suggests nortriptyline or lithium.

Summary

- Wellness means something different to each patient
- Actions at specific receptors or even combinations of receptors can theoretically yield targeted therapeutic effects, and can be achieved through multi-mechanism monotherapies or augmentation/combination strategies
- When combining, adding an atypical antipsychotic has the best evidence but tolerability considerations
- Specific residual symptoms and side effects may be treated by targeting specific mechanisms

References

Adell A et al. J Neurochem. 2001; 79(1): 172–182.
Aiken CB. J Clin Psychiatry 2007;68(8):1230-6.
Al-Ruthia YS et al. Res Social Adm Pharm 2015;11(2):228-40.
Appelberg BG et al. J Clin Psychiatry 2001;62:448-53.
Aronson R et al. Arch Gen Psychiatry 1996;53:842-8.
Artigas F. Pharmacol Ther 2013;137:119-31.
Assié MB et al. Br J Pharmacol 2006; 149(2): 170–178.
Barbon A et al. Neurochem Int 2011;59(6):896-905.
Berk M et al. Trends Pharmacological Sci 2013;34(3):167-77.
Berlim MT et al. Neuropsychopharmacology 2013;38:543-51.
Blumberger et al. Curr Psychiatry Rep 2013;15(7):368.
Bostwick JM. Mayo Clin Proc 2010;85(6):538-50.
Bottiglieri T. Psychiatr Clin North Am 2013;36:1-13.
Brunoni AR et al. Int J Neuropsychopharmacol 2008;11:1169-80.
Bull SA et al. JAMA 2002;288:1403-9.
Bunney BG, Bunney WE. Int J Neuropsychopharmacol 2012;15:695-713.
Calabrese JR et al. J Clin Psychiatry 2010;71(10):1363-70.
Carr GV, Lucki I. Psychopharmacology (Berl) 2011; 213(2–3): 265–287.
Cascade E et al. Psychiatry (Edgmont) 2009;6(2):16-8.
Cassano P et al. Can J Psychiatry 2005;50(6):357-60.
Celada P et al. Frontiers Integrative Neurosci 2013;7:25.
Chiu CT, Chuang DM. Pharmacol Ther 2010;128:281-304.
Ciranna L. Curr Neuropharmacol 2006;4(2):101-14.
Citrome L. Postgrad Med 2010;122(4):39-48.
Connolly RK, Thase ME. Drugs 2011;71(1):43-64.
Conradi HJ et al. Psychol Med 2011;41(6):1165-74.

Crossley NA, Bauer M. J Clin Psychiatry 2007;68(6):35-40.
Crupi R et al. Curr Med Chem 2011;18(28):4284-98.
Dallaspezia S, Benedetti F. Expert Rev Neurother 2011;11(7):961-70. 14.
Da Prada M et al. J Neural Transm Suppl 1988;26:31-56.
Dolberg OT et al. Am J Psychiatry 1998;155(8):1119-21.
Dowlati Y et al. Biol Psychiatry 2010;67:446-57.
Duffy FF et al. Psychiatr Serv 2008;59(10):1148-54.
Duman RS, Voleti B. Trends Neurosci 2012;35(1):47-56.
Dvir Y, Smallwood P. Gen Hosp Psychiatry 2008;30(3):284-7.
Fava M et al. J Clin Psychiatry 2005;66(1):85-93.
Fekadu A et al. Can J Psychiatry 2011;56(9):549-57.
Fink KB, Gothert M. Pharmacol Rev. 2007; 59(4): 360–417.
Freeman MP et al. J Clin Psychiatry 2006;67:1954-67.
Gardier AM et al. Fundam Clin Pharmacol. 1996; 10(1): 16–27.
Gartlehner R et al. Int Clin Psychopharmacol 2005;20:59-69.
Gelenberg AJ et al. APA 2010. Available at http://www.psychiatryonline.com/pracGuide/PracticePDFs/PG_Depression3rdEd.pdf.
Gerrits MM et al. Pain 2012;153(2):429-36.
Gillman PK. Br J Pharmacol 2007;151(6):737-48.
Giovannini MG et al. J Pharmacol Exp Ther 1998;285(3):1219-25.
Goethe JW et al. J Clin Psychopharmacol 2007;27:451-8.
Golden RN et al. Am J Psychiatry 2005;162(4):656-62.
Goss AJ et al. J Clin Psychiatry 2013;74(11):1101-7.
Grandjean EM, Aubry JM. CNS Drugs 2009;23(4):331-49.
Harshing LG Jr et al. Neurochem Res 2004;29(8):1487-97.
Howren MB et al. Psychosom Med 2009;71:171-86.
Husain MM et al. J Clin Psychiatry 2004;65(4):485-91.
Insel T et al. Am J Psychiatry 2010;167(7):748-51. 2011;71(1):43-64.
Iovieno N A et al. Depress Anxiety 2011;28(2):137-44.
Joffe RT et al. Can J Psychiatry 2006;51:791-3.
Johnson DE et al. J Pharmacol Exp Ther 2012;341:681-91.
Judd LL et al. J Affect Disord 1998;50(2-3):97-108.
Kalu UG et al. Psychological Med 2012;42(9):1791-800.
Karege F et al. Psychiatry Res 2002;109:143-8.
Kelly K et al. Dialogues Clin Neurosci 2008;10(4):109-18.
Kennedy N, Paykel ES. J Affect Disord 2004;80(2-3):135-44.

Khoraminya N et al. Aust N Z J Psychiatry 2013;47(3):271-5.
Kjærgaard M et al. Br J Psychiatry 2012;201(5):360-8.
Kobak KA et al. J Clin Psychiatry 2002;63:727-32.
Kubota Y. Current Opin Neurobiology 2014;26:7-14.
Li N et al. Science 2010;329(5994):959-964.
Li N et al. Biol Psychiatry 2011;69(8):754-761.
Little A. Am Fam Physician 2009;80(2):167-72.
Lin PY et al. Mol Psychiatry 2012;17:1161-3.
Lorenz TA et al. Depression Anxiety 2014;31:188-95.
Mahli GS et al. Bipolar Disord 2012;14(suppl 2):1-21.
Mann JJ. Philos Trans R Soc Lond B Biol Sci 2013;368(1615):20120537.
Martins JG et al. Mol Psychiatry 2012;17(12):1144-9.
Masand PS. Clin Ther 2003;25(8):2289-304.
McClintock SM et al. J Clin Psychopharmacol 2011;31(2):180-6.
McDowell AK et al. Mayo Clin Proc 2011;86(8):792-800.
McNamara RK, Strawn JR. PharmaNutr 2013;1:41-9.
Miller AH et al. Biol Psychiatry 2009;65(9):732-41.
Mitsikostas DD et al. Psychiatry Res 2014;215:82-6.
Mora MS et al. Philos Trans R Soc Lond B Biol Sci 2011;366(1572):1879-88.
Morehouse R et al. J Affective Disord 2011;132:S14-20.
Musazzi L et al. Neurochem Int 2011;59(2):138-49.
Nierenberg AA et al. Am J Psychiatry 2006;163:1519-30.
Ohno et al. Biol Pharm Bull 2013;36(9):1396-1400.
O'Reardon JP et al. Biol Psychiatry 2007;62(11):1208-16.
Pace TW et al. Brain Behav Immun 2007;21:9-19.
Pail G et al. Neuropsychobiology 2011;64(3):152-62.
Palazidou E. Br Med Bull 2012;101:127-45.
Papakostas GI et al. Biol Psychiatry 2006;60(12):1350-5.
Papakostas GI et al. Am J Psychiatry 2010;167:942-8.
Pariante CM. Ann NY Acad Sci 2009;1179:144-52.
Pehrson AL, Sanchez C. CNS Spectr 2014; 19(2): 121–133.
Pittaluga A et al. Neuropharmacology 2007;53(1):27-36.
Pittenger C, Duman RS. Neuropsychopharmacology 2008;33(1):88-109.
Puig MV et al. J Neurosci 2010;30(6):2211-22.
Racagni G, Popoli M. Dialogues Clin Neurosci 2008;10(4):385-400.

Rethorst CD et al. Sports Med 2009;39(6):491-511.
Rimer J et al. Cochrane Database Syst Rev 2012;(7):CD004366.
Rizvi SJ et al. J Psychosom Res 2011;70:99-109.
Roca M et al. J Affect Disord 2011;134(1-3):235-41.
Romero L et al. Neuropsychopharmacology 1996;15(4):349-60.
Rost K. Nord J Psychiatry 2009;63:17-21.
Rush AJ et al Am J Psychiatry 2006;163(11):1905-17.
Samples H, Motjabai MHS. Psychiatr Serv 2015;66(5):455-62.
Sarkisyan G et al. Behav Brain Res 2010;209(1):99-108.
Saveanu R et al. J Psychiatr Res 2015;61:1-12.
Sen S et al. Biol Psychiatry 2008;64:527-32.
Serfaty MA et al. Int Clin Psychopharmacol 2010;25(3):132-42.
Serretti A, Mandelli L. J Clin Psychiatry 2010;71(10):1259-72.
Srikiatkhachorn A. Curr Pain Headache Rep 2001;5(6):537-44.
Stahl SM. New York, NY: Cambridge University Press;2013.
Stahl SM. New York, NY: Cambridge University Press;2014.
Stahl SM. CNS Spectr 2015a;20(2):93-7.
Stahl SM. CNS Spectr 2015b;in press.
Stahl SM. CNS Spectr 2015c;in press.
Stahl SM. CNS Spectr 2015d;in press.
ten Doesschate MC et al. J Clin Psychiatry 2010;71(8):984-91.
Thase ME et al. Prim Care Companion J Clin Psychiatry 2010;12(6):pii:PCC.08m00676.
Trivedi MH et al. N Engl J Med 2006;354:1243-52.
Trivedi MH. J Clin Psychiatry 2009;70 Suppl 6:26-31.
Trivedi MH et al. J Clin Psychiatry 2013;74(8):802-9.
Valuck RJ et al. J Clin Psychiatry 2009;70(8):1069-77.
Wang HR et al. Int J Neuropsychopharmacol 2015;Epub ahead of print.
Warden D et al. Int J Neuropsychopharmacol 2009;12(4):459-73.
Watanabe N et al. J Clin Psychiatry 2011;72(12):1651-8. 16.
Wimbiscus M et al. Cleve Clin J Med 2010;77(12):859-82.
Zajecka JM. J Clin Psychiatry 2007;68(suppl 10):23-7.
Zhou FM, Hablitz JJ. J Neurophysiol 1999;82(6):2989-99.

CME Posttest and Certificate

Release/Expiration Dates
Print Monograph Released: August, 2015
Electronic Books Released: December, 2015
CME Credit Expires: August, 2018

CME Posttest Study Guide
The posttest questions have been provided below solely as a study tool to prepare for your online submission. ***NOTE: Posttests can only be submitted online. Faxed/mailed copies of the posttest cannot be processed*** and will be returned to the sender.

1. A 34-year-old man presents with a major depressive episode characterized by depressed mood, insomnia, problems concentrating, weight loss, and suicidal ideation. Which of the following symptoms is the most likely to be residual following otherwise successful treatment?

    A. Depressed mood
    B. Insomnia
    C. Suicidal ideation

2. A 24-year-old man with moderate depression achieves remission after 16 weeks on a therapeutic dose of an antidepressant. According to the neurotrophic hypothesis of depression, which of the following is most likely true of his BDNF expression before and after his successful treatment?

    A. BDNF expression was abnormally low while he was depressed, and increased during antidepressant treatment
    B. BDNF expression was abnormally high while he was depressed, and decreased during antidepressant treatment
    C. BDNF expression was normal while he was depressed, and was unaffected during antidepressant treatment

3. A current leading hypothesis posits that depression may be related to:

    A. Glutamate hypoactivity
    B. Glutamate hyperactivity

4. A 25-year-old patient with first-episode major depressive disorder is being prescribed an antidepressant. The time course for therapeutic effects of antidepressants correlates with:

    A. Increase in presynaptic neurotransmission
    B. Increase in postsynaptic neurotransmission
    C. Changes in receptor sensitivity and expression

5. 5HT3 antagonists may increase release of which of the following?

    A. Acetylcholine
    B. Dopamine
    C. Glutamate
    D. B and C
    E. A, B, and C

6. A clinician has decided to adminster an alpha 2 antagonist to his patient. Alpha 2 antagonists have what effect on neurotransmission?

    A. Decrease norepinephrine and increase serotonin
    B. Decrease norepinephrine and decrease serotonin
    C. Increase norepinephrine and decrease serotonin
    D. Increase norepinephrine and increase serotonin

7. A 44-year-old woman has been taking an SSRI for 3 months. At her follow-up visit, she informs you that although her mood has improved with treatment, she is having problems engaging in sexual activity with her husband. What pharmacological treatment option might be appropriate to address her sexual dysfunction?

    A. 5HT2 antagonist
    B. 5HT3 antagonist
    C. 5HT6 antagonist

8. A 36-year-old patient has only partially responded to his second monotherapy with a first-line antidepressant. Which of the following has the best evidence of efficacy for augmenting antidepressants in patients with inadequate response?

    A. Adding an atypical antipsychotic
    B. Adding buspirone
    C. Adding a stimulant

9. N A 36-year-old man with depression has had 3 therapeutic trials of serotonin reuptake inhibitors (SRIs) without notable improvement. His clinician is now considering switching the patient's SRI to a monoamine oxidase inhibitor (MAOI). Which of the following is an appropriate switching strategy in this situation?

    A. Cross-titrate SRI with MAOI
    B. Discontinue SRI, then initiate MAOI
    C. Discontinue SRI, then wait 5 half-lives before initiating MAOI
    D. Discontinue SRI, then wait I4 days before initiating MAOI

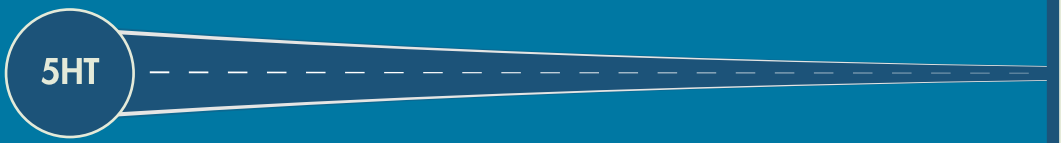
CME Online Posttest and Certificate

There is no posttest fee nor fee for CME credits.

I. Read the book in sequence, evaluating the content presented
2. Complete the posttest and activity evaluation, available only online at **www.neiglobal.com/CME** (under "Book")
3. Print your certificate (if a score of 70% or more is achieved)

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

Posttest and Evaluation



ISBN 1-4225-0089-6
90000
9 781422 500897

NEI PRESS
www.neiglobal.com