Understanding and Managing the Pieces of Major Depressive Disorder
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Overview
The successful treatment of major depressive disorder depends largely on a proper diagnosis, an adequate choice of medication, and adherence to pharmacotherapy. This booklet explains the mechanisms of action of antidepressants, illustrates how to treat women across their life cycle, and discusses various comorbidities of major depressive disorder.

Target Audience
This CME activity has been developed for MDs specializing in psychiatry. There are no prerequisites for this activity. Physicians in all specialties who are interested in psychopharmacology, as well as nurses, psychologists, and pharmacists, are welcome for advanced study.

Statement of Need
The following unmet needs regarding major depressive disorder were revealed following a critical analysis of activity feedback, expert faculty assessment, literature review, and through new medical knowledge:

• Clinicians continue to amass information on the neurobiology of depression, which can only help to serve their understanding of symptoms and select appropriate treatment options
• Treatments for major depressive disorders continue to evolve; older generation antidepressants may still be useful, whereas newer generation antidepressants and novel treatment options continue to surface
• Treating specific populations with major depressive disorder can be difficult—special considerations are indicated for pediatric populations, as well as women and the elderly

To help fill these unmet needs, quality improvement efforts need to provide education regarding:

1. The neurophysiology and mechanisms that contribute to depression
2. Current and emerging treatment options for depression
3. The recognition and management of comorbid conditions often associated with depression, in addition to recognizing specialized care for subpopulations

Learning Objectives
After completing this activity, participants should be better able to fulfill the following learning objectives:

• Identify neural implications of depression and describe neurobiologic symptoms
• Utilize treatment options available for depression on a per-case basis
• Discuss comorbidities associated with depression

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Individual Disclosure Statements
Author
Laurence Mignon, PhD
Senior Medical Writer, Neuroscience Education Institute, Carlsbad, CA
Stockholder: Aspreva Pharmaceuticals Corporation; Vanda Pharmaceuticals Inc.; ViroPharma Incorporated

Content Editors
Meghan Grady
Director, Content Development, Neuroscience Education Institute, Carlsbad, CA
No other 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
Grant/Research: Forest; Johnson & Johnson; Novartis; Organon; Pamlab; Pfizer; Sepracor; Shire; Takeda; Vanda; Wyeth
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Speakers Bureau: Pfizer; Wyeth

Peer Reviewer
Scott A. Irwin, MD, PhD
Director, Psychiatry Programs, The Institute for Palliative Medicine at San Diego Hospice, San Diego, CA
No other financial relationships to disclose.

Design Staff
Nancy Muntner
Director, Medical Illustrations, Neuroscience Education Institute, Carlsbad, CA
No other financial relationships to disclose.

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Chapter 1

Neurobiology of Depression

Depression can affect every aspect of life. A patient undergoing a major depressive episode who receives treatment with any antidepressant will often experience symptomatic improvement. However, oftentimes treatment does not reach the goal of remission (complete cessation of all symptoms of depression) until several different pharmacotherapies have been utilized, possibly in combination. Understanding the neurobiology underlying depressive symptomatology may give clinicians the opportunity to treat the symptoms specifically, based upon brain mechanisms and the interplay among genes, circuits, and symptoms.

This chapter aims to identify neural implications of depression and describe neurobiological symptoms in order to provide advanced education regarding the neurophysiology of depression and mechanisms that contribute to the disorder.
Mood Chart

FIGURE 1.1. Mood charts illustrate a spectrum of syndromal states upon which a patient's mood can be charted over time. Mood monitoring can be conducted intermittently in a clinical setting or continuously via patient self-report in the form of a mood diary. Tracking the course of illness can greatly assist in identifying disease states, diagnosing accurately, and assessing treatment response.
Deppressive Temperament and Dysthymia

**FIGURE 1.2.** Patients with a depressive temperament may be regularly sad or apathetic but do not have a sufficient degree or number of symptoms to qualify for the diagnosis of dysthymia or a major depressive episode. Individuals with depressive temperament may be more at risk for future mood disorders.

**FIGURE 1.3.** Dysthymia is a less severe form of depression than major depressive disorder, but is long-lasting and generally unrelenting for two years or more.
Identifying Mood Disorders: Depression and Double Depression

**FIGURE 1.4.** Major depressive disorder (MDD) is characterized by a single or recurrent major depressive episode(s); most people with MDD will experience recurrent episodes.

**FIGURE 1.5.** Double depression is characterized by unremitting dysthymia interrupted by major depressive episode(s), and accompanied by poor inter-episode recovery between episodes.
Chapter 1

Unipolar vs. Bipolar Depression

FIGURE 1.6. Although both patients in this mood chart are presenting with identical current symptoms of a major depressive episode over the past several days (A), patient 1 has unipolar depression whereas patient 2 has bipolar depression. So, what is the difference? The pattern of past symptoms (B) is quite different; for example, patient 1 has experienced a prior depressive episode while patient 2 has experienced a prior hypomanic episode. Furthermore, it has been suggested that un(der)treated unipolar depression can develop into a bipolar spectrum condition, and eventually lead to treatment resistance.
FIGURE 1.7. (A) As per the Diagnostic and Statistical Manual, version IV (DSM-IV), diagnosis of major depressive disorder requires at least one of the symptoms in the top row, and at least four of the symptoms in the bottom two rows. (B) Malfunctioning of certain brain regions, manifesting as either hypo- or hyperactivity, may hypothetically be altered due to aberrant neuronal activity and information processing, leading to the different presenting symptoms of depression.

Circuits and Symptoms in Depression:
Part 2

FIGURE 1.8. (A) Inefficient or dysfunctional serotonin (SHT), norepinephrine (NE), and/or dopamine (DA) projections to the amygdala (A) and ventromedial prefrontal cortex (VMPFC) are hypothetically involved in depressed mood. (B) Inefficient information processing in the prefrontal cortex (PFC; SHT, NE, and DA projections), the cerebellum (C; SHT and NE projections), the striatum (S; SHT and DA projections), and the nucleus accumbens (NA; SHT and DA projections) is hypothetically involved in psychomotor agitation or retardation. (C) Hypoactivation of SHT, NE, and DA projections from brainstem nuclei to the hypothalamus (Hy), thalamus (T), basal forebrain (BF), and PFC is hypothetically involved in sleep disturbances.
FIGURE 1.9. (A) Inefficient information processing from norepinephrine (NE) and dopamine (DA) projections to the dorsolateral prefrontal cortex (DLPFC) is hypothetically linked to problems with emotional regulation, self-monitoring, goal-setting, priority planning, and organization, all of which could lead to executive dysfunction. (B) Inefficient information processing from NE projections to the prefrontal cortex (PFC) and hypothalamus (Hy) and the DA projections to the PFC, Hy, and nucleus accumbens (NA) is hypothetically linked to apathy. Although superficially similar to depressed mood, apathy is actually a distinct symptom of depression, associated with lack of pleasure including decreased libido, linked to loss of interest and motivation, and often experienced by geriatric patients. Additionally, apathy is also hypothetically regulated by different brain circuits than depressed mood. (C) Inefficient information processing from NE and DA projections to the PFC is hypothetically involved in mental fatigue. Physical fatigue is linked to deficient NE functioning in the descending spinal cord (SC) and deficient DA functioning in the striatum, NA, Hy, and spinal cord.
Circuits and Symptoms in Depression:
Part 4

FIGURE 1.10. (A) Inefficient or dysfunctional serotonin (SHT) projections to the amygdala (A) and the ventromedial prefrontal cortex (VMPFC) could theoretically cause feelings of guilt and worthlessness, which are regulated by these “emotional” brain regions. (B) Inefficient or dysfunctional SHT projections to the hypothalamus (Hy) could theoretically lead to problems with weight and appetite. (C) SHT projections to the “emotional” brain regions including the amygdala, VMPFC, and orbital frontal cortex (OFC), could hypothetically be involved in suicidal ideation.
Major Depressive Disorder

Monoamine Hypothesis of Depression

FIGURE 1.11. (A) As seen in Figures 1.8 through 1.10, dopamine (DA), norepinephrine (NE), and serotonin (SHT) are the three key monoamines involved in depression. (B) The classical “monoamine hypothesis of depression” states that depression results from a deficiency in one or more of these three neurotransmitters.
FIGURE 1.12. Theoretically, antidepressant medications should be able to normalize the levels of the three neurotransmitters affected in depression by blocking presynaptic monoamine transporters (also called reuptake pumps), and thereby increasing the synaptic availability and actions of these monoamines.
Major Depressive Disorder

Monoamine Receptor Hypothesis of Depression

**FIGURE 1.13.** The monoamine receptor hypothesis builds on the classic monoamine hypothesis of depression by suggesting that decreased activity of monoamine neurotransmitters (dopamine, norepinephrine, and serotonin) causes upregulation of postsynaptic receptors (red circle) which may lead to depression.
FIGURE 1.14. The monoamine receptor hypothesis suggests that if depression is caused by upregulation of monoamine receptors, antidepressants act by ultimately downregulating monoamine receptors over time. (A) An antidepressant can acutely block the reuptake pump, allowing for more neurotransmitter (NT) in the synapse (red circle). (B) A chronic increased availability of neurotransmitter over time can lead to the downregulation of receptors (red circle). The time course for this downregulation to occur (days to weeks) is consistent with both the delayed onset of antidepressant effects and the time required to develop tolerance to side effects.
FIGURE 1.15. Based on the monoamine hypothesis of depression, antidepressants can theoretically create a return to a normal mood state by increasing the levels of monoamines. The downstream consequences of increased monoamine production by antidepressants leads to a cascade of effects such as expression of critical genes and down or upregulation of various gene products.
FIGURE 1.16. Antidepressant drugs have three time courses: one for clinical changes, a second one for neurotransmitter changes, and a third one for receptor sensitivity changes. While the neurotransmitter changes often occur rapidly after initial administration, clinical changes and receptor changes (i.e., downregulation) take longer to occur. This observation has resulted in the hypothesis that neurotransmitter receptor sensitivity may mediate the clinical changes seen after antidepressant administration, including the production of therapeutic antidepressant effects and the development of tolerance to side effects, all of which occur over a few weeks of time.
FIGURE 1.17. As mentioned previously, serotonin plays an integral part in mediating the symptoms of depression. Depicted in this figure are the major serotonergic projections. Ascending projections originate from the raphe nucleus to the cerebellum, thalamus, hypothalamus, basal forebrain, prefrontal cortex, striatum, nucleus accumbens, amygdala, and hippocampus. Mood, appetite, suicidal ideation, and sleep are regulated and affected by 5HT (see Figures 1.8 and 1.10). Descending projections to the spinal cord affect pain pathways.

FIGURE 1.18. Serotonin (SHT) is one of the three principal monoamines involved in depression. (A) Serotonin is synthesized from the amino acid tryptophan (TRY), which enters the serotonin neuron via the tryptophan transporter, a transporter that is distinct from the serotonin transporter (SERT). After tryptophan is pumped into the serotonin neuron, it is hydroxylated to 5-hydroxy-tryptophan (5HTP) by the rate-limiting enzyme tryptophan hydroxylase (TRY-OH). 5HTP is then decarboxylated to 5HT by the enzyme aromatic amino acid decarboxylase (AAADC), and is packaged into vesicles by the vesicular monoamine transporter 2 (VMAT2) pump. There it is stored until released during neurotransmission. (B) After 5HT has been released into the synapse it can either be transported back into the serotonin neuron via the serotonin transporter (SERT) or it can be metabolized and destroyed extraneuronally by either monoamine oxidase A or B (MAO-A or MAO-B). If 5HT is transported into the neuron, but not repackaged rapidly enough into synaptic vesicles, it will be destroyed intraneuronally by MAO-B.
FIGURE 1.19. (A) Presynaptic 5HT1B/D receptors are located on the axon terminal, and act as “gatekeeper” for their neurotransmitter. (B) When serotonin builds up in the synapse and binds to 5HT1B/D receptors (red circle), the further release of serotonin will be inhibited. These receptors aid in modulating the appropriate release of serotonin.
FIGURE 1.20. (A) Presynaptic 5HT1A receptors are located on the cell body and dendrites of a neuron, and are thus termed somatodendritic autoreceptors. (B) When serotonin (5HT) binds to these somatodendritic receptors (red circle), they will reduce neuronal electrical activity leading to a shutdown of 5HT impulse flow and therefore a decrease in the amount of 5HT released at the synapse (on the right).
FIGURE 1.21. Norepinephrine (NE) also plays an integral part in mediating the symptoms of depression. Ascending projections originate from the locus coeruleus of brainstem to the cerebellum, thalamus, hypothalamus, basal forebrain, prefrontal cortex, amygdala, and hippocampus. Mood, arousal, and cognition are regulated and affected by NE (see Figures 1.8 and 1.9). Descending projections from the spinal cord affect pain pathways.

Synthesis and Metabolism of Norepinephrine

**FIGURE 1.22.** (A) Norepinephrine (NE) is synthesized from the amino acid tyrosine (TYR), which is transported into the NE neuron by the tyrosine transporter, a transporter that is distinct from the NE transporter (NET). After tyrosine is pumped into the NE neuron, it is hydroxylated to DOPA by the rate-limiting enzyme tyrosine hydroxylase (TOH). DOPA is then decarboxylated to dopamine (DA) by the enzyme DOPA decarboxylase (DDC). In the DA neuron, synthesis stops here. However, in the NE neuron, DA is hydroxylated to NE by the enzyme dopamine beta hydroxylase (DBH) which is actually located at synaptic vesicles. NE is then packaged into synaptic vesicles via the vesicular monoamine transporter 2 (VMAT2). There it is stored until released during neurotransmission. (B) After NE is released into the synapse, it is either transported back into the NE neuron or metabolized and destroyed extraneuronally by either monoamine oxidase A or B (MAO-A or MAO-B), or by catechol-O-methyl transferase (COMT). If NE is transported into the neuron, but not repackaged rapidly enough into synaptic vesicles, it will be destroyed intraneuronally by MAO-A or MAO-B.
FIGURE 1.23. (A) Presynaptic alpha 2 norepinephrine (NE) receptors on the NE neuron’s axon terminals work similarly to the 5HT1B/D receptors, acting as “gatekeepers” for their neurotransmitter. (B) When NE builds up in the synapse and binds to alpha 2 receptors (red circle), the further release of NE will be inhibited. These receptors aid in modulating the appropriate release of NE.
FIGURE 1.24. (A) Presynaptic alpha 2 adrenergic somatodendritic autoreceptors, located on the cell body and dendrites of a norepinephrine (NE) neuron, work similarly to somatodendritic 5HT1A receptors. (B) When NE binds to these somatodendritic autoreceptors (red circle), this will lead to a reduction in neuronal electrical activity leading to a shutdown of NE impulse flow and therefore a decrease in the amount of NE released at the synapse (on the right).
**Dopamine Pathways**

**FIGURE 1.25.** Dopamine (DA) projections ascend from the brainstem to the prefrontal cortex, basal forebrain, nucleus accumbens, striatum, thalamus, hypothalamus, amygdala, hippocampus, and cerebellum. DA neurotransmission is associated with cognition, psychosis, pleasure and reward, movement, and other functions (see Figures 1.8 and 1.9).

Synthesis and Metabolism of Dopamine

FIGURE 1.26. (A) Dopamine (DA) is synthesized from the amino acid tyrosine (TYR) which is transported into the DA neuron by the tyrosine transporter, a transporter that is distinct from the DA transporter (DAT). After tyrosine is pumped into the DA neuron, it is hydroxylated to DOPA by the rate-limiting enzyme tyrosine hydroxylase (TOH). DOPA is then decarboxylated to DA by the enzyme DOPA decarboxylase (DDC). DA is then packaged into synaptic vesicles via the vesicular monoamine transporter 2 (VMAT2). There it is stored until released during neurotransmission. (B) After DA is released into the synapse, it is either transported back into the DA neuron or metabolized and destroyed extraneuronally by either monoamine oxidase A or B (MAO-A or MAO-B), or by catechol-O-methyl transferase (COMT). If DA is transported into the neuron, but not repackaged rapidly enough into synaptic vesicles, it will be destroyed intraneuronally by MAO-A or MAO-B.
Major Depressive Disorder

Dopamine Receptors:  
Part 1

FIGURE 1.27. (A) Presynaptic dopamine (DA) D2 receptors on the DA neuron’s axon terminals work similarly to 5HT1B/D and alpha 2 receptors, acting as “gatekeepers” for their neurotransmitter. (B) When DA builds up in the synapse and binds to D2 receptors (red circle), the further release will be inhibited. These receptors aid in modulating the appropriate release of DA.
FIGURE 1.28. (A) Presynaptic D2 somatodendritic autoreceptors, located on the cell body and dendrites of a dopamine (DA) neuron, work similarly to somatodendritic 5HT1A and alpha 2 receptors. (B) When DA binds to these somatodendritic autoreceptors (red circle), this will lead to a reduction in neuronal electrical activity leading to a shutdown of DA impulse flow and therefore a decrease in the amount of DA released at the synapse (on the right).
**Monoamine Interactions**

**FIGURE 1.29.** (A) Norepinephrine (NE) can boost serotonin (5HT) release via an excitatory input from the locus coeruleus projecting to the raphe and acting at alpha 1 receptors on serotonergic cell bodies and dendrites in the raphe (5HT accelerator; red box, bottom left). NE can also reduce 5HT release via an inhibitory input from NE nerve terminals acting at 5HT nerve terminals on alpha 2 receptors on 5HT axon terminals (5HT brake; red box, top right).

(B) In the nigrostriatal dopamine (DA) pathway, the release of 5HT acts as a brake on DA release. 5HT leads to inhibition of DA release, both at the level of DA cell bodies in the substantia nigra (red circle, bottom left) and at the level of axon terminals in the striatum (red circle, top right).
FIGURE 1.30. (A) The serotonin (5HT) accelerator: When norepinephrine (NE) binds alpha 1 receptors on somatodendritic regions of 5HT neurons (red circle), this causes excitation of the 5HT neuron, with increased neuronal impulse flow and increased release of 5HT from its axon terminals. (B) The 5HT brake: When NE occupies alpha 2 heteroreceptors on 5HT axon terminals (red circle), this causes inhibition of 5HT release from the 5HT neuron.
Serotonin-Dopamine Interactions: 5HT2A and 5HT1A Receptors Have Opposite Actions on Dopamine Release

**FIGURE 1.31.** Serotonin (SHT) neurons can act on somatodendritic regions of dopamine (DA) neurons. Specifically, 5HT1A and 5HT2A receptors have opposite actions on DA release. Stimulation of 5HT1A receptors increases DA release, and thus 5HT1A receptors act as a DA accelerator. Stimulation of 5HT2A receptors inhibits DA release; thus 5HT2A receptors act as a DA brake. SHT can regulate DA release directly or indirectly. (A) When SHT binds to 5HT2A receptors on DA neurons or on GABA neurons, DA release is decreased directly or via inhibition through GABA release, respectively. (B) Upon binding to 5HT1A receptors, SHT causes inhibition of its own release. A lack of SHT results in disinhibition of DA release, and therefore increased DA output.
Serotonin-Dopamine-Norepinephrine Interactions: 5HT2C Receptors Reduce Release of Dopamine and Norepinephrine in Prefrontal Cortex

**FIGURE 1.32.** 5HT2C receptors inhibit both dopamine (DA) and norepinephrine (NE) release. This occurs when serotonin (SHT) binds to 5HT2C receptors on GABA interneurons in the brainstem and excites them, causing release of the inhibitory neurotransmitter GABA onto both NE (on the left) and DA neurons (on the right).
FIGURE 1.33. (A) Neuroimaging studies indicate that the resting activity in the dorsolateral prefrontal cortex (DLPFC, black circle) is decreased in depressed patients. (B) On the other hand, the resting activity in the amygdala and ventromedial prefrontal cortex (VMPFC, black circles) is increased in depressed patients. (C) Additionally, depressed patients show underactivation in response to induced happiness and overactivation of VMPFC and amygdala in response to induced sadness.
FIGURE 1.34. Major depressive disorder (MDD) may not be inherited per se, but risk for MDD may be inherited as a series of risk genes (indicated here as P, Q, and R). Whether a risk manifests itself as overt MDD may depend upon exposure of genetically vulnerable circuits to stress. In the presence of major stressors, circuits rendered vulnerable by risk genes to developing inefficient information processing under stress may break down, and if sufficient symptoms prevail, MDD may result.
Chapter 2

Treatments for Depression

Today’s psychopharmacologist has a vast array of medications to choose from when treating major depressive disorder, and depending on their mechanism of action some medications may be more useful than others for various individuals. This chapter aims to provide education regarding current and emerging treatment options for depression, with an emphasis on mechanisms of action. Therefore, this chapter is separated into different sections based on the mechanisms of actions of the medications discussed.

Section 1 reviews some of the most commonly used first-line antidepressant drug options, the selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs). For patients who do not completely remit on an SSRI or SNRI, oftentimes augmentation and/or combinations are introduced or the patient is switched to a second-line treatment.

Section 2 reviews the antidepressant drugs that are norepinephrine dopamine reuptake inhibitors (NDRIs) and selective norepinephrine reuptake inhibitors (NRIs). NDRIs are considered first-line treatment, and NRIs are often used as second-line options.

Section 3 reviews the antidepressant drugs that work as alpha 2 antagonists and are also known as serotonin and norepinephrine disinhibitors (SNDIs; i.e., mirtazapine) or the drugs that work as serotonin antagonist/reuptake inhibitors (SARIs; i.e., trazodone and nefazodone). The focus is on the unique characteristics of alpha 2 antagonism and SARIs, both of which are second-line treatment options.

Section 4 reviews the classical antidepressants known as monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs). The focus here is on mechanisms of action of these particular drugs and how these “old-fashioned” medications can be quite powerful options for treating depression.

Section 5 reviews the concepts of trimonoamine modulators and gives various examples of some trimonoamine modulators that have proven efficacy in treating depression.

Section 6 introduces novel treatment options and augmenting agents used to treat depression.

Section 7 finally summarizes the importance of treating depression and offers different “pharmacies” to do so.
Selecting Serotonin Reuptake Inhibitors and Serotonin Norepinephrine Reuptake Inhibitors

**FIGURE 2.1.1.** The depression pharmacy illustrates the vast number of treatment options used in depression. For section 1, only selective serotonin reuptake inhibitors (SSRI) and serotonin norepinephrine reuptake inhibitors (SNRI) are highlighted on the shelf to indicate that these treatments are first-line monotherapies. This figure will be utilized throughout the book to indicate where on the pharmacy shelves the various pharmacotherapies under discussion fall in the sequence of selecting treatments for depression.


Selective Serotonin Reuptake Inhibitors: Overview

FIGURE 2.1.2. (A) Six agents are considered selective serotonin reuptake inhibitors (SSRI): fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram. Each shares the common property of inhibiting the serotonin transporter (SERT) leading to serotonin reuptake inhibition (SRI) which is the core feature of this class of drugs. (B) By binding to SERT and thereby inhibiting the reuptake of serotonin, SSRIs allow for more neurotransmitter to remain in the synapse which results in their antidepressant effect. The molecular mechanism of action of SSRIs, including downstream effects on receptors, is illustrated in detail on the following pages.
Major Depressive Disorder

Mechanism of Action of Selective Serotonin Reuptake Inhibitors: Parts 1 and 2

FIGURE 2.1.3. The depressed state is characterized by low serotonin (5HT) levels, up-regulated receptors, and a low number of signals in the neuron to release more 5HT.

FIGURE 2.1.4. By blocking SERT, selective serotonin reuptake inhibitors (SSRI) cause a rapid increase in 5HT in the somatodendritic area (red circle) with only a little increase in 5HT at the axon (right).
Mechanism of Action of Selective Serotonin Reuptake Inhibitors: Parts 3 and 4

**FIGURE 2.1.5.** The increase in serotonin (SHT) causes the autoreceptors to desensitize/downregulate (red circle).

**FIGURE 2.1.6.** Once the autoreceptors have downregulated, there is no longer an inhibition of impulse flow in the SHT neuron, and neuronal impulse flow is thus turned on. This leads to increased release of SHT at the axon terminal (red circle).
**Mechanism of Action of Selective Serotonin Reuptake Inhibitors: Part 5**

**FIGURE 2.1.7.** The increase of serotonin (SHT) at the axon causes the postsynaptic receptors to desensitize/downregulate (red circle). This desensitization may result in a reduction of side effects of selective serotonin reuptake inhibitors as tolerance develops.
Other Pharmacological Actions of Selective Serotonin Reuptake Inhibitors

**FIGURE 2.1.8.** While selective serotonin reuptake inhibitors (SSRI) all share their high affinity for serotonin reuptake inhibition (SRI), each has different secondary pharmacological actions, which include norepinephrine reuptake inhibition (NRI), dopamine reuptake inhibition (DRI), 5HT2C antagonism, muscarinic/cholinergic antagonism (m-ACh), sigma-1 receptor actions (σ), and inhibition of NOS (nitric oxide synthetase) and various CYP450 enzymes such as 2D6, 3A4, and 1A2. Pharmacologic properties of each of the six SSRIs are shown in the following figures.
**Main Selective Serotonin Reuptake Inhibitors: Part 1**

**FIGURE 2.1.9.** Besides its actions at the serotonin (5HT) reuptake pump, fluoxetine has antagonist actions at 5HT2C receptors, leading to norepinephrine (NE) and dopamine (DA) release. Normally 5HT inhibits DA and NE release at 5HT2C receptors (Figure 1.32). When 5HT2C receptors are blocked, the inhibition is stopped, which is also called “disinhibition.” Thus, blockade of 5HT2C receptors results in NE and DA disinhibition; therefore 5HT2C antagonists such as fluoxetine are NE and DA disinhibitors (NDDIs). Fluoxetine also inhibits CYP450 2D6 and 3A4. Fluoxetine has a long half-life, while its active metabolite has an even longer half-life; these factors may reduce the incidence of sudden withdrawal symptoms. Fluoxetine may be useful in conjunction with atypical antipsychotics, including olanzapine, to increase the effectiveness of their antidepressant action in bipolar depression.

**FIGURE 2.1.10.** Paroxetine is often preferred in the treatment of depression for patients with anxiety symptoms. This may be due to paroxetine’s anticholinergic effects (M1 muscarinic antagonism). In addition to this and the serotonin reuptake inhibition (SRI) properties, paroxetine has weak norepinephrine transporter (NET) inhibition properties, thus acting as a norepinephrine reuptake inhibitor (NRI) with potent inhibitory actions at CYP450 2D6. Paroxetine is a substrate as well as an inhibitor of 2D6, which can lead to a rapid decline in its plasma drug levels when paroxetine is discontinued, contributing to the withdrawal symptoms experienced upon sudden discontinuation. Inhibition of nitric oxide synthetase (NOS) may contribute to its sexual dysfunction side effects.
Main Selective Serotonin Reuptake Inhibitors: Part 2

FIGURE 2.1.11. Sertraline is unique in that it binds to sigma-1 receptors as well as the dopamine transporter (DAT), acting as a dopamine reuptake inhibitor (DRI) in addition to its serotonin reuptake inhibitory (SRI) properties. While sigma-1 actions are not well understood, they may contribute to anxiolytic effects and may be useful in psychotic depression. The actions at DAT may be weak, but perhaps only a small amount of DAT inhibition is enough to cause improvement of certain depressive symptoms when utilized in conjunction with inhibition of the serotonin transporter. Sertraline may be added to bupropion, another DAT inhibitor, increasing that property and aiding in alleviation of depressive symptoms.

FIGURE 2.1.12. Fluvoxamine has potentially important secondary actions at sigma-1 receptors as well. This action is more potent for fluvoxamine than sertraline, with fluvoxamine’s properties thought to be agonistic at sigma-1 receptors, contributing to its efficacy as an anxiolytic. Additionally, fluvoxamine is also therapeutically effective as a treatment option in psychotic and delusional depression. Currently available as a controlled-release formulation, once-a-day administration is possible and favored, with clinical trials reporting robust remission rates in obsessive compulsive disorder and anxiety disorder. Fluvoxamine is also available in immediate-release formulation, but due to shorter half-life, this requires twice-daily administration. Fluvoxamine was one of the first antidepressants marketed worldwide, though it was never approved for depression in the U.S. (currently used more often in treatment of obsessive compulsive disorder and anxiety). It is a potent inhibitor of CYP450 1A2 and 3A4.
**Main Selective Serotonin Reuptake Inhibitors: Part 3**

**FIGURE 2.1.13.** Citalopram consists of two enantiomers, R and S. Taken together, this agent is known as racemic citalopram, with mild antihistamine and 2D6 inhibitory properties residing in the R enantiomer. Citalopram is generally a well-tolerated selective serotonin reuptake inhibitor (SSRI) and is useful in treating elderly patients with depression. However, at its lowest dose, citalopram may be somewhat inconsistent in therapeutic action, potentially requiring a dose increase to optimize treatment response. This may be due to a recent finding that the R enantiomer may be active at the serotonin transporter (SERT), thus interfering with the ability of the S enantiomer to inhibit SERT. This interference could lead to reduced inhibition of SERT, reduced synaptic serotonin, and possibly reduced therapeutic action.

**FIGURE 2.1.14.** Escitalopram is, in essence, citalopram without the R enantiomer. In this case, the pure active SERT properties of the S enantiomer are the cause of its antidepressant properties. By removing the R enantiomer, this also removes the antihistaminic and CYP450 2D6 inhibitory properties of citalopram. Additionally, by removing the R enantiomer, which can interfere with SERT, the lowest dose of escitalopram may be more effective. Escitalopram is known as one of the better-tolerated SSRIs with the fewest CYP450-mediated drug interactions, though it is comparatively expensive, as no generic is yet available.
Mechanism of Action of Serotonin Norepinephrine Reuptake Inhibitors: Part 1

FIGURE 2.1.15. Serotonin norepinephrine reuptake inhibitors (SNRI) act on two monoamines specifically. (A) In the prefrontal cortex, the serotonin reuptake inhibition (SRI) property of SNRIs plugs into the serotonin transporter (SERT) resulting in an increase in synaptic serotonin and an antidepressant effect. (B) In this brain area, the SNRIs will also block the norepinephrine transporter (NET) and through their norepinephrine reuptake inhibition (NRI) property, they will lead to an increased amount of norepinephrine in the synapse and again an antidepressant effect.
FIGURE 2.1.16. (A) In the prefrontal cortex (PFC), the dopamine (DA) neuron is devoid of DA transporters. Here, DA is inactivated by the norepinephrine transporter (NET). Thus after being released, DA diffuses until it reaches a NET on a norepinephrine (NE) neuron. (B) NETs actually have higher affinity for DA than they do for NE! Thus, in the PFC, NETs inactivate both NE and DA, and blockade of NETs will lead to an increase in both NE and DA levels.
Main Serotonin Norepinephrine Reuptake Inhibitors: Part 1

FIGURE 2.1.17. Venlafaxine was the first serotonin norepinephrine reuptake inhibitor (SNRI) on the U.S. market, and has become one of the most frequently prescribed antidepressants on the market. Venlafaxine has varying degrees of inhibition of norepinephrine reuptake (NRI) depending on the dose, whereas serotonin reuptake inhibition (SRI) is moderately potent and present at all approved doses. Venlafaxine is a substrate for CYP450 2D6, which converts it to the active metabolite desvenlafaxine. After venlafaxine is administered, plasma levels of venlafaxine are normally around half that of desvenlafaxine. If a CYP450 2D6 inhibitor is taken concurrently, this may shift the plasma levels more toward venlafaxine, reducing the amount of norepinephrine transporter (NET) inhibition. This variability of plasma levels may also accompany CYP450 2D6 genetic polymorphisms, with poor metabolizers shifting the plasma concentration more toward venlafaxine, which may result in a reduction of NET inhibition. Dose titration of venlafaxine or administration of desvenlafaxine itself may solve this problem. Venlafaxine may have withdrawal reactions, especially after sudden discontinuation. The extended-release formulation is much better tolerated than the immediate-release formulation.

FIGURE 2.1.18. Desvenlafaxine has greater NET inhibition than serotonin transporter (SERT) inhibition compared to venlafaxine. Since desvenlafaxine is not a substrate of CYP450 enzymes including 2D6, plasma levels should be more consistent than with venlafaxine. Desvenlafaxine is also unaffected by genetic polymorphisms of CYP450. Thus, the relative amount of NET versus SERT inhibition should also be more consistent, and greater at comparable doses. Desvenlafaxine has been tested for treatment of vasomotor symptoms associated with perimenopause, with positive results.
Main Serotonin Norepinephrine Reuptake Inhibitors: Part 2

FIGURE 2.1.19. Duloxetine is the first serotonin norepinephrine reuptake inhibitor (SNRI) approved for treatment of painful neuropathy (diabetic peripheral neuropathic pain), in addition to treating major depression and generalized anxiety disorder. This agent appears to be useful in treating the painful physical symptoms associated with a major depressive episode, as well as treating geriatric depression, which is often associated with cognitive dysfunction. Duloxetine has shown efficacy in treating the pain associated with fibromyalgia and may also be useful for cognitive symptoms in fibromyalgia. Improvement of cognition in various disorders may be due to inhibition of prefrontal cortical norepinephrine transporters (NET). Duloxetine is a CYP450 2D6 inhibitor, which may result in various drug interactions that should be monitored. Duloxetine may be administered once daily, though in some difficult-to-treat patients, higher doses may be utilized, which may be dosed twice daily.

FIGURE 2.1.20. Milnacipran is somewhat different in that among the four approved SNRIs, it has the strongest relative actions at the norepinephrine transporter (NET) versus the serotonin transporter (SERT). Other SNRIs generally exhibit the opposite properties. Data suggest that milnacipran may have efficacy both for pain and cognitive symptoms in fibromyalgia. In several countries outside the U.S., milnacipran is approved for the treatment of depression, and approval for fibromyalgia is pending worldwide. Milnacipran may be more energizing and activating than some other SNRIs due to its relatively potent noradrenergic actions, and may cause more sweating and urinary hesitancy. Milnacipran is generally given twice daily due to its short half-life.
Norepinephrine Dopamine Reuptake Inhibitors and Norepinephrine Reuptake Inhibitors

**FIGURE 2.2.1.** Norepinephrine dopamine reuptake inhibitors (NDRIs) are on the first-line treatment shelf, whereas norepinephrine reuptake inhibitors (NRIs) are considered second-line monotherapies.

FIGURE 2.2.2. As their name suggests, norepinephrine dopamine reuptake inhibitors (NDRI) inhibit both the norepinephrine (NET) and the dopamine transporter (DAT), whereas selective norepinephrine inhibitors (NRI) only inhibit NET. This will lead to different actions in different brain regions, depending on the presence of NETs and DATs.
Comparing the Regional Effects of Norepinephrine Dopamine Reuptake Inhibitors vs. Norepinephrine Reuptake Inhibitors

**FIGURE 2.2.3.** Both norepinephrine dopamine reuptake inhibitors (NDRI) and selective norepinephrine reuptake inhibitors (NRI) raise both norepinephrine (NE) and dopamine (DA) levels in the prefrontal cortex (PFC) via inhibition of norepinephrine transporters (NET; top figures). Due to a lack of NE terminals and therefore NETs in the striatum and nucleus accumbens, NRIs will lack any effect in these areas, while NDRIs will raise only DA in those two areas.
**Norepinephrine Dopamine Reuptake Inhibitor**

**FIGURE 2.2.4.** Bupropion blocks the norepinephrine and dopamine transporters (NET and DAT) less potently than selective serotonin reuptake inhibitors (SSRI) and serotonin norepinephrine reuptake inhibitors (SNRI) block the serotonin transporter (SERT). This implies that (1) NET and DAT inhibition are insufficient explanations of bupropion’s antidepressant actions, or that (2) lesser amounts of NET and DAT inhibition are necessary to be an antidepressant compared to the inhibition of SERT. The latter possibility is supported by observations that much less NET inhibition than SERT inhibition occurs with SNRI use and that high degrees of DAT inhibition include abusable stimulants such as amphetamine, cocaine, and methylphenidate, rather than antidepressants. Thus, low levels of combined NET plus DAT inhibition may be ideal for a non-abusable antidepressant like bupropion. Bupropion may be useful in treating nicotine addiction due to its ability to occupy DAT in the striatum and nucleus accumbens, mitigating cravings but not becoming abusable itself. Bupropion was originally marketed in the United States only, in an immediate-release formulation. Recent formulations have been developed in twice-daily (bupropion SR) and once-daily doses (bupropion XL). These advances not only provide convenience but are also beneficial in reducing the risk of seizures at peak plasma drug levels associated with the original formulation. Bupropion is generally a stimulating agent, and does not appear to cause sexual dysfunction that may be associated with use of other antidepressants. Bupropion has been very useful for patients who experience reduced positive affect, or the “dopamine-deficiency syndrome.” Oftentimes, augmentation with bupropion to an existing SSRI or SNRI can be useful for patients who have not responded to previous serotonergic-focused treatment.
Norepinephrine Reuptake Inhibitors

**FIGURE 2.2.5.** Atomoxetine was never developed as an antidepressant in the United States, and it is currently marketed only for attention deficit hyperactivity disorder. Nevertheless, due to its mechanism of action as norepinephrine reuptake inhibitor (NRI), it may be useful when given as an augmenting agent with selective serotonin reuptake inhibitors or other agents for treatment-resistant depression.

**FIGURE 2.2.6.** Reboxetine is approved as an antidepressant in Europe, but not in the United States. Reboxetine may be useful as an augmenting agent in treatment-resistant depression, similar to atomoxetine, or on its own as a mono-therapy after selective serotonin reuptake inhibitors have failed or “pooped out.”
FIGURE 2.3.1. The alpha 2 antagonist mirtazapine and the serotonin antagonist/reuptake inhibitors (SARI) trazodone and nefazodone are listed as second-line mono-therapies. They may be useful as monotherapies in situations where patients have not experienced full remission while taking a selective serotonin reuptake inhibitor (SSRI) and/or a serotonin norepinephrine reuptake inhibitor (SNRI), or as augmentation and/or combination strategies with SSRIs/SNRIs.

FIGURE 2.3.2. Unlike serotonin norepinephrine reuptake inhibitors (SNRI), alpha 2 antagonists do not block monoamine transporters to achieve their therapeutic effects. By blocking alpha 2 receptors, alpha 2 antagonists result in norepinephrine (NE) no longer being able to turn off its own release. This causes "disinhibition" of NE release (i.e., an increase in NE). Similarly, alpha 2 antagonists do not allow NE to turn off serotonin (5HT) release, resulting in "disinhibition" of 5HT release (i.e., an increase in 5HT) as well. An additional mechanism of alpha 2 antagonists which aids in increasing 5HT release is the disinhibition of NE in the noradrenergic pathway to the midbrain raphe. NE neurons from the locus coeruleus innervate cell bodies of 5HT neurons in the midbrain raphe; thus, this pathway enhances 5HT release via stimulation of alpha 1 receptors with an alpha 2 antagonist. Therefore, alpha 2 antagonists are serotonin and norepinephrine disinhibitors (SNDIs), with dual action increases of both NE and 5HT release.
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Mechanism of Action of Alpha 2 Antagonist

**FIGURE 2.3.3.** (A) Alpha 2 antagonists increase norepinephrine (NE) neurotransmission via "cutting the brake cable" by blocking presynaptic alpha 2 autoreceptors, causing NE release to be disinhibited, i.e., increased. (B) The brake cable can also be cut for serotonergic (SHT) neurotransmission via blockade of alpha 2 heteroreceptors, resulting in disinhibition of SHT release.
Noradrenergic and Specific Serotonergic Antidepressant

**FIGURE 2.3.4.** Mirtazapine has a complex but very interesting pharmacology. It has been called a noradrenergic and specific serotonergic antidepressant (NaSSA), with actions at alpha 2 receptors as well as at three serotonin (5HT) receptors—2A, 2C, and 3. In addition, mirtazapine blocks histamine H1 receptors. By blocking alpha 2 receptors, mirtazapine increases both 5HT and norepinephrine (NE) and is thus a serotonin and norepinephrine disinhibitor or SNDI. Mirtazapine administration thus causes 5HT to be released onto all receptors; however, since 5HT2A, 5HT2C, and 5HT3 receptors are blocked by mirtazapine, the net stimulation falls on the 5HT1A receptors. This further results in release of dopamine (DA), which may be helpful in depression as well as anxiety.

Mirtazapine’s antagonist actions at 5HT2A and 2C receptors also results in increased release of DA and NE, and these 5HT2A and 5HT2C antagonist actions may also provide useful anxiolytic and antidepressant properties, as well as providing sleep-restoring properties. In addition, mirtazapine is able to increase 5HT release without causing sexual dysfunction.

Due to its 5HT2A and 5HT2C antagonist properties, and thus its ability to disinhibit both NE and DA release, mirtazapine is further classified as a norepinephrine and dopamine disinhibitor (NDDI). 5HT3 antagonist action may reduce nausea, with H1 action potentially relieving insomnia and improving anxiety, but causing weight gain. So, this complex molecule is an NDDI (due to 5HT2A and 5HT2C antagonism), an SNDI (due to alpha 2 antagonism), plus a 5HT3 and H1 antagonist!
FIGURE 2.3.5. Serotonin2A antagonist/reuptake inhibitors (SARIs) block 5HT2A and 5HT2C receptors, the serotonin transporter (SRI), and alpha 1 adrenergic receptors. Trazodone also has histamine H1 receptor antagonism properties, whereas nefazodone also blocks the norepinephrine transporter (NRI).
Mechanism of Action of Serotonin Antagonist/Reuptake Inhibitors

FIGURE 2.3.6. (A) At baseline postsynaptic action, the neuron fires. (B) Serotonin (SHT) is excitatory at SHT2A receptors. (C) SHT is inhibitory at SHT1A receptors. (D) SHT2A antagonism therefore potentiates the inhibitory actions of SHT at SHT1A receptors.
Main Serotonin Antagonist/Reuptake Inhibitors

FIGURE 2.3.7. In many ways, trazodone is two drugs: a low dose hypnotic and a high dose antidepressant. At low doses, trazodone's most potent actions at 5HT2A, alpha 1, and even H1 receptors provide hypnotic actions. However, blockade of the serotonin transporter (SERT) from serotonin reuptake inhibition (SRI actions) does not occur at levels great enough to increase serotonin (5HT) levels unless trazodone is given in high doses. It is this SERT blockade working in synergy with 5HT2A and 5HT2C antagonism that gives trazodone its ability to act as an antidepressant and why it is called an SARI (serotonin 2A/2C antagonist and reuptake inhibitor) at high doses. Trazodone lacks sexual side effects because of this SARI action.

FIGURE 2.3.8. Nefazodone has strong 5HT2A antagonist actions with weaker 5HT2C antagonism and weaker SERT inhibition. This particular drug is currently not used very often due to the potential for rare liver toxicity. Similarly to trazodone, nefazodone is approved for the treatment of depression. Nefazodone can be additionally used as a relapse prevention in major depressive disorders.
Tricyclic Antidepressants and Monoamine Oxidase Inhibitors

FIGURE 2.4.1. Tricyclic antidepressants (TCA) and monoamine oxidase inhibitors (MAOI) are generally considered second- or third-line monotherapies. These agents may be utilized in difficult-to-treat cases, where other first-line treatments may have failed to produce results.

Properties of Tricyclic Antidepressants

FIGURE 2.4.2. (A) All tricyclic antidepressants (TCA) block the norepinephrine transporter (NET) and are therefore norepinephrine reuptake inhibitors (NRI); some also block the serotonin transporter (SERT) and are therefore serotonin reuptake inhibitors (SRI). Both properties can lead to an antidepressant effect. (B) In addition, all TCAs share the secondary properties of inhibition of histamine H1, alpha 1, and muscarinic cholinergic receptors (M1). (C) Finally, some have additional antagonist properties at 5HT2A and 5HT2C receptors. TCAs also block voltage-sensitive sodium channels, which is why they can be lethal in overdose.
**Mechanism of Action of Tricyclic Antidepressants:**

**Part 1**

**FIGURE 2.4.3.** (A) Here a tricyclic antidepressant (TCA) is depicted inserted into the serotonin (5HT) reuptake pump, blocking it and causing 5HT accumulation in the synapse, which results in an antidepressant effect. (B) Also depicted here is the norepinephrine reuptake inhibition (NRI) portion of the TCA inserted to cause synaptic accumulation of norepinephrine which also results in an antidepressant effect.
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Mechanism of Action of Tricyclic Antidepressants: Part 2

FIGURE 2.4.4. (A) When tricyclic antidepressants (TCA) block serotonin 5HT2A receptors, an antidepressant effect is achieved (perhaps through disinhibition of dopamine (DA) and norepinephrine (NE) release, as previously discussed). In addition, sleep problems may improve. (B) TCAs inserted into the 5HT2C receptors result in their blockade and also produce an antidepressant effect, perhaps through disinhibition of DA and NE release as well.
Side Effects of Tricyclic Antidepressants

FIGURE 2.4.5. Some of the additional receptors of tricyclic antidepressants (TCA) can lead to side effects. (A) Inhibition of alpha 1 receptors can lead to dizziness, drowsiness, and decreased blood pressure. (B) Inhibition of H1 receptors is known to induce weight gain and drowsiness. (C) Blockade of M1 receptors can result in constipation, blurred vision, dry mouth, and drowsiness. (D) One of the properties of all TCAs is their ability to block voltage-sensitive sodium channels. When these channels are blocked in the brain and the heart, side effects can include coma and seizure (due to central nervous system actions), arrhythmia, and death (due to peripheral cardiac actions), especially in overdose.
Monoamine Oxidase A and B Inhibition and Antidepressant Action

FIGURE 2.4.6. Monoamine oxidase A (MAO-A) metabolizes serotonin (5HT), norepinephrine (NE), and dopamine (DA), whereas monoamine oxidase B (MAO-B) preferentially metabolizes DA (left panels). Combined inhibition of MAO-A and MAO-B results in greater increases in all three neurotransmitters than does inhibition of only MAO-A or MAO-B (right panels).
Monoamine Oxidase Interaction With Serotonin Reuptake Inhibitors

FIGURE 2.4.7. Serotonin (SHT) can be increased via the inhibition of the serotonin transporter (SERT) by selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors (A) or via the inhibition of monoamine oxidase (MAO) by MAO inhibitors (MAOI) (B). However, when both SERT and MAO are inhibited, SHT levels can dramatically increase. Thus, excessive stimulation of postsynaptic SHT receptors can occur to dangerous levels (C) and cause hyperthermia, coma, seizures, cardiovascular problems, and death. This is known as the “serotonin syndrome” and is why the combination of an MAOI with any drug that inhibits serotonin reuptake is strictly contraindicated.
Major Depressive Disorder

Drugs to Avoid With MAOIs

**TABLE 2.4.1.** Pharmacotherapeutic agents that, when combined with a monoamine oxidase inhibitor (MAOI), may result in potentially dangerous hypertensive reactions (A) or potentially lethal combinations causing hyperthermia (B).

### Potentially Dangerous Hypertensive Combos: Agents That, When Combined With MAOIs, Can Cause a Hypertensive Crisis (Theoretically via Adrenergic Stimulation)

**Decongestants**
- phenylephrine (alpha1 selective agonist)
- *ephedrine (ma hunag, ephedra) (alpha and beta agonist; central NE and DA releaser)
- *pseudoephedrine (active stereoisomer of ephedrine – same mechanism as ephedrine)
- *phenylpropanolamine (alpha1 agonist; less effective central NE/DA releaser than ephedrine)

**Stimulants**
- amphetamines
- methylphenidate

**Appetite Suppressants with NRI**
- sibutramine
- phentermine

**Antidepressants with NRI**
- TCAs
- NRIs
- SNRIs
- NDRIs

### Potentially Lethal Combos: Agents That, When Combined with MAOIs, Can Cause Hyperthermia/Serotonin Syndrome (Theoretically via SERT Inhibition)

**Antidepressants**
- SSRIs
- SNRIs
- TCAs

**Opioids**
- dextromethorphan
- meperidine
- tramadol
- methadone
- propoxyphene

**Other TCA Structures**
- Cyclobenzapine
- Carbamazepine

**Sibutramine (SNRI for weight loss)**

**TABLE 2.4.1.** Pharmacotherapeutic agents that, when combined with a monoamine oxidase inhibitor (MAOI), may result in potentially dangerous hypertensive reactions (A) or potentially lethal combinations causing hyperthermia (B).
### Identifying a Hypertensive Crisis and Ways to Avoid It

**Hypertensive Crisis**

- Defined as having a diastolic blood pressure > 120 mmHg
- Potentially fatal reaction characterized by:
  - Occipital headache which may radiate frontally
  - Palpitation
  - Neck stiffness or soreness
  - Nausea
  - Vomiting
  - Sweating (sometimes with fever)
  - Dilated pupils, photophobia
  - Tachycardia or bradycardia that can be associated with constricting chest pain

**Suggested Tyramine Dietary Modifications for MAO Inhibitors**

<table>
<thead>
<tr>
<th>Food to Avoid</th>
<th>Food Allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dried, aged, smoked, fermented, spoiled, or improperly stored meat, poultry, and fish</td>
<td>Fresh or processed meat, poultry, and fish</td>
</tr>
<tr>
<td>Broad bean pods</td>
<td>All other vegetables</td>
</tr>
<tr>
<td>Aged cheeses</td>
<td>Processed and cottage cheese, ricotta cheese, yogurt</td>
</tr>
<tr>
<td>Tap and nonpasteurized beers</td>
<td>Canned or bottled beers and alcohol (have little tyramine)</td>
</tr>
<tr>
<td>Marmite, sauerkraut</td>
<td>Brewer’s and baker’s yeast</td>
</tr>
<tr>
<td>Soy products/tofu</td>
<td></td>
</tr>
</tbody>
</table>

*TABLE 2.4.2.* (A) Signs of a hypertensive crisis, and (B) ways that this crisis may be avoided when using monoamine oxidase inhibitors (MAOI) with dietary restrictions.
How to Prevent Tyramine Reactions

**FIGURE 2.4.8.** (A) Monoamine oxidase A (MAO-A) is present in both the brain and the gut. The need to block MAO-A in the brain to induce an antidepressant effect leads to the dilemma that concomitant inhibition of MAO-A in the gut can lead to increased risk of tyramine reaction. (B) The solution may be to use reversible inhibitors of MAO-A (RIMA). In the case of RIMA, the norepinephrine (NE) released by tyramine (1) can displace the RIMA (2), allowing for normal destruction of the extra NE. (C) Transdermal selegiline is one solution for MAO-A and MAO-B antidepressant effects without tyramine reactions. Bypassing the liver via transdermal administration allows for a high dose and thus both MAO-A and MAO-B inhibition in the brain while bypassing delivery to the gut, thus avoiding tyramine reactions due to low MAO-A inhibition in the gut.
Possible Trimonoamine Modulators

| TABLE 2.5.1. Presented here are therapeutic interventions for major depression that work in ways other than inhibiting monoamine transporters and which are often used to augment drugs that inhibit monoamine transporters. Trimonoaminergic modulators (TMMs) are similar in that they all modulate monoamines, though each one may work in a different way to modulate/enhance monoamines and be of a different make-up (e.g., hormone, vitamin, medical food, non-pharmaceutical, etc.) |

1. Lithium
2. Thyroid hormones (T3, T4)
3. L-methyl-folate (MTHF, 5-L-methyltetrahydrofolate)
4. S-adenosyl-methionine (SAMe)
5. Omega-3 fatty acids
6. Vitamin D
7. Estrogen
8. Testosterone
9. Buspirone
10. Brain stimulation/neuromodulation (ECT, VNS, TMS, DBS)
11. Psychotherapy

FIGURE 2.5.1. Although the mechanism of action of lithium is still not completely known, it is posited to act by modulating G proteins (middle), or to inhibit second-messenger enzymes such as inositol monophosphate (right), both of which affect signal transduction. Lithium might also act within various downstream signal transduction cascades (left). Lithium can be a useful booster of antidepressant action, both in patients with unipolar depression that is non-responsive to antidepressant monotherapy, and in bipolar depression to augment other mood stabilizers.
Lithium and Thyroid as Trimonoamine Modulators

FIGURE 2.5.2. Lithium can boost the actions of all three monoamines, supposedly via one of the mechanisms depicted in the previous figure. Lithium is commonly used as an augmenting agent for patients who have not responded to previous antidepressant treatment. Thyroid hormone (T3/T4) can also be considered a potential trimonoamine modulator (TMM), as it binds to a nuclear hormone receptor that may lead to changes in neuronal gene expression that modulates one or more of the three monoamine neurotransmitters. Patients who are theoretically deficient in one or more of the three monoamines (dopamine, norepinephrine, and serotonin), despite treatment with an antidepressant (top), can have their monoamine activity theoretically restored when lithium or T3/T4 are added (bottom).
How Does L-methylfolate Work? Part 1: L-methylfolate is the Centrally Active Form of the Vitamin Folic Acid

**FIGURE 2.5.3.** Neurotransmitter synthesis for all monoamines is dependent upon L-methylfolate (shown above as MTHF), which is formed from synthetic folic acid dietary supplements, from natural dietary dihydrofolate (green vegetables, liver, etc.) or provided by direct treatment with synthetic L-methylfolate (MTHF) itself. In depressed patients, conversion of folate/folic acid into MTHF can be reduced by poor diet (e.g., alcoholism, eating disorder), by concomitant treatment with anticonvulsants that can interfere with absorption (e.g., valproic acid, carbamazepine) or inhibit the enzyme DHFR (dihydrofolate reductase) involved in L-methylfolate synthesis (e.g., lamotrigine), or by genetic factors/polymorphisms that can reduce the activity of the enzyme MTHFR (methylene tetrahydrofolate reductase), also involved in L-methylfolate synthesis. Since folic acid itself cannot cross the blood-brain barrier, and multiple factors may interfere with its conversion to L-methylfolate, treatment can be provided instead by giving L-methylfolate itself.

**FIGURE 2.5.4.** (A) L-methylfolate (MTHF) enhances the synthesis of tetrahydrobiopterin (BH4), a critical cofactor for the rate-limiting enzymes, tyrosine hydroxylase for dopamine (DA) and norepinephrine (NE) and tryptophan hydroxylase for serotonin (5HT). (B) In the absence of BH4 cofactor, tyrosine hydroxylase is inactive (left, depicted as sleeping blue enzyme). The blue enzyme lacks BH4 binding (depicted as an empty 4) and cannot bind tyrosine (depicted as a stellate binding site that does not fit the tyrosine icon). However, when BH4 binds to tyrosine hydroxylase, it “activates” the enzyme (depicted as turning purple with the yellow 4 as cofactor), leading to a change in the stellate binding site to a round shape in the purple enzyme. Now tyrosine can bind and be converted into both DA and NE. (C) A similar action occurs at tryptophan hydroxylase, the rate-limiting enzyme for 5HT.
L-methylfolate as a Trimonoamine Modulator

**FIGURE 2.5.5.** L-methylfolate enhances the synthesis of all three monoamines (dopamine, norepinephrine, and serotonin), and thus is another type of trimonoamine modulator (TMM). Patients who are theoretically deficient in one or more of the monoamines (top), despite treatment with an antidepressant, can have their monoamine activity theoretically restored when L-methylfolate is added (bottom).
Chapter 2

Neuromodulation as a Trimonoamine Modulator

**FIGURE 2.5.6.** Stimulation of specific areas of the brain appears to be a useful therapy for difficult-to-treat depression. Vagus nerve stimulation (VNS) and deep brain stimulation (DBS) both utilize implanted devices in the chest wall. In VNS, a lead is wrapped around the vagus nerve in the neck. This then sends signal pulses to the midbrain raphe and locus coeruleus, thereby boosting the monoamines serotonin and norepinephrine, respectively.

**FIGURE 2.5.7.** Transcranial magnetic stimulation (TMS) involves a coil placed on the scalp which sends magnetic stimulation specifically to the dorsolateral prefrontal cortex (DLPFC). This may boost trimonoamine neurotransmitter synthesis and release, thereby improving depressed symptoms. Whereas VNS is approved for treatment of depression, TMS is not yet approved. It is available in some countries, and is currently being reviewed by the Food and Drug Administration.

**FIGURE 2.5.8.** In deep brain stimulation (DBS) leads are placed directly into the brain, often in the ventromedial prefrontal cortex and subgenual area of the anterior cingulate cortex. An implanted electrical stimulator sends repeated pulses and can theoretically boost the synthesis or release of the three monoamines.
Psychotherapy adjunct to pharmacotherapy has been shown to improve overall quality-of-life in patients with major depressive disorder. Behavioral and educational therapies help improve factors such as total functioning, relationship functioning, life satisfaction, compliance with medication, and personal coping mechanisms. Psychotherapy can provide a necessary regular forum for patients to express and work through the progression of their illness and the coping mechanisms they use to overcome their limitations.
Augmenting Strategies and New Treatments on the Horizon

FIGURE 2.6.1. Insomnia is one of the most common symptoms of major depression to persist following treatment with an antidepressant such as a selective serotonin reuptake inhibitor (SSRI). Not surprisingly, treatment of such residual insomnia with a hypnotic can improve this symptom. However, shown here is also the improvement of remission rates of both major depression and generalized anxiety disorder (GAD) when the hypnotic eszopiclone is added to an SSRI. Eszopiclone, like zolpidem and zaleplon, is sometimes called a “Z-drug” or more precisely, a positive allosteric modulator (PAM) of GABA-A receptors. Here, not only does insomnia improve in major depression and GAD when eszopiclone is added to an SSRI, but so do other core symptoms of these disorders, resulting in improvement of remission rates.
The Evolving Antidepressant Actions of Atypical Antipsychotics

FIGURE 2.6.2. Atypical antipsychotics are best known as treatments of psychosis in schizophrenia and acute mania in bipolar disorder. However, these agents are increasingly being used to treat depression as well. This includes use as an augmenting agent to selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors for patients with major depression who have inadequate responses to first-line monotherapy, i.e., for treatment-resistant unipolar depression. Aripiprazole is currently approved by the FDA for this use, particularly at low doses, but all agents in this class are used as augmenting agents in treatment-resistant unipolar depression. Atypical antipsychotics are also employed both as first-line treatments for bipolar depression and as augmenting agents to mood stabilizers for bipolar depression. Quetiapine is currently approved by the FDA for this use, but all atypical antipsychotics are used in bipolar depression. Finally, these agents are sometimes used as monotherapy for major depression, and for anxiety disorders such as GAD, with pending FDA approval of quetiapine for this use.
New Antidepressant Treatments on the Horizon

**FIGURE 2.6.3.** Triple reuptake inhibitors (TRIs) block all three monoamine transporters, thus building on the concept that if “two mechanisms are better than one” (i.e., serotonin norepinephrine reuptake inhibitors compared to selective serotonin reuptake inhibitors), then “three mechanisms may be better than two.” At this point, the question is how much blockade of each of the three monoamine transporters would be ideal and several of these agents are now in clinical trials. Some TRIs that are in testing also have actions at multiple additional neurotransmitter receptors.

**FIGURE 2.6.4.** Agomelatine is known as a norepinephrine dopamine disinhibitor (NDDI) because of its 5HT2C antagonist properties of inhibiting serotonin (5HT), thereby disinhibiting dopamine (DA) and norepinephrine (NE) release. In addition to its 5HT2C antagonist properties, agomelatine is also an agonist at melatonin 1 (MT1) and melatonin 2 (MT2) receptors and has 5HT2B antagonist properties. Thus, in addition to being useful in treating depression due to 5HT2C antagonist properties, its actions at MT1 and MT2 receptors can aid in sleep improvement. This agent is in clinical trials.

**FIGURE 2.6.5.** Saredutant, a neurokinin2 (NK2) antagonist, may be effective in patients with major depressive episodes. This agent has shown promising results in animal models of depression. Hypothetically, conditions associated with excessive release of endogenous neurokinin A (NKA) benefit from blocking NK2 receptors which may explain saredutant’s potential antidepressant effect. This NK2 antagonist is currently in clinical trials.
Other Antidepressants in Development

### Neurokinin 1 receptors
- Also called substance P receptors
- Agonist is substance P
- Multiple substance P antagonists (also known as NK1 antagonists) tested and failed in depression and pain

### Neurokinin 2 receptors
- Agonist is NKA (neurokinin A, and its extended and shortened versions)
- Antagonist is saredutant, with preclinical evidence and preliminary clinical evidence of efficacy as an antidepressant

### Neurokinin 3 receptors
- Agonist is NKB (neurokinin B)
- Multiple NK3 antagonists in testing for depression, schizophrenia, and other disorders

### Monoamine mechanisms
- 5HT1A partial agonists (gepirone)
- Beta-3 agonist (amebegron)
- D3/D2 partial agonists (RGH-188/cariprazine; pramipexole; ropinirole; aripiprazole)

### Glutamate mechanisms
- Ketamine
- Memantine
- NMDA antagonists

### Novel mechanisms
- Glucocorticoid antagonists (mifepristone)
- CRF1 antagonists
- Vasopressin 1B (V1B) antagonists
- Nemifitide (injectable pentapeptide)

<table>
<thead>
<tr>
<th>TABLE 2.6.1.</th>
<th>Three major neurokinins exist in the brain: substance P (also known as neurokinin 1 or NK1) binds the NK1 receptor, neurokinin A (NKA) binds the neurokinin 2 (Nk2) receptor, and neurokinin B (NKB) binds the neurokinin 3 (NK3) receptor.</th>
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<tr>
<td></td>
<td>Treatment options are coming to light for major depressive disorder that previously may not have been considered for use. Aripiprazole was recently approved for use as an add-on for treating unipolar depression, and quetiapine is currently being tested for use as a unipolar first-line treatment option. Some of the agents listed above were discussed in this chapter. Please refer to Stahl’s Essential Psychopharmacology, 3rd ed. for further detail.</td>
</tr>
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FIGURE 2.7.1. (A) As seen during an eight-week clinical trial, treatment with most antidepressants will yield 67% responders and 33% non-responders. (B) Administration of placebo, on the other hand, will lead to 33% responders and 67% non-responders.
Remission Rates in Major Depressive Disorder and Residual Symptoms in Nonremitters

**FIGURE 2.7.2.** Only 1/3 of patients remit after initial antidepressant treatment (ADT). After one year of treatment with four different antidepressants for 12 weeks each, only 2/3 of patients eventually achieve remission.

**FIGURE 2.7.3.** While antidepressants are more likely to improve mood, suicidal ideation, and psychomotor retardation in depressed patients, several symptoms often remain in nonremitters, especially insomnia, but also fatigue and problems concentrating.
FIGURE 2.7.4. Once remission is achieved, there appears to be a protective factor in experiencing a relapse. However, as treatment administration increases, the protective effect of remission decreases. Thus, as shown above, the chances of staying in remission decline as the number of treatments required to attain remission increases.
First-line Monotherapies Followed by Classical Evidence-based Antidepressant Augmentation Therapies

**FIGURE 2.7.5.** The algorithm depicted above shows steps that may be taken when treating depression. (A) First-line treatments regularly include SSRIs, SNRIs, and NDRIs as monotherapy or in combination with each other (e.g., SSRI/SNRI plus NDRI). (B) Thereafter augmentation strategies can be used if the monotherapy alone is not sufficient. The most common augmentation therapies for major depression have often included lithium, thyroid hormones, or the 5HT1A partial agonist buspirone. However, recent evidence-based studies do not suggest which patient should get each of these and are not able to determine which is superior to the others.

SSRI: selective serotonin reuptake inhibitors. SNRI: serotonin norepinephrine reuptake inhibitors. NDRI: norepinephrine and dopamine reuptake inhibitors. 5HT1A: serotonin 1A agonists. T3/T4: thyroid hormone.
FIGURE 2.7.6. (A) If a monotherapy plus an augmenting agent are not successful in attaining symptom remission, a second-line monotherapy may be introduced. (B) Finally, ancillary treatment options may also be recommended.

Following First-line Monotherapies With Symptom-based Antidepressant Augmentation Strategies

FIGURE 2.7.7. (A) A symptom-based approach after failure of first-line monotherapies could be a hypnotic for residual insomnia, modafinil for residual fatigue/problems concentrating, or L-methylfolate for patient with problems tolerating prior treatments, since this should have few if any side effects. (B) If the patient is still not in remission, augmentation with an atypical antipsychotic (e.g., aripiprazole) starting at low doses may be considered.

Chapter 3
Comorbidities and a Woman’s Life Cycle

This chapter aims to provide education regarding the recognition and management of comorbid conditions often associated with depression. In order to reach full remission of depression, the comorbid disorders should be addressed in parallel. The lifecycle of a woman, with the accompanying fluctuating estrogen levels, can make her prone to depression, and the most effective treatments may vary throughout her life. This chapter will also discuss special considerations that are indicated for treating women at every stage of their life.
Common Comorbidities in Major Depressive Disorder

FIGURE 3.1. Some common comorbidities in major depressive disorder (MDD) include sleep/wake problems, anxiety, attention deficit hyperactivity disorder (ADHD), substance abuse, and chronic pain. For a patient to obtain full remission, it is imperative to concomitantly treat all disorders. It is therefore a good idea to solicit information on any of these comorbid conditions when taking the history of symptoms before and after treatment with an antidepressant intervention to assess underlying disorders and/or residual symptoms. This will hopefully lead to the resolution of all symptoms and to better quality-of-life.
Insomnia and Depression

**Insomnia and Psychiatric Illnesses**
- Insomnia as a psychiatric “vital sign”
- No remission unless sleep normalized
- Increased risk of relapse unless sleep normalized
- Panic disorders and nocturnal panic: insomnia through conditioned arousal/conditioned insomnia
- PTSD: nightmares, decreased stage 3/4 sleep, increased arousal and conditioned arousal, conditioned insomnia
- Depression: increased and disrupted REM sleep, decreased stage 3/4 sleep
- Schizophrenia, mania: severe insomnia may precede relapse
- Schizophrenia: Stage 3/4 sleep decreases as negative symptoms increase

**Insomnia and Medical Illnesses**
- The more diagnosed medical illnesses you have, the more insomnia you have
- Perimenopause: nocturnal awakenings correlate with hot flashes, hypothalamic dysregulation, and relapse/onset of major depression
- Dementia: disrupted sleep correlates with cognitive decline, especially disturbed circadian rhythm and “sundowning,” nocturnal wandering, daytime sleepiness
- Parkinson’s disease: nighttime pain and rigidity as meds wear off, nightmares, hallucinations, REM behavior disorder, sleep talking, and narcolepsy-like daytime symptoms
- Activation of HPA in OSA, obesity, and diabetes is a risk factor for insomnia with decreased sleep associated with increased weight and appetite

**TABLE 3.1.** Insomnia can be primary or it can be secondary, i.e., a side effect of a psychiatric or medical condition. In either case, resolution of both the insomnia and the depression will be enhanced if the other ailment is treated alongside.

PTSD: posttraumatic stress disorder. REM: rapid eye movement. HPA: hypothalamic pituitary axis. OSA: obstructive sleep apnea
Attention Deficit Hyperactivity Disorder and Depression

**FIGURE 3.2.** Adults with attention deficit hyperactivity disorder (ADHD) can have many different comorbid disorders including depression, anxiety disorders, substance use disorders, and bipolar disorders. These can all have the same devastating effects, both for the patients and for society as a whole. Patients with ADHD might need more time to finish their projects than their non-ADHD counterparts, which may lead to patients feeling depressed, anxious, and stressed. The initial diagnosis of ADHD, if it occurs in adulthood, may also cause depression in patients, as they may feel they have “missed opportunities” in their life due to the undiagnosed disorder. As the mechanism of action of treatments for ADHD are similar to those for depression, namely increasing monoamine levels, one medication may help alleviate some of the symptoms of the other disorder. Full remission, however, may only be reached by augmenting a stimulant with an antidepressant.
What Proportion of Mood Disorders Are Bipolar?

FIGURE 3.3. Over the last few years, there has been a paradigm shift with regards to the recognition and diagnosis of mood disorders. In the old paradigm, many patients were once considered to have major depressive disorder, but they are now, in the shifting paradigm, recognized as having bipolar II disorder or another form of bipolar illness within the bipolar spectrum. This paradigm shift is also likely to improve treatment. If patients with bipolar disorder are first treated with an antidepressant, this may lead to increased mood cycling, mixed states, conversion to hypomania and mania, and contribute to an increase in suicidality especially in adult patients below twenty-five years of age. These patients should be first treated with lithium, an anticonvulsant mood stabilizer, and/or an atypical antipsychotic. Since symptomatic patients with bipolar II disorder spend more time in the depressed state than the manic or hypomanic state, it can be quite difficult to differentiate depressed patients with bipolar II disorder from major depressive disorder. The following figures will show how to better diagnose depressed patients.
**Unipolar vs. Bipolar Depression?**

**Check the History**

**FIGURE 3.4.** Although both patients in this mood chart are “today” presenting with identical current symptoms of a major depressive episode (blue dot on mood chart), patient 1 has unipolar depression while patient 2 has bipolar depression. So, what is the difference? The pattern of past symptoms is quite different and relevant, with patient 1 having experienced a prior depressive episode and patient 2 a prior hypomanic episode. Gaining a complete picture may often require additional interviews with family members or close friends of the patient.

**FIGURE 3.5.** Although they can occur in either disorder, some symptoms of depression are more prevalent or frequent in bipolar depression than in unipolar depression. Observing patients’ sleep and eating habits and looking for the presence of anxiety, motor slowing, mood lability, psychotic symptoms, and/or suicidal ideation can aid in differentiating bipolar from unipolar depression.
Chapter 3

Pain as a Concomitant Symptom

FIGURE 3.6. Pain can be a symptom of depression or anxiety; in fact it is one of the most commonly complained-about presenting symptoms for these disorders. It has been found that nearly 70% of patients with depression report only physical symptoms as the reason for their visit; more than 10% deny psychological symptoms of depression on direct questioning. Patients who present with chief somatic complaints are often repeatedly misdiagnosed, hindering their recovery. This highlights the need to consider depression or anxiety when patients present with chief somatic complaints, and also to consider pain disorders in patients for whom mood or anxiety disorders are suspected. Clinicians should be sure that pain is treated with at least equal priority as the depression, in order to achieve the greatest possible level of remission.
Pain as a Comorbidity of Mood and Anxiety Disorders

FIGURE 3.7. In patients with three or more physical symptoms, it has been found that around 30% have comorbid major depressive disorder and over half have comorbid anxiety disorder. The number of unexplained physical symptoms, in fact, correlates directly with the likelihood of the presence of a treatable mood or anxiety disorder. In patients with specifically painful symptoms, it has been found that nearly 30% have comorbid major depressive disorder.

Anxiety and depression comorbidities have also been examined in more specific populations. Comorbid anxiety disorders and mood disorders are present in 35% and 22%, respectively, of patients with osteoarthritic pain, and these rates are similar for these comorbidities with spinal pain. Following severe accidental injury, patients with chronic pain exhibit significantly more symptoms of PTSD, anxiety, and depression. Among men with chronic back pain and depression, 58% said the depression followed the onset of pain.

Although it is clear that there is a relationship between pain, anxiety, and mood disorders, the directional causality of this relationship and the effects on disease course and treatment are not clear. The prevalence of comorbidity highlights the need to recognize and treat all existing symptoms for optimum patient outcome.
Fibromyalgia as a Comorbidity

FIGURE 3.8. Mood and anxiety disorders are commonly comorbid with fibromyalgia. In total, over 73% of patients with fibromyalgia also have either major depressive disorder or bipolar disorder and nearly 76% have some type of comorbid anxiety disorder. The figure breaks down particular types of mood and anxiety disorders that are commonly comorbid with fibromyalgia.

OCD: obsessive compulsive disorder.
Is Fibromyalgia an Affective Spectrum Disorder?
Part 1

FIGURE 3.9. Pain is not a formal diagnostic feature of depression or anxiety disorders but is frequently present in patients with these disorders. The reverse is also true: depressed mood, anxiety, and other symptoms are common in pain disorders, especially in functional somatic syndromes such as fibromyalgia, irritable bowel syndrome, and various forms of headache. Thus, rather than being discrete groups of illnesses, affective spectrum disorders and functional somatic syndromes may instead exist along the same spectrum, and this is supported by some of the neurobiological commonalities of these symptoms.

GAD: generalized anxiety disorder. MDD: major depressive disorder.
Is Fibromyalgia an Affective Spectrum Disorder?
Part 2

FIGURE 3.10. Clinical observations suggest that there is a powerful association between painful symptoms on one hand and mood and anxiety symptoms on the other hand, so that the higher the number of painful physical symptoms a patient has, the greater the likelihood that a patient has a mood or anxiety disorder. Thus, the modern psychopharmacologists can no longer brush aside pain symptoms in mood and anxiety disorders, or mood and anxiety symptoms in pain disorders, but they need to address them simultaneously.
Children and Adolescents with Depression

**FIGURE 3.11.** (A) Diagnosing depressive disorders in children and adolescents can be quite difficult as, depending on the developmental stage, the presentation of symptoms can vary widely. Additionally, children can exhibit times of sadness, and adolescents are known to be moody. So diagnosis needs to be done using a “developmental lens.” For some children and adolescents with mild depressive symptoms, it may be sufficient to use supportive counseling and problem-solving discussions as well as family education to treat them. For more severe cases it may be necessary to use pharmacotherapy, such as selective serotonin reuptake inhibitors (SSRI). (B) Determining which medication to use may be tricky in adolescents. In 2006, the FDA found an increased risk of suicidality in adolescent patients taking SSRIs versus placebo. Later studies, however, showed that more adolescents benefit from SSRI treatment than are harmed, by a 14:1 ratio. Additionally, it has been argued that since the black box warnings for SSRIs were implemented and the number of prescriptions for SSRIs has decreased, the number of adolescent suicide attempts has increased, suggesting that SSRI treatment of depression is saving lives. Thus, it will be necessary to find the perfect balance between drug-induced versus disease-induced suicide attempts in adolescents.
Rates of Depression Across the Life Span: Men vs. Women

FIGURE 3.12. The rates of depression among women (top) and men (bottom) across the life span. In women, there is a link with estrogen but in men there is no established link with testosterone.
Depression and the Link to Fluctuating Estrogen Levels Across the Female Life Cycle

FIGURE 3.13. Postpartum and perimenopausal periods indicate the highest risk of depression for women across the life span. These periods correspond with the times of greatest fluctuations of estrogen levels across the life span.

FIGURE 3.14. Pharmacotherapy use (including antidepressants and/or estrogen over the female life cycle) may vary based on the time/age of administration. Illustrated above are some of the issues that may arise in treating depression in women.

Reproductive Hormones and Synaptogenesis Across the Menstrual Cycle

FIGURE 3.15. In the early phase of the menstrual cycle, estradiol levels rise, inducing dendritic spine formation and synaptogenesis. Progesterone peaks as well, resulting in greatest spine formation after the first half of the cycle, when estrogen is also at its highest. After this point though, estrogen levels begin to fall while progesterone continues to rise. This leads to a downregulation of dendritic spines and removal of formed synapses by the end of the menstrual cycle.
Activity-dependent Spine Formation by Estradiol

**FIGURE 3.16.** Estrogen exerts a cyclical inhibitory influence on gamma-aminobutyric acid (GABA) interneurons, which in turn regulate pyramidal neurons. (A) When estrogen levels are low, GABA interneurons are active and thus pyramidal neurons are inhibited. (B) As estrogen levels rise early in the menstrual cycle, this reduces GABA inhibition, thus disinhibiting pyramidal neurons and leading to glutamate release. (C) Sustained activation of N-methyl-d-aspartate (NMDA) receptors by glutamate, achieved by the middle or late cycle, can trigger long-term potentiation and trophic changes that include formation of dendritic spines. As estrogen levels fall by the end of the menstrual cycle, GABA interneurons become active again and resume inhibition of pyramidal neurons, preventing maintenance of dendritic spine formation (A).
Estrogen as a Transcription Factor

FIGURE 3.17. (A) Estrogen binds to estrogen receptors, modulating gene expression. However, estrogen receptors differ from neurotransmitter receptors in that they are located in the neuronal cell nucleus. Thus, the receptor is near the gene. (B) Estradiol activation of these genes requires dimerization of two estrogen receptors after they bind to estradiol (E2) in order to activate transcription. (C) Gene products expressed by this process include nerve growth factor and brain-derived neurotrophic factor. Gene products also include enzymes and receptors for monoamine neurotransmitters.
Depression, Perimenopause, or Both?

FIGURE 3.18. The clinical link between vasomotor symptoms of perimenopause/ menopause and depression involves a high degree of overlapping symptoms, including low energy, poor concentration, insomnia, weight gain, and decreased libido. Some experts consider vasomotor symptoms (hot flashes) as a sign of erratically fluctuating estrogen levels and not just a symptom of perimenopause, but also a risk factor for onset or recurrence of a major depressive episode in a perimenopausal woman.
Chapter 3

Estrogen as a Trimonoamine Modulator for Vasomotor Symptoms

FIGURE 3.19. Vasomotor symptoms, also called hot flashes or flushes, are often accompanied by sweating and insomnia, all of which are well known symptoms that accompany perimenopause. Vasomotor symptoms are the clinical indication that estrogen levels are fluctuating irregularly and are increasingly recognized as a sign of onset or relapse of major depression during perimenopause. Fluctuating estrogen levels can theoretically create monoaminergic dysfunction in the brain. Hypothetically, dysregulation of monoaminergic control of the hypothalamic thermoregulatory centers could lead to vasomotor symptoms (left). Such patients could also hypothetically respond to the administration of estrogen with reduction of vasomotor symptoms (right). Because of its effects on promoting neuronal gene expression, estrogen could hypothetically act as a trimonoamine modulator (TMM). Patients whose fluctuating estrogen levels cause vasomotor symptoms via dysregulation of one or more of the monoamines in hypothalamic thermoregulatory centers may restore monoamine function and thereby relieve vasomotor symptoms when given estrogen. However, many women are not willing to take estrogen for vasomotor symptoms, and most prescribers are not willing to treat long-term with estrogen due to concerns about long-term health risks. This has created the need for a non-estrogen treatment for vasomotor symptoms.
Vasomotor symptoms are theoretically linked to fluctuating estrogen levels and may cause dysregulation of monoamines in hypothalamic thermoregulatory centers (top). Selective serotonin reuptake inhibitors (SSRI) show inconsistent benefit for vasomotor symptoms (bottom), although there are some positive results reported for paroxetine, which may in fact be a weak serotonin norepinephrine reuptake inhibitor.
Selecte Norepinephrine Reuptake Inhibitors for Vasomotor Symptoms?

FIGURE 3.21. Vasomotor symptoms are theoretically linked to fluctuating estrogen levels and may cause dysregulation of monoamines in hypothalamic thermoregulatory centers (top). Serotonin norepinephrine reuptake inhibitors (SNRI) may show benefit for vasomotor symptoms (bottom), although such agents are not approved for this use. Under investigation is whether SNRIs have the same effect size of benefit as estrogen, and whether the benefit-to-risk ratio justifies the use of SNRIs in treating vasomotor symptoms in perimenopausal women.
Estrogen as a Trimonoamine Modulator for Depression?

FIGURE 3.22. As a trimonoamine modulator (TMM), estrogen can theoretically boost the actions of one or more of the three monoamines (dopamine, norepinephrine, and serotonin). Patients who are theoretically deficient in one or more of the three monoamines, as may theoretically occur in women particularly in the postpartum and perimenopausal periods when estrogen levels can fluctuate widely, or in the post-menopausal period when estrogen levels are low (top), can have their monoamine activity theoretically restored when estrogen is added (bottom). However, this is not an approved use for estrogen, and many women and their prescribers wish to avoid estrogen use due to long-term risks to health. An in-depth and up-to-date benefit-to-risk ratio should always be determined when considering estrogen treatments.
Selective Serotonin Reuptake Inhibitors for Perimenopausal or Postmenopausal Depression?

**FIGURE 3.23.** Due to the association of vasomotor symptoms with the onset or recurrence of a major depressive episode, experts now debate whether prescribers should identify and treat vasomotor symptoms as well as the traditional symptoms of depression in perimenopausal women. Actually, the treatments for these two conditions overlap. Treating vasomotor symptoms could theoretically prevent a major depressive episode in vulnerable women. Furthermore, failure to treat vasomotor symptoms in a perimenopausal woman who also has a major depressive episode may stand in the way of reaching full remission of the major depressive episode, or of sustaining that remission in the long run. That is, remission of the classic symptoms of depression while vasomotor symptoms persist is a likely signal that fluctuating estrogen levels are still affecting the brain and may continue to create vulnerability for relapse. Ongoing research is seeking to determine whether targeting vasomotor symptoms in women with depression or who are at risk for depression will achieve better outcomes. In the meantime, if selective serotonin reuptake inhibitors (SSRI) for such women are not effective, it may be worthwhile to treat with serotonin norepinephrine reuptake inhibitors (SNRI). Furthermore, SSRIs seem to work better in the presence of estrogen than in the absence of estrogen (right). Thus, SSRIs may be more reliable in premenopausal women or in peri- or postmenopausal women who are taking estrogen.
Serotonin Norepinephrine Reuptake Inhibitors for Perimenopausal Depression?

FIGURE 3.24. To treat both vasomotor symptoms and symptoms of a major depressive episode in a perimenopausal woman with fluctuating estrogen levels or in a postmenopausal woman with low estrogen levels (top), serotonin norepinephrine reuptake inhibitors (SNRI) may be preferred (bottom). There is some evidence that SNRIs can not only relieve vasomotor symptoms, but also treat symptoms of a major depressive episode in peri- and postmenopausal women, even if they are not taking estrogen (bottom). However, further research is in progress.
FIGURE 3.25. So what should a psychopharmacologist do with a patient with major depressive disorder and comorbid disorders? Once the proper diagnosis has been reached, it is imperative to treat all disorders appropriately, and in terms of highest degree of impairment. This might mean that in one patient it is necessary to first stabilize the alcohol abuse, while in another patient the symptoms of depression might be more impairing than the underlying anxiety disorder. Additionally, some medications used to treat these disorders could exacerbate the comorbid ailment. Thus, care needs to be taken when choosing the appropriate treatment. An individualized treatment plan should therefore be established for each patient, depending on his/her symptomatic portfolio.
Major Depressive Disorder
Summary

- Three neurotransmitters are involved in the regulation of depressive symptomatology: serotonin (SHT), norepinephrine (NE), and dopamine (DA)

- Circuits include pathways extensively traveled by SHT, NE, and DA

- Various genes are risk factors for depression

- Depression can often be treatment-resistant, resulting in the need for several different drug combinations prior to achieving response and full remission

- There are currently many classes of antidepressants available, with selective serotonin reuptake inhibitors (SSRI), serotonin norepinephrine reuptake inhibitors (SNRI), and norepinephrine dopamine reuptake inhibitors (NDRI) most often considered first-line treatment options

- Augmentation of these first-line treatments can be selected by using a symptom-based strategy; that is, choose treatments most likely to reduce each individual patient’s specific symptoms based upon the underlying neurobiological rationale for these symptoms

- Several new treatments for depression are on the horizon

- Comorbidities should be addressed alongside major depressive disorders if full remission is to be attained
References

Levinson DF. Biol Psychiatry 2006;60:84–92.
Major Depressive Disorder

References (cont.)

1. What percentage of patients will achieve remission after four successive 12-week antidepressant treatments over the course of one year?
   A. 33%
   B. 40%
   C. 50%
   D. 67%

2. Your patient has been taking his antidepressant medication as indicated for the last two weeks, but his depressive symptoms have not subsided yet. He wonders whether this medication will work for him. You are telling him that the time course of antidepressant effects depends on a
   A. Decrease in monoamine levels
   B. Downregulation of monoamine receptors
   C. Decrease in neuronal firing

3. Serotonin 5HT2A and 5HT1A receptors have opposing actions on dopamine. The release of dopamine can be decreased by:
   A. Stimulation of 5HT1A and 5HT2A receptors
   B. Stimulation of 5HT1A receptors or blockade of 5HT2A receptors
   C. Blockade of 5HT1A receptors or stimulation of 5HT2A receptors
   D. Blockade of 5HT1A and 5HT2A receptors

4. A patient on a monoamine oxidase inhibitor goes to a restaurant. Which menu should he avoid?
   A. Soy-based burger with locally produced tap beer
   B. Spinach salad with raspberry iced tea
   C. Fish taco with margarita
   D. Beef burger with canned beer

5. A 59-year-old woman presents with depressed mood and vasomotor symptoms. She has not seen her college-aged children in a while because it is hard to muster up the energy to leave the house, and because she does not like to be in public when she starts sweating. If her levels of estrogen are low, which class of medication would be best for her depression?
   A. Serotonin norepinephrine reuptake inhibitor
   B. Norepinephrine dopamine reuptake inhibitor
   C. Selective serotonin reuptake inhibitor
   D. Norepinephrine reuptake inhibitor
CME Posttest (cont.)

6. An overdose of tricyclic antidepressants can be lethal due to which of their properties:
   A. Blockade of H1 receptors
   B. Blockade of 5HT2A/2C receptors
   C. Blockade of voltage-sensitive sodium channels
   D. Blockade of voltage-sensitive calcium channels

7. A patient presents with depressed mood and feelings of guilt and worthlessness. Inefficient information processing of monoamines in which brain areas could hypothetically best explain these symptoms?
   A. Striatum and orbitofrontal cortex
   B. Amygdala and ventromedial prefrontal cortex
   C. Nucleus accumbens and dorsolateral prefrontal cortex
   D. Basal forebrain and anterior cingulate cortex

8. A 70-year-old patient is diagnosed with major depression. He is taking many medications for various ailments, so the psychiatrist prescribes escitalopram as it is theoretically better tolerated. What is the relationship between citalopram and escitalopram?
   A. Citalopram is the parent drug; escitalopram is the metabolite
   B. Citalopram is the racemic; escitalopram is the enantiomer
   C. Citalopram is the prodrug; escitalopram is the active molecule

9. The medical food L-methylfolate can be advantageous in treating depression in patients with low levels of folic acid. How does L-methylfolate impact the synthesis of monoamines?
   A. It enhances the synthesis of tyrosine hydroxylase (TOH)
   B. It enhances the synthesis of DOPA decarboxylase
   C. It enhances the synthesis of tetrahydrobiopterin (BH4)
   D. It enhances the synthesis of monoamine oxidase A (MAO-A)

10. Alpha 2 antagonists, such as mirtazapine, do not act on monoamine transporters to lead to their therapeutic effect. How do they increase which monoamines?
    A. Disinhibition of norepinephrine and serotonin
    B. Disinhibition of dopamine and serotonin
    C. Disinhibition of dopamine and norepinephrine
Understanding and Managing the Pieces of Major Depressive Disorder

Posttest and Activity Evaluation Answer Sheet

Please complete the posttest and activity evaluation answer sheet on this page and return by mail or fax. Alternatively, you may complete these items online and immediately print your certificate at www.neiglobal.com/cme.

Please circle the correct answer.

Posttest Answer Sheet (score of 70% or higher required for CME credit)

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Activity Evaluation: Please rate the following, using a scale of:
1-poor  2-below average  3-average  4-above average  5-excellent

1. The overall quality of the content was...
   1  2  3  4  5

2. The overall quality of this activity was...
   1  2  3  4  5

3. The relevance of the content to my professional needs was...
   1  2  3  4  5

4. The level at which the learning objective was met of teaching me to identify neural implications of depression and describe neurobiologic symptoms...
   1  2  3  4  5

5. The level at which the learning objective was met of teaching me to utilize treatment options available for depression on a per-case basis...
   1  2  3  4  5

6. The level at which the learning objective was met of teaching me to discuss comorbidities associated with depression...
   1  2  3  4  5

7. The level at which this activity was objective, scientifically balanced, and free of commercial bias was...
   1  2  3  4  5

8. Based on my experience and knowledge, the level of this activity was...
   Too Basic  Basic  Appropriate  Complex  Too Complex

9. My confidence level in understanding and treating this topic has __________ as a result of participation in this activity.
   A. Increased
   B. Stayed the same
   C. Decreased
Understanding and Managing Major the Pieces of Depressive Disorder

Posttest and Activity Evaluation Answer Sheet (cont.)

10. Based on the information presented in this activity, I will…
   A. Change my practice
   B. Seek additional information on this topic
   C. Do nothing as current practice reflects activity’s recommendations
   D. Do nothing as the content was not convincing

11. What barriers might keep you from implementing changes in your practice you’d like to make as a result of participating in this activity?

12. The following additional information about this topic would help me in my practice:

13. How could this activity have been improved?

14. Additional comments:

15. Number of credits I am claiming, commensurate with the extent of my participation in the activity (maximum of 3.0): _________

Name: ____________________________________________ Credentials: ____________________

Address:  ______________________________________________________________________________

City: _________________________________________ State: __________ Zipcode: ___________________

Email:  __________________________________________________________________________________

Mail or fax both sides of this form to:
Mail:  CME Department  Fax: 760-931-8713
Neuroscience Education Institute  Attn: CME Department
1930 Palomar Point Way, Suite 101
Carlsbad, CA 92008