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# Chapter 88: Depressive Disorders

Amy M. VandenBerg

## CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 69, Depressive Disorders.

## KEY CONCEPTS

### KEY CONCEPTS

1. Multiple guidelines are available to guide the treatment of major depressive disorder (MDD), including medication management. Clinicians treating individuals with MDD should be familiar with key tenets of these guidelines.

2. Other potential causes of symptoms such as medical conditions, medications, and other substances must first be ruled out when evaluating a patient for a diagnosis of MDD.

3. The goals of treatment for MDD are the resolution of current symptoms (ie, remission) and the prevention of further episodes of depression (ie, relapse or recurrence).

4. When counseling patients with MDD who are receiving traditional antidepressant medications, the patient should be informed that transient adverse medication reactions might occur initially, while the symptoms of depression may take 2 to 4 weeks to improve and up to 3 months for full resolution. Adherence to the treatment plan is essential for a successful outcome, and tools to help increase medication adherence should be discussed with each patient.

5. Since available antidepressants are considered equally efficacious for MDD, factors such as comorbid medical conditions, age, adverse effect profile, and past history of response are used to guide medication selection.

6. When determining if a particular medication is ineffective for a patient, it is essential to evaluate the dose and duration of treatment as well as patient adherence to the medication.

7. Novel antidepressants that target GABA and glutamate systems may have a more rapid and transient effect on symptoms. They are typically used in conjunction with traditional antidepressants for refractory symptoms.

8. Pharmacogenetic tests are now commercially available. Resources are available to guide their use when clinicians are presented with testing results as it relates to antidepressant treatment of MDD.

9. When evaluating antidepressant response, the clinician must consider quality-of-life issues, such as social, and occupational functioning in addition to target signs and symptoms. The tolerability of the agent should also be assessed due to the occurrence of adverse medication reactions that may lead to medication nonadherence. This is especially important in cases of recurrent episodes and long-term medication management.

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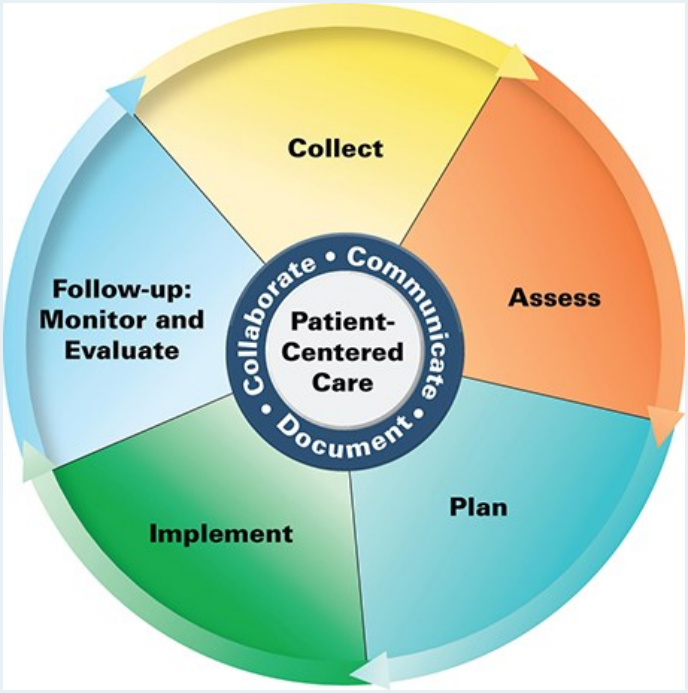
# PATIENT CARE PROCESS

**Patient Care Process for Major Depressive Disorder**




Watch the video of the Patient Care Process for Major Depressive Disorder.

**Collect**

- Patient characteristics (eg, age, sex, gender identity, race, pregnancy status)
- Current and past medical/psychiatric history (including information on first-degree family members)
- Past medication history, including medications not tolerated and any medication allergies (also collect on first-degree family members)
- Social history (eg, tobacco, ethanol, and other substance use as well as social supports and/or stressors)
- Current medications including over-the-counter (OTC), herbal products, dietary supplements, and medical or recreational cannabis use
- Objective data
  - Blood pressure, heart rate, weight
  - Labs including thyroid function tests, serum creatinine, complete blood count (CBC), liver function tests, urine toxicology screen, blood alcohol level, medication serum concentrations, and pharmacogenomics testing if available
  - Reported symptoms of depression or other rating scale assessment (eg, Patient Health Questionnaire 9 [PHQ-9], Beck Depression inventory [BDI]) (Tables 88-1 and 88-2 and Chapter e81, "Evaluation of Psychiatric Illness")

**Assess**

- Suicidality (eg, Columbia-Suicide Severity Scale)
- Severity of illness/need for hospitalization

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- Impact of substance use on symptoms and whether a substance use disorder is contributing to symptoms
- Presence of physical conditions that may overlap with depression symptoms (eg, pain resulting in insomnia or limited activity, gastrointestinal symptoms resulting in weight loss) or medications that may be contributing to depressive symptoms (Table 88-1)
- Past response and adherence (personal or family) to antidepressant medications
- Ability/willingness to follow up with psychiatry services including antidepressant medication management, cognitive behavioral therapy (CBT), outpatient groups
- Barriers to participation in medication management or CBT
- Barriers to adjunctive treatments (eg, exercise, stretching, yoga)
- Pharmacogenomics testing results

**Plan***

- Medication therapy regimen including specific agent(s), dose, frequency, and titration plan if applicable (Table 88-3)
- Monitoring parameters including efficacy (looking for some improvement in 2-4 weeks), safety (change in suicidality), and adverse medication reactions (may be seen in first 1-2 weeks of treatment) (Table 88-11)
- Patient education (eg, purpose of treatment, medication-specific information, medication adherence, and review of laboratory/pharmacogenomics results)
- Patient education regarding self-monitoring, when to call the clinic with questions or concerns, and when to seek emergency medical attention (eg, suicidality)
- Obtain release of information to gather collateral information (eg, family members, therapists, medical providers)
- Nonpharmacological interventions (eg, diet, exercise, mindfulness)
- Make referrals to other providers when appropriate (eg, neurologist, pain specialist, substance use disorder treatment)
- Potential for medication interactions (Tables 88-5, 88-9, and 88-10)

**Implement***

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching to maximize adherence
- Schedule follow-up to monitor and assess medication effectiveness (eg, PHQ-9, BDI) and adherence to treatment plan, including therapeutic medication monitoring when appropriate.

**Follow-up: Monitor and Evaluate**

- Resolution of depressive symptoms using standardized rating scales
- Presence of adverse medication reactions (Table 88-11)
- Laboratory follow-up when indicated (eg, sodium, liver function tests)
- Patient adherence to treatment plan based in multiple sources of information (eg, medication refill records, patient/caregiver report)
- Consider scheduling early or more frequent (every 1-2 weeks) follow-up visits after initiating therapy to monitor response and behavioral risks

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such as suicidality. Reevaluate initial response at 2 to 4 weeks and again at 8 to 12 weeks. Reevaluate treatment plan quarterly and reevaluate duration of therapy after patient achieves remission.

*Collaborate with patient, caregivers, and other healthcare professionals.*

## BEYOND THE BOOK

**BEYOND THE BOOK**

Watch the TED talk entitled Depression the Secret We Share by Andrew Solomon. This talk provides an engaging patient perspective on the experience of depression including Solomon's own experiences and that of others he interviewed.

Alternatively, watch "Pharmacology – Antidepressants – SSRIs, SNRIs, TCAs, MAOIs, lithium (Made Easy)" at https://www.youtube.com/watch?v=T25jvLC6X0w. This 19-minute video provides a brief visual narrated overview of the monoamine theory of depression and mechanisms of commonly used antidepressant medications.

## INTRODUCTION

Major depressive disorder (MDD) is diagnosed when an individual experiences one or more major depressive episodes without a history of mania or hypomania. A major depressive episode and MDD are defined by the criteria listed in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*).[1] Depression is associated with significant functional disability, morbidity, and mortality. Antidepressants, such as the selective serotonin reuptake inhibitors (SSRIs), are equally effective and better tolerated than older agents, such as the tricyclic antidepressants (TCAs) and the monoamine oxidase inhibitors (MAOIs). While depressive episodes also occur in bipolar disorder, this chapter focuses exclusively on the diagnosis and treatment of MDD.

1 Three key evidence-based guidelines on the assessment and management of MDD are available to assist the clinician. The American Psychiatric Association *Practice Guideline for the Treatment of Patients with Major Depressive Disorder*, Third Edition (2010) (available at www.psych.org) is a practical guide to the management of MDD based on both available data and clinical consensus.[2] The updated British Association of Psychopharmacology (BAP) *evidence-based guidelines for treating depressive disorders with antidepressants* (2015) provide recommendations for antidepressant treatment of MDD.[3] Finally, the Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 *Clinical Guidelines for the management of adults with major depressive disorder* outline evidence-based pharmacological treatments for MDD.[4] These three guidelines have many similarities in recommendations.

## EPIDEMIOLOGY

While the actual prevalence of depressive disorders, including undiagnosed cases, is unknown, the estimated rate has increased over the past 25 years, with additional increases since 2020.[5-8] Overall, the lifetime prevalence of depression is estimated at 7% to 15% with rate in females 1.5- to 2.5-fold higher than males.[2,3] In looking at non-sex factors, the prevalence of depression is highest in those less than 60 years of age, within non-White populations, and in individuals at high poverty levels compared to White populations over the age of 60 without poverty.[9] Intersectionality, or the study of how different social classes intersect, and its relationship to depression epidemiology is becoming a high priority field of study. Adolescent depression is increasingly common with an annual prevalence (2015) of 19.4% in females and 6.4% in males between 12 and 17 years of age (up from 13.1% and 4.5%, respectively, in 2004).[2,10] In addition, transgender and non-gender conforming individuals are also at risk for increased mental health issues. In particular adolescents in these groups with poor social support report a higher degree of suicidal ideation and attempts.[11]

Depressive disorders and suicide tend to occur within families. Approximately 8% to 18% of patients with MDD have at least one first-degree relative (father, mother, brother, or sister) with a history of depression, compared with 5.6% of those without depression.[12] First-degree relatives of patients

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with depression are 1.5 to 3 times more likely to develop depression than those without the family history.[4,12] The heritability of liability for MDD has been estimated at 37%, with the remaining 63% of the variance in liability due to individual-specific environment (eg, high stress, trauma).[12] Therefore, MDD is relatively common, and occurs more frequently in females than in males, and prevalence is influenced by both genetic and environmental factors.

## ETIOLOGY

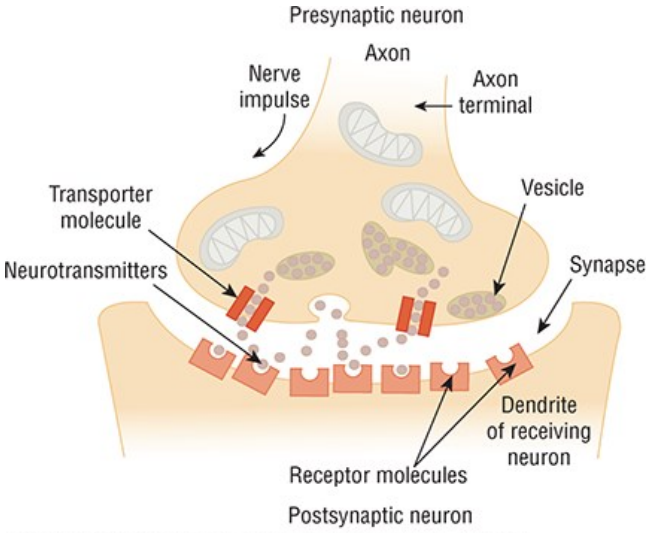
The etiology of depressive disorders is too complex to be explained by a single social, developmental, or biologic theory. Several factors appear to work together to cause or precipitate depressive disorders. Interactions between important factors such as individual's sex, gender identity, race, ethnicity, culture, social status, genetics, and environment are at the heart of understanding the role of intersectionality on the etiology of depression.

## PATHOPHYSIOLOGY

The monoamine hypothesis that depression is caused by decreased brain levels of serotonin (5-HT), dopamine (DA), and norepinephrine (NE) has been supported for over 50 years. However, the actual chemical basis for depression remains elusive.[13] This biogenic amine hypothesis evolved as a result of several observations made in the early 1950s that the antihypertensive medication reserpine depleted neuronal storage of NE, 5-HT, and DA and produced clinically significant depression in 15% or more of patients.[14] Subsequently, the hypothesis was supported by the mechanism(s) of antidepressant medications. Additionally, recurrence of depression has been induced by acute depletion of tryptophan (precursor of 5-HT) and 5-HT metabolite levels in cerebrospinal fluid are lower in some patients with MDD.[15] Evidence reveals the complexities of the monoamine systems in the brain. These systems are mediated by gamma aminobutyric acid (GABA), neuroactive steroids, endogenous opioids, and nutritional imbalances.[16-22] For the purposes of this chapter, the focus of medication mechanism of action will be the monoamine hypothesis unless otherwise specified (Figs. 88-1 and 88-2).

**FIGURE 88-1**

Monoamine neurotransmitter (NT) regulation at the neuronal level. NTs carry messages between cells. Each NT generally binds to a specific receptor, and this coupling initiates a cascade of events. NTs are reabsorbed back into nerve cells by reuptake pumps (ie, transporter molecules) at which point they may be recycled for later use or broken down by enzymes. For their primary mechanism of action, most antidepressants are thought to inhibit the transporter molecules and allow more NT to remain in the synapse. *(Reprinted from Mind Over Matter: The Brain's Response to Drugs—Teacher's Guide Revision. NIH Publication No. 05-3592. Office of Science Policy and Communications, National Institutes of Health. Revised May 2005. https://teens.drugabuse.gov/sites/default/files/moms-combined_0.pdf.)*

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Monoamine systems do not function independently, but serve as feedback mechanisms for each other. Therefore, a medication that preferentially enhances NE transmission may secondarily alter both 5-HT and DA activity.[23,24]

Although increase in synaptic monoamines (eg, NE, DA, and 5-HT) occurs rapidly after initiation of an antidepressant, the clinical effects (ie, measurable symptom improvement) are generally delayed by weeks.[15,23] This delay may be the result of a cascade of events from receptor occupancy to gene transcription, downregulation of presynaptic feedback mechanisms, and secondary effects on other neurotransmitter symptoms or neuroplasticity.[13,15,25] This led researchers to focus on the adaptive changes induced by antidepressants. In the mid-1970s, chronic, but not acute, administration of antidepressants to animals caused desensitization of NE-stimulated cyclic adenosine monophosphate synthesis. In fact, for most antidepressants, downregulation of β-adrenergic receptors accompanies this desensitization.[26,27] Studies of many antidepressants have demonstrated that either desensitization or downregulation of NE receptors corresponds the time course for antidepressant effects.[27] Other studies have revealed desensitization of presynaptic 5-$HT_{1A}$ autoreceptors following chronic administration of antidepressants.[15] These theories based on changes in receptor sensitivity provide a cogent explanation for the delayed onset of therapeutic response with antidepressant medications. The dysregulation hypothesis incorporates the diversity of antidepressant activity with the adaptive changes occurring in receptor sensitization over several weeks. In this theory, emphasis is placed on a failure of homeostatic regulation of NT systems rather than on absolute increases or decreases in their activities. According to this hypothesis, effective antidepressant agents restore efficient regulation to the dysregulated NT system.[13]

Traditional explanations of the biologic basis of depressive disorders have focused largely on NE and 5-HT. However, most of the evidence that coalesced into the biogenic amine hypothesis of depression does not clearly distinguish between NE and DA. There is an abundance of evidence suggesting that DA transmission is decreased in depression, and agents that increase dopaminergic transmission have been found to be effective antidepressants.[23] Specifically, increased DA transmission in the mesolimbic pathway accounts for at least part of the mechanism of action of antidepressant medications.[23] The mechanisms by which antidepressant medications alter DA transmission remain unclear, but may be mediated either directly by dopaminergic changes or indirectly by primary actions at NE or 5-HT terminals. The complexity of the interaction between 5-HT, NE, and DA is gaining greater appreciation, but a more in-depth understanding of the precise mechanism is needed. The availability of dopaminergic-based first-line and augmentation antidepressant strategies (eg, bupropion, high-dose venlafaxine, second-generation antipsychotics) may help answer remaining questions.

Neuroactive steroids are a growing area of research in depression as a link between the progesterone metabolite, allopregnanolone, and depression has been found. Allopregnanolone release is increased in the setting of acute stress and may serve a neuroprotective role. However, with chronic stress and MDD central nervous system (CNS) concentrations of allopregnanolone may decrease. Rapid decline in allopregnanolone levels in the postpartum period has been associated with postpartum depression.[28] Furthermore, certain antidepressants have been shown to increase cerebral spinal fluid (CSF) levels of allopregnanolone proportional to depressive symptom response.[18]

Another proposed pathway for depression involves a complex interplay of inflammation and overexcitation resulting in decreased neuroplasticity and neuronal differentiation. Brain-derived neurotrophic factor (BDNF) is a primary mediator of these neuronal changes as well as synaptogenesis. Chronic stress, associated with increased glucocorticoids such as cortisol, may lead to decreased BDNF expression. Evidence suggests this process may be prevented, or possibly even reversed, by antidepressant medications or electroconvulsive therapy (ECT).[29] Increased BDNF expression after treatment initiation follows timeline similar to antidepressant response.[29]

Chronic stress and inflammation also alter glutamate and GABA transmission, changes that have been linked to depression and decreased BDNF. Increased $GABA_A$ receptor activity is associated with decreased transmission of 5-HT and increased NE transmission while increased $GABA_B$ receptor activation is associated with decreased 5-HT and NE transmission.[24] Increased serum and extrasynaptic glutamate has been associated with MDD symptom severity. Many available antidepressants decrease serum glutamate concentrations and are thought to increase BDNF activity.[16,29] An example of this is ketamine which inhibits extrasynaptic NMDA receptors, theoretically increasing synaptic glutamate activity, triggering BDNF release from synaptic vesicles.[30] Further, BDNF has been shown to decrease expression of $GABA_A$ receptors possibly resulting in increased 5-HT and NE transmission linking it back to the monoamine hypothesis.[29] The interaction of all of these related systems is not fully understood. However, the complexities could partially explain differences in response to medications as there are likely distinct subtypes of depression with different pathogenesis.

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## Biologic Markers

Investigators continue to search for biologic markers to assist in the diagnosis and treatment of MDD. Although no gold-standard biologic marker has been discovered, several biologic abnormalities have been variably identified in patients with MDD. Hypersecretion of cortisol or a lack of cortisol suppression after dexamethasone administration (ie, a positive dexamethasone suppression test) has been positively correlated to depression as well as risk of suicide.[31] Although the widespread use of this test has fallen out of favor in recent decades (due to limited sensitivity and specificity), the inability of the brain to suppress the hypothalamic–pituitary–adrenal (HPA) axis and the associated stress response could contribute to depression, possibly due to excessive glutamate and decreased BDNF discussed above.[31] According to this theory, there is a disruption somewhere in the normal negative feedback system that controls cortisol levels.

**FIGURE 88-2**

The presynaptic regulation and postsynaptic actions of serotonin and norepinephrine are multifaceted and many of the steps have been implicated in the pathophysiology of depression. Currently available oral antidepressants have mechanisms focused on presynaptic regulation. Most first-line antidepressants target serotonin and/or norepinephrine transporters which are responsible for “reuptake” of the neurotransmitters into presynaptic neurons (hence, selective serotonin reuptake inhibitors or serotonin and norepinephrine reuptake inhibitors). Polymorphisms in these transporters have been associated with depression and may impact efficacy of medications that target the transporters. Other medication targets include MAO, 5HT1A receptors (vilazodone, vortioxetine), and α2 receptors (mirtazapine). Due to the complexity of these systems, there are numerous other targets at various stages of investigation. *(Reproduced, with permission, from DeBattista C. Antidepressant Agents. Katzung BG, ed. Basic & Clinical Pharmacology. 15th ed. New York, NY: McGraw-Hill; 2021.)*

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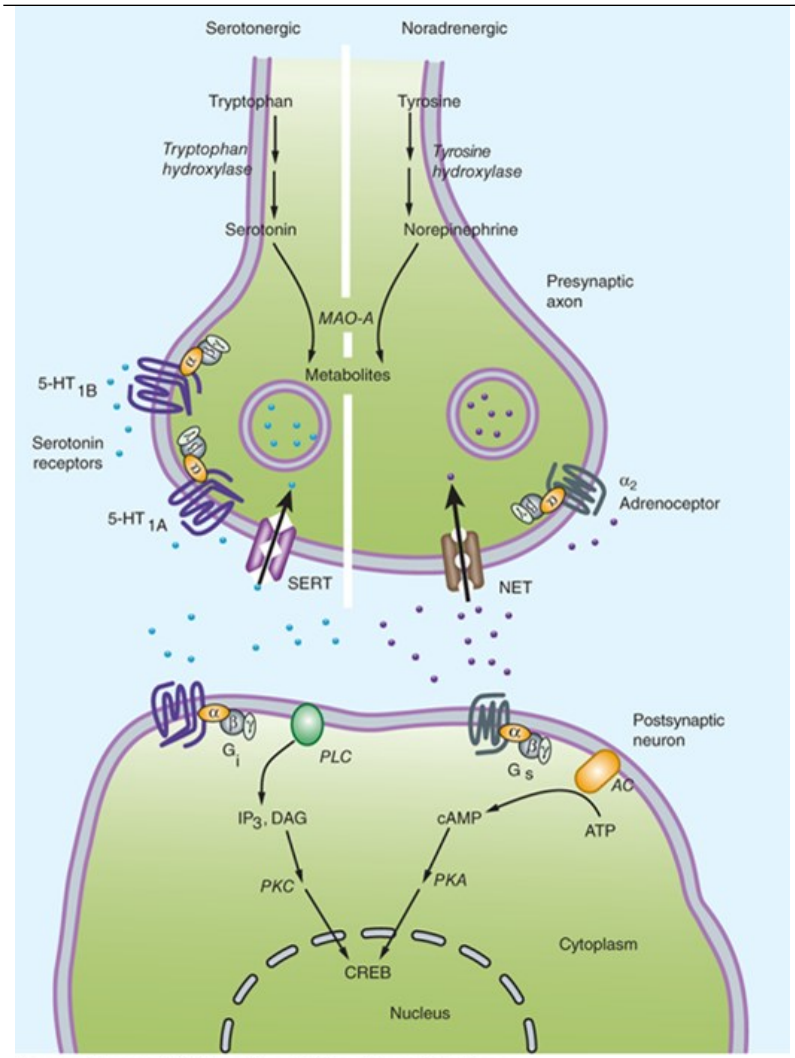


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Emerging evidence provides promise for both biologic and genetic markers for MDD. As previously mentioned serum levels of glutamate have correlated with MDD severity and rising concentrations of BDNF in the CNS have correlated to antidepressant response. The genes coding for BDNF production have been identified with polymorphisms that result in lower levels of BDNF.[29] Another focus of pharmacogenomics has been on polymorphisms of methylenetetrahydrofolate reductase (*MTHFR*) as they relate to differences in rates of depression and antidepressant response (inconsistent results to date).[32] Multiple other phenotypes have been identified and are available for testing with commercially available products, but evidence to date does not support routine testing for diagnosis or to predict treatment response.[33] Nor is there enough evidence to support testing CNS concentrations of BDNF or serum concentrations of glutamate.

## CLINICAL PRESENTATION

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**CLINICAL PRESENTATION: Depressive Disorder**

### Emotional Symptoms

- Diminished ability to experience pleasure
- Loss of interest and pleasure in usual activities, hobbies, or work (anhedonia)
- Pessimism, hopelessness regarding feeling better
- Anxiety
- Voices (eg, auditory hallucinations) saying negative comments or suggesting suicide

### Physical Symptoms

- Chronic fatigue resulting in decreased ability to attend to daily tasks (eg, bathing, grooming)
- Fatigue does not improve with rest and is often associated with pain, headache
- Changes in sleep (eg, early morning awakening, difficulty falling asleep, frequent awakening or increased sleep with associated fatigue)[34]
- Appetite changes (eg, most common decreased appetite and unintentional weight loss; increased appetite/weight gain atypical)[34,35]
- Gastrointestinal disturbances, genitourinary issues, cardiovascular complaints (eg, palpitations), loss of libido

### Cognitive Symptoms[35]

- Decreased concentration or slowed thinking
- Poor memory for recent events (especially older adults)
- Confused or indecisive

### Psychomotor Disturbances

- Slow physical movements, speech and thought processes (psychomotor retardation)
- Restlessness (eg, pacing, wringing of hands), outbursts of anxiety or agitation (eg, crying or yelling); together known as psychomotor agitation

2 When a patient presents with depressive symptoms, it is necessary to investigate the possibility of a contributing medical or medication-induced etiology. All patients evaluated for depression should have a complete physical examination, mental status examination, and basic laboratory workup, including a complete blood count (CBC) with differential, thyroid function tests, and electrolytes, to identify any potential medical problems. While a complete discussion of medical conditions associated with depression is beyond the scope of this chapter, multiple common medical conditions are associated with development of depressive symptoms, such as stroke, Parkinson disease, traumatic brain injury, and hypothyroidism. Other conditions associated with increased risk for depression include pain, diabetes, seizures, and coronary artery disease.[36] The *DSM-5* describes a diagnostic category for both "Depressive Disorder Due to Another Medical Condition" and "Substance/Medication-Induced Depressive Disorder,"[1] which emphasizes the importance of ruling out alternative causes of symptoms. A complete medication review should include both current and previous medications to assess for both helpful and contributing medications. Additionally, consider the contribution of substance withdrawal (eg, cocaine, cannabis, or alcohol) to depressive symptoms. Table 88-1 lists medications commonly associated with causing or exacerbating depressive symptoms.[37-44]

Once other medical-, medication-, or substance-related causes of symptoms have been ruled out, the patient should be evaluated for MDD. According

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to the *DSM-5*, a single major depressive episode is characterized by five (or more) of the symptoms described in Table 88-2.[1] At least one of the symptoms is depressed mood (often an irritable mood in children or adolescents) or loss of interest or pleasure in nearly all activities.[1] These symptoms must have been present nearly every day for at least 2 weeks and must represent a change from the patient's previous level of functioning. The diagnostic code for MDD is determined by whether this is a single or recurrent depressive episode, current severity, presence of psychotic features, and remission status. The diagnosis can be followed by specifiers that apply to the current episode. The possible specifiers include anxious distress, mixed features (ie, presence of manic/hypomanic features), melancholic features, atypical features, mood-congruent or incongruent psychotic features, catatonia, peripartum onset, and seasonal pattern. The clinician must consider presenting symptoms, their duration, and the patient's current level of social, occupational, or other important areas of functioning. Significant stressors or life events may trigger depression in some individuals; however, not all patients will have a clear precipitant.[1]

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TABLE 88-1

**Select Medications Associated with Depressive Symptoms**

| Medication Class | Individual Agents | Comments |
|---|---|---|
| **Acne treatment** | Isotretinoin | • REMS program iPledge recommends monitoring psychiatric symptoms |
| **Antiseizure medications** | All FDA-approved antiseizure medications (including clorazepate and clonazepam) | • Specific warning added to labeling under Warnings and Precautions regarding increased risk of suicidal thoughts or behavior<br>• Not all agents with warning have demonstrated increased risk<br>• Controversial |
| **Cardiovascular medications** | Reserpine | • Rarely used due to historical reports of depression due to depletion of monoamines |
| | Angiotensin receptor blockers<br>β-Blockers<br>Calcium channel blockers<br>Clonidine<br>Methyldopa | • Conflicting data for most agents<br>• β-Blockers classically linked to depression; however, most evidence supports only physical symptoms of fatigue and low energy<br>• Link between cardiovascular disease and depression must be considered |
| **Central nervous system agents** | Deutetrabenazine<br>Tetrabenazine<br>Valbenazine | • Deplete synaptic monoamines via decreasing vesicular transport in presynaptic neurons<br>• Deutetrabenazine and tetrabenazine have boxed warning for depression and suicidality |
| **Hormonal therapy** | Gonadotropin-releasing hormone<br>Oral contraceptives | • Linked to alterations in progesterone and estrogens and possible link to monoamine oxidase activity |
| | Steroids (eg, prednisone) | • Possible association with inflammation and HPA axis changes in depression |
| **Immunologic agents** | Interferons | • Labeled warning |
| **Smoking cessation medications** | Varenicline | • Reports to FDA MedWatch after release<br>• Large postmarketing study does not support increased risk |

REMS, Risk Evaluation and Mitigation Strategy; FDA, Food and Drug Administration.

*Data from References 2 and 37-44.*

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TABLE 88-2

**Diagnostic Criteria for Major Depressive Episode**

| | |
|---|---|
| **S** | Suicidal ideation with or without plan, suicide attempt; recurrent thoughts of death |
| **I** | Interest—loss of interest or pleasure in activities; anhedonia |
| **G** | Guilt—inappropriate or excessive in nature; feelings of worthlessness |
| **E** | Energy decreased |
| **C** | Concentration decreased; difficulty making decisions |
| **A** | Appetite changes; typically decreased; resulting in 5% change in weight from baseline |
| **P** | Psychomotor agitation or retardation |
| **S** | Sleep impairment; typically insomnia but may be hypersomnia |

- At least five symptoms must be consistently present over a 2-week period.
- Symptoms must include depressed mood or anhedonia.
- Symptoms must cause substantial distress or impairment in functioning.
- Other medical conditions or substance use do not account for symptoms.

*Data from Reference 1.*

## Depression Rating Scales

Instruments to assess the severity of depressive symptoms can be used for both clinical and research purposes. For example, the Montgomery-Åsberg Depression Rating Scale (MADRS) is a clinician-administered scale that is commonly used in clinical trials given its sensitivity to change.[45] Some depression rating scales are self-administered such as the Beck Depression Inventory (BDI) that takes only 5 to 10 minutes to complete by the respondent.[46] The PHQ-9 is another brief scale that has been validated for use.[47] For a more detailed explanation of these instruments, as well as other rating scales and evaluation approaches, refer to Chapter e81.

## Emotional Symptoms

A major depressive episode is characterized by a persistent, diminished ability to experience pleasure, and as such a loss of interest and pleasure in usual activities, hobbies, or work is common. Patients appear sad or depressed, and they are often pessimistic and believe that nothing will help them feel better. The occurrence of guilty feelings that are unrealistic is common, and these may reach delusional levels where patients feel that they deserve punishment and may view their present illness as a punishment. A patient suffering from MDD with psychotic features may hear voices, usually auditory hallucinations saying that they are a bad person or should try to die by suicide. Depression with psychotic features may require hospitalization, especially if the patient becomes a danger to self or others. Additionally, anxiety symptoms are present in almost 90% of outpatients with depression, which may have treatment implications.

## Additional Symptoms of Depression

Physical symptoms, rather than emotional symptoms, often motivate patients, especially older adults, to seek medical attention. Chronic fatigue, with a decreased ability to perform normal daily tasks is a common presenting symptom. The fatigue seen in patients with depression often appears worse

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in the morning, does not improve with rest, and is frequently accompanied by pain, especially headache.

Sleep disturbances generally present as early morning awakening with difficulty returning to sleep. This may coexist with difficulty falling asleep and frequent nighttime awakening, daytime exhaustion or fatigue. Hypersomnia (increased sleep) is less common. Recognition and management of sleep disturbances among patients with depression are crucial, as approximately 60% to 90% of patients experiencing MDD report sleep disturbances.[34]

Appetite disturbances, specifically decreased appetite, often result in substantial weight loss, especially in older adults.[34,35] Some patients lose 2 lb (0.9 kg) or more per week without dieting. Other patients may overeat and gain weight, although they typically do not enjoy eating.

Patients may present with a variety of other symptoms such as gastrointestinal (GI) issues (eg, pain, nausea, diarrhea, constipation), genitourinary issues (eg, incontinence, pain), cardiovascular complaints (eg, palpitations), cognitive impairment (especially older adults), or muscle fatigue. Lastly, patients frequently present with a loss of sexual interest or libido.

In addition to physical symptoms patients with MDD frequently experience cognitive and psychomotor disturbances noted in the Clinical Presentation box.

## Suicide Risk Evaluation and Management

As of 2018, the Centers for Disease Control and Prevention listed death by suicide as the tenth leading cause of death among Americans and the second leading cause of death among 10- to 44-year-olds.[6] Suicide rates increased between 6% and 58% in 49 of 50 states between 1999 and 2016 and the rates in adolescents in particular are rising in the face of the COVID pandemic.[8,48] All patients diagnosed with MDD should be assessed for suicidal thoughts and factors associated with increased risk for suicide including other psychiatric disorders, substance use disorders, adolescents and younger adults, physical illness, recent stressful life event, childhood trauma, hopelessness, and male gender.[49] Those with a higher level of risk often have high degree of suicidal intent and describe more specific plans, in particular, plans that are violent and irreversible.[49] The risk of death by suicide in those recovering from MDD may increase as they develop the energy and capacity to act on a plan made earlier in a course of illness. Despite factors to help identify those at greatest risk, it remains very difficult to predict suicidality in any given individual. Therefore, when suicidal intent is suspected, it is important to ask, “Are you thinking about harming or killing yourself?” (See Chapter e81 for more information.) If the risk is significant, the patient must be referred immediately to an appropriate healthcare professional. Certain depression rating scales, such as the MADRS and PHQ-9 discussed above, include questions that target suicidality, which may help identify those patients at risk. Additionally, the Columbia-Suicide Severity Rating Scale is widely accepted in clinical practice as a validated assessment of suicide risk.[50]

In September 2004, the FDA required manufacturers of antidepressants to add a boxed warning stating that all antidepressants increase the risk of suicidal thinking and behavior in short-term studies in children and adolescents with depressive disorders. These risks have become a new source of concern among those treating their patients with antidepressants. In order to help deal with the confusion these warnings have caused, experts have recommended the following[51]:

1. It is especially important to closely monitor patients for suicidal ideation and behavior at the beginning of treatment and among younger patients.
2. Discuss the possibility that adverse medication reactions may occur, including behavioral agitation or anger, and encourage patients to seek help should this occur.
3. Deal with the subject of suicide directly.

Withholding antidepressant treatment may not decrease the risk of suicide and may actually increase the risk. Furthermore, it may be that longer-term medication is needed for any protective effects against suicidality.[51]

In May 2007, the FDA expanded the boxed warning regarding suicidality to include young adults 18 to 24 years of age, during the initial stages of treatment. The warning also applies to any medication with either monotherapy or adjunct treatment of depression as an FDA-approved indication even if not classified as an “antidepressant” (eg, aripiprazole, quetiapine).

Assessment of actual suicide risk has proven to be difficult as there are differences in coding of events in clinical trials and complete case data from trials is often not available. Additionally, there appears to be an increased risk of suicidality in the 30 days after antidepressant discontinuation, which

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is not routinely evaluated in clinical trials.[52] An increased risk of suicidality in children and adolescents has been found in multiple studies and this population should be evaluated carefully upon initiation or discontinuation of antidepressant treatment. The complex relationships between antidepressant use and suicidality will continue to be explored with the hopes of more unequivocal recommendations.

# TREATMENT

## Desired Outcomes

3 The goal of treating depression is resolution of depressive symptoms and return to previous level functioning. Initial treatment may occur in the hospital or in outpatient treatment settings. Hospitalization is more likely when there is a high risk of suicide, poor physical health, limited social support or psychotic symptoms. Response, typically defined as 50% decrease in symptoms and is achieved in 40% to 50% of patients 8 to 12 weeks after medication initiation. Remission (absence of symptoms) is achieved in 25% to 30% of patients within 8 to 12 weeks after medication initiation.[3]

## General Approach to Treatment

There are three treatment phases for patients with MDD: (a) the *acute* phase lasting approximately 6 to 12 weeks in which the goal is remission; (b) the *continuation* phase lasting 4 to 9 months after remission is achieved, in which the goal is to eliminate residual symptoms or prevent relapse (ie, return of symptoms within 6 months of remission); and (c) the *maintenance* phase lasting at least 12 to 36 months in which the goal is to prevent recurrence (ie, a separate episode of depression).[2,53] The duration of antidepressant therapy depends on the risk of recurrence which increases with each depressive episode. Some guidelines recommend lifelong maintenance therapy for persons at greatest risk for recurrence (younger than 40 years of age with two or more prior episodes or any age with three or more prior episodes).[2] An alternative guideline is to treat for at least 2 years in patients considered to be at high risk for relapse.[3] The decision as to "when" and "how" to taper/discontinue an antidepressant regimen is always going to depend on patient- and medication-specific variables. Both SSRIs and SNRIs have an idiosyncratic discontinuation syndrome that may occur; therefore, it is recommended to slowly taper these agents over weeks to months to minimize risk. However, a slow taper is not always effective in preventing discontinuation symptoms.[54]

4 Educating the patient and their support system (eg, family and friends) regarding the delay in antidepressant effects and the importance of medication adherence should occur before and during the entire course of treatment. The treatment of MDD generally includes both nonpharmacologic and pharmacologic strategies.

## Nonpharmacologic Therapy

In addition to pharmacologic interventions, psychotherapy ("talk therapy") should be employed whenever the patient is able and willing to participate. Traditionally, psychotherapy alone is recommended only for mild to moderately severe cases of MDD. However, evidence supports the benefit of cognitive behavioral therapy (CBT) for even severe MDD.[55] Psychotherapy should not be the primary treatment modality for patients with psychotic features. The effects of psychotherapy and antidepressant medications are considered to be additive, thus combined treatment may be advantageous for patients with partial responses to either treatment alone and for those with a chronic course of illness. In practice, CBT as primary treatment is limited significantly by cost and logistics (eg, need for more frequent appointments and time off work). Additionally, many insurance plans do not adequately cover the cost of psychotherapy, the availability of providers may be limited in certain areas, and patients may be more reluctant to spend the time in therapy versus taking medication. In the Sequenced Treatment Alternatives to Relieve Depression study (STAR*D), evaluation of the psychotherapy arm was limited by low participation rates.[56]

Electroconvulsive therapy (ECT) is a safe and effective treatment for severe MDD. Ideally it is used when a rapid response is needed (eg, severe suicidality, nutritional deficiency, catatonic symptoms), risks of other treatments outweigh potential benefits, symptoms refractory to two antidepressant trials, or there is history of good response to ECT, and the patient expresses a preference for ECT. Another nonpharmacologic approach is repetitive transcranial magnetic stimulation (rTMS), which has demonstrated efficacy in treating MDD symptoms without the anesthesia required for ECT.[57]

The health benefits of physical activity have long been recognized for many medical conditions, and data suggest benefits in depressed patients. The

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Treatment with Exercise Augmentation for Depression (TREAD) study demonstrated that 16 kcal (67 kJ) per kilogram per week (KKW) exercise was associated with greater MDD remission rates compared with 4 KKW, when both were used as augmentation to an SSRI.[58] According to APA Task Force, integrating exercise into the MDD treatment plan is medically appropriate and confers many well-accepted health benefits.[59]

## Pharmacologic Therapy

Antidepressants are considered first-line treatment for a moderate-to-severe depressive episode.[2-4] They can be classified in several ways, including by chemical structure and the presumed mechanism of antidepressant activity. Although the link between the presumed mechanism of action and antidepressant response is tenuous, this classification has the advantage of being based on established pharmacology and clearly explains some of the common, but expected, adverse medication reactions. The knowledgeable clinician can use these antidepressant properties to tailor treatment to individual patient needs optimizing treatment outcomes. Currently available antidepressants, including dosing guidance, are provided in Table 88-3.[2,3,53,60-62]

TABLE 88-3

**Adult Dosing Guidance for Currently Available Antidepressant Medications**

| Medication (Brand Name) | Initial Dose (mg/day) | Usual Dosage Range (mg/day) | Comments (eg, Maximum Daily Dosage, Suggested Therapeutic Plasma Concentration) |
|---|---|---|---|
| **Selective Serotonin Reuptake Inhibitors (SSRIs)**<br>Patients with significant anxiety should start with lower initial dose to improve tolerability; however, target dose does not differ. | | | |
| Citalopram (Celexa) | 10-20 | 20-40 | Doses >40 mg/day not recommended due to QTc prolongation risk; maximum 20 mg/day for CYP2C19 poor metabolizers, coadministration with CYP2C19 inhibitors or patients older than 60 years of age |
| Escitalopram (Lexapro) | 5-10 | 10-20 | Maximum 20 mg/day; dose may be increased to maximum daily dose after 1 week |
| Fluoxetine (Prozac) | 10-20 | 20-60 | Maximum 80 mg/day; dose may be increased in 20-mg increments |
| Fluvoxamine (Luvox) | 25-50 | 50-300 | Maximum 300 mg/day; daily doses >100-mg total dose should be divided twice daily, with the larger dose given at night<br>Maximum 300 mg/day (ER formulation) |
| Paroxetine (Paxil) | 10-20 | 20-50 | Maximum 50 mg/day (IR formulation); titrate 10 mg/day increments weekly<br>Maximum 62.5 mg/day (CR formulation); titrate 12.5 mg/day increments weekly |
| Sertraline (Zoloft) | 25-50 | 50-200 | Maximum 200 mg/day; titrate 25 mg/day increments weekly |
| **Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)** | | | |

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| | | | |
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| *Newer-generation SNRIs* | | | |
| Desvenlafaxine (Pristiq) | 50 | 100 | Doses up to 400 mg/day have been studied; however, tolerability decreases with doses >50 mg. Dose reductions or discontinuation may be required if sustained hypertension occurs |
| Duloxetine (Cymbalta) | 30 | 30-90 | Maximum 120 mg/day (given once or twice daily); doses >60 mg/day not shown to provide increased efficacy for the treatment of MDD |
| Venlafaxine (Effexor) | 37.5-75 | 75-225 | Maximum 375 mg/day (IR); maximum 225 mg/day (ER); may increase in increments up to 75 mg/day at a minimum of every 4 days. Dose reductions or discontinuation may be required if sustained hypertension occurs |
| Levomilnacipran (Fetzima) | 20 | 40-120 | Initial dose (20 mg) for 2 days before dose increases is recommended at intervals of 2 or more days. Dose adjustment or discontinuation may be required if sustained elevated heart rate or hypertension occurs |
| *Tricyclic antidepressants (TCAs)* | | | |
| Amitriptyline (Elavil) | 25 | 100-200 | Maximum 300 mg/day for MDD; as single daily dose at bedtime or divided doses; therapeutic serum level 80-200 ng/mL (mcg/L; ~300-740 nmol/L); parent medication plus metabolite (nortriptyline) |
| Desipramine (Norpramin) | 25 | 100-200 | Maximum 300 mg/day; suggested therapeutic concentration range for combined imipramine + desipramine: 100-300 ng/mL (mcg/L; ~370-1,100 nmol/L) |
| Doxepin (Sinequan) | 25 | 100-200 | Maximum 300 mg/day as a single daily dose at bedtime (if tolerated) or in divided doses; a single dose should not exceed 150 mg |
| Imipramine (Tofranil) | 25 | 100-200 | Maximum 300 mg/day as single daily dose at bedtime (if tolerated) or divided doses; suggested therapeutic concentration range for combined imipramine + desipramine: 150-300 ng/mL (mcg/L; ~550-1,100 nmol/L) |
| Nortriptyline (Pamelor) | 25 | 50-150 | Maximum 150 mg/day as single daily dose (if tolerated) or divided doses; therapeutic serum level 50-150 ng/mL (mcg/L; 190-570 nmol/L) |
| **Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)** | | | |
| Bupropion (Wellbutrin) | 150 (75 mg given twice daily) | 150-450 | Maximum 450 mg/day (IR, ER), 400 mg/day (SR); ER dosed once daily; SR dosed once or twice daily; IR may be dosed up to three times daily. Adhering to labeled maximum daily and maximum single doses minimizes effect on seizure threshold |
| **Mixed Serotonergic Effects (Mixed 5-HT)** | | | |

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| | | | |
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| Nefazodone (Serzone) | 100 | 200-400 | Maximum 600 mg/day; daily doses should be divided twice daily; boxed warning hepatotoxicity |
| Trazodone (Desyrel) | 50 | 150-300 | Maximum 600 mg/day |
| Vilazodone (Viibryd) | 10 | 20-40 | Target dose 20-40 mg/day unless coadministered with CYP3A4 inhibitor (dose not to exceed 20 mg/day). Dose titration: 10 mg/day for 7 days, 20 mg/day for 7 days, and then may increase to 40 mg/day. Dose must be taken with food to ensure adequate absorption |
| Vortioxetine (Trintellix) | 10 | 20 | Maximum 20 mg/day |
| **Serotonin and $\alpha_2$-Adrenergic Antagonist** | | | |
| Mirtazapine (Remeron) | 15 | 15-45 | Maximum 45 mg/day |
| **Monoamine Oxidase Inhibitors (MAOIs)** | | | |
| Phenelzine (Nardil) | 15 | 30-90 | Maximum 90 mg/day; divided dosing; increase by 15 mg at 1- to 3-week intervals |
| Selegiline (transdermal) (Emsam) | 6 | 6-12 | Not to exceed 12 mg/24 hours; dose may be increased by 3 mg/day increments every 2 weeks; site of application should be rotated |
| Tranylcypromine (Parnate) | 10<br>10-20 | 20-40<br>30-60 | Maximum 60 mg/day; divided dosing; increase by 10 mg at 1- to 3-week intervals |
| Isocarboxazid (Marplan) | 10-20 | 30-60 | Maximum 60 mg/day; divided dosing |
| **Second-generation Antipsychotics (SGA) as Augmentation ($5HT_{2A}$ and $D_2$ modulators)** | | | |
| Aripiprazole (Abilify) | 2 | 2-15 | FDA-approved for augmentation; CANMAT Level 1 evidence, 1st line |
| Brexpiprazole (Rexulti) | 1 | 1-3 | Not FDA-approved for augmentation; CANMAT Level 1 evidence, 2nd line |
| Olanzapine (Zyprexa) | 2.5 | 2.5-10 | Not FDA-approved for augmentation; CANMAT Level 1 evidence, 2nd line |

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| | | | |
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| Olanzapine/fluoxetine (Symbyax) | 3/25 | 6-12/25-50 | FDA-approved for treatment-resistant depression |
| Quetiapine (Seroquel) | 50 | 150-300 | FDA-approved for augmentation; CANMAT Level 1 evidence, 1st line |
| Risperidone (Risperdal) | 1 | 1-3 | Not FDA-approved for augmentation; CANMAT Level 1 evidence, 1st line |
| **Alternative Augmentation Agents (Not FDA-Approved for Antidepressant Augmentation)** | | | |
| Buspirone (Buspar) | 10 | 10-60 | Divided dosing 2 to 3 times daily<br>5HT1A partial agonist |
| Lithium | 300 | 600-1,200 | Dose based on therapeutic levels (target 0.6-1 mEq/L [mmol/L])<br>Mechanism in depression not fully understood |
| Triiodothyronine (Cytomel) | 0.025 | 0.025-0.05 | Once daily dosing; monitor free T3 levels |

CANMAT, Canadian Network for Mood and Anxiety Treatments; CR, continuous release; ER, extended release; IR, immediate release; MDD, major depressive disorder; SR, sustained release.

*Data from References 2, 3, 53, and 60-62.*

5 Antidepressants are of *equivalent efficacy* when administered in comparable doses. Because one cannot predict which antidepressant will be the most effective in an individual patient, the initial choice is made empirically. Factors that often influence antidepressant choice include the patient's history of response, history of familial antidepressant response, concurrent medical illnesses and medications, presenting symptoms (eg, insomnia vs hypersomnia), potential for medication interactions, adverse medication reactions, patient preference, and medication cost. Although the precise pathophysiology of MDD remains elusive, clinicians can now select from multiple approved medications with different mechanisms of action (Tables 88-3 and 88-8).[2-4,63] Failure to respond to one antidepressant class or one antidepressant agent within a class does not predict a failed response to another class or another agent within the same class (Fig. 88-3). Approximately 50% to 60% of patients with MDD improve with acute medication therapy, compared with about 30% to 40% who improve with placebo.[3,64]

### Selective Serotonin Reuptake Inhibitors

The efficacy of SSRIs is superior to placebo and comparable to other antidepressant classes in treating patients with MDD.[2,53] They are generally chosen as *first-line* due to relative safety in overdose and improved tolerability over TCAs and MAOIs. The decision of which SSRI to use is typically based on the nuances of each medication, such as differences in interaction profile and pharmacokinetic (PK) parameters (eg, half-life). These concepts will be discussed in greater detail later in this chapter. The STAR*D trial demonstrated that nonresponse to one SSRI does not predict nonresponse to an alternative SSRI and a recent meta-analysis found no differences in efficacy between agents.[56,65]

The SSRIs, as the name implies, have a low affinity for other receptors including alpha$_1$-adrenergic (α1), histaminic (H1), and muscarinic (M1) receptors. Given this pharmacology, they are associated with lower rates of orthostatic hypotension, sedation, weight gain, and anticholinergic effects compared to TCAs.[2-4,63] The most common dose-dependent tolerability issues with SSRI use, which generally are mild and limited to 1 to 2 weeks after initiation or dose increases, are GI symptoms (eg, nausea, vomiting, and diarrhea), anxiety, and headache.[66] Both somnolence and insomnia have been

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reported with all SSRIs.[67] Additionally the SSRIs may cause clinically relevant impairment in all three stages of the human sexual response (arousal, libido, orgasm)[68]; however, it is important to note that depression itself may be associated with sexual dysfunction. A discontinuation or withdrawal syndrome may occur if SSRIs are abruptly discontinued (see details below with SNRIs). Paroxetine has more anticholinergic and antihistaminergic activity that has been linked with increased sedation and weight gain compared to other SSRIs.[2-4,63] The FDA released a safety announcement linking citalopram to a dose-dependent increase in QT interval, with recommended, age-dependent dose limits.[69] There has since been controversy regarding this safety warning and potential unintended consequences (eg, underdosing, discontinuation leading to relapse).[69,70] Dose-dependent increase in QT interval may also be associated with escitalopram; however, clinical significance of the QT increase is questionable with both agents.[69]

## Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)

### Tricyclic Antidepressants

Although TCAs are effective in treating MDD, use has diminished greatly due to the availability of equally effective therapies that are better tolerated and much safer in overdose. All TCAs potentiate the activity of NE and 5-HT by blocking their reuptake. However, the potency and selectivity of TCAs for the inhibition of NE and 5-HT reuptake vary greatly among these agents (see Table 88-4). Nortriptyline is most commonly used and may be selected in patients with comorbid migraine headaches, neuropathic pain, or fibromyalgia.

TABLE 88-4

**Relative Potencies of Norepinephrine and Serotonin Reuptake Blockade and Select Receptor Antagonism Profile of Antidepressants**

| | Reuptake Antagonism | | M1 | H1 | α1 |
|---|---|---|---|---|---|
| | NE | 5-HT | | | |
| **Selective Serotonin Reuptake Inhibitors (SSRIs)** | | | | | |
| Citalopram | 0 | ++++ | 0 | + | 0 |
| Escitalopram | 0 | ++++ | 0 | 0 | 0 |
| Fluoxetine | + | ++++ | 0 | 0 | 0 |
| Fluvoxamine | 0 | ++++ | 0 | 0 | 0 |
| Paroxetine | ++ | ++++ | ++ | + | 0 |
| Sertraline | 0 | ++++ | 0 | 0 | + |
| **Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)** | | | | | |
| Duloxetine | +++ | ++++ | 0 | 0 | 0 |
| Levomilnacipran | ++++ | +++ | + | 0 | 0 |
| Venlafaxine[a] and desvenlafaxine | +++ | ++++ | 0 | 0 | 0 |
| **Tricyclic Antidepressants (TCAs)** | | | | | |
| Amitriptyline | ++ | ++++ | ++++ | ++++ | +++ |

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| | | | | | |
|---|---|---|---|---|---|
| Desipramine | ++++ | ++ | + | ++ | ++ |
| Doxepin | ++ | ++ | +++ | ++++ | +++ |
| Imipramine | ++ | ++++ | +++ | ++++ | +++ |
| Nortriptyline | ++++ | ++ | ++ | +++ | ++ |
| **Mixed Serotonergic (Mixed 5-HT)** | | | | | |
| Nefazodone | 0 | ++ | 0 | +++ | +++ |
| Trazodone | 0 | ++ | 0 | ++ | +++ |
| Vilazodone | 0 | ++++ | 0 | + | 0 |
| Vortioxetine | 0 | ++++ | 0 | + | 0 |
| **Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)** | | | | | |
| Bupropion[b] | + | 0 | + | 0 | 0 |
| **Serotonin and $\alpha_2$-Receptor Antagonist** | | | | | |
| Mirtazapine | 0 | 0 | 0 | +++ | + |

M1, antimuscarinic/anticholinergic adverse reactions; H1, antihistamine, sedation; α1 antiadrenergic, hypotension.

++++, high; +++, moderate; ++, low; +, very low; 0, absent or not adequately studied.

[a]Venlafaxine: primarily 5-HT at lower doses, NE at higher doses, and DA at very high doses.

[b]Bupropion: also blocks dopamine reuptake.

*Data from References 2-4, 53, and 63.*

The TCAs affect other neurotransmitters and produce a wide range of pharmacologic actions, including several unwanted, but expected, adverse medication reactions. The most commonly occurring dose-related adverse reactions are anticholinergic in nature and include dry mouth, constipation, blurred vision, urinary retention, dizziness, and tachycardia (see Table 88-8). In older adult patients or with very high doses, memory impairment or delirium may occur.[71] Although some tolerance does develop, these reactions have the potential to impact patient adherence, particularly in older adults and those receiving long-term maintenance therapy. Additional tolerability issues that decrease TCA adherence include weight gain and sexual dysfunction.[71]

Orthostatic hypotension is a common, dose-related reaction attributed to the affinity of the TCAs for $\alpha_1$ receptors.[63] In patients with history of myocardial infarction, TCAs should be avoided due to risk of severe arrhythmias (QTc prolongation, torsades de pointes) thought to be associated with their class IA antiarrhythmic effects.[72] Additionally, TCAs can cause cardiac conduction delays, may induce heart block in patients with a preexisting conduction disorder, and overdose is associated with severe arrhythmias.[71] Desipramine's prescribing information reflects an increased risk of death in patients receiving the medication who have a *family history* of sudden cardiac death, cardiac dysrhythmias, and cardiac conduction disturbances. More on this reaction can be found at the FDA's MedWatch Website. Caution should be exercised when prescribing these agents, especially in higher doses, to patients with clinically significant cardiac disease, and to patients with a family history of a cardiac event.

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Venlafaxine and its primary active metabolite, desvenlafaxine, inhibit 5-HT reuptake at low doses, and NE reuptake at higher doses, whereas duloxetine equally inhibits both 5-HT and NE reuptake inhibition across all doses. This difference in receptor binding has not been associated with significant differences in efficacy. According to some studies, the SNRIs may be associated with higher rates of response and remission than other antidepressants; however, most of these studies involved venlafaxine, and not all studies support this conclusion.[65] The BAP guidelines discuss the possibility of a slight efficacy advantage (ie, lower number needed to treat; NNT) for venlafaxine (as well as escitalopram and sertraline) compared to other antidepressants.[3]

The most recent SNRI to be FDA-approved for MDD is levomilnacipran. This is a single-isomer, extended-release formulation of milnacipran which is FDA-approved only for the treatment of fibromyalgia. It is too soon to determine its place in therapy for MDD; however, pharmacologically it is relatively unique among the SNRIs given its greater potency at inhibiting NE reuptake compared to 5-HT reuptake.[63,73] One NE selective reuptake inhibitor, reboxetine, available in non-US markets, was not FDA-approved due to poor tolerability and lack of efficacy.

The most commonly reported tolerability issues with SNRIs, similar to those of SSRIs, may be dose-related and include nausea, sexual dysfunction, and activation.[2-4] Hyperhidrosis (excessive sweating) occurs primarily with SNRIs. Dose-related increases in blood pressure have been reported more with venlafaxine and levomilnacipran but may also occur with duloxetine and desvenlafaxine.[2] Blood pressure should be monitored at baseline and regularly during therapy, especially after dose increases. The discontinuation or withdrawal syndrome that can occur when treatment is stopped appears to be more severe with SNRIs than SSRIs. Common withdrawal symptoms include headache, fatigue, sweating, musculoskeletal pain, electric shock sensations, and anxiety. While slowly tapering off the medication may help to reduce the risk of the withdrawal syndrome, it may not fully prevent.[54] Duloxetine has also been associated with idiosyncratic hepatotoxicity (1 per 100,000 case exposures) with enzyme elevations more than three times upper limit of normal in 1% of patients, but does not carry the boxed warning associated with nefazodone.[74]

### Mixed Serotonergic Medications (Mixed 5-HT)

Trazodone and nefazodone have dual actions on serotonergic neurons, acting as both postsynaptic 5-$HT_2$ antagonists and presynaptic 5-HT reuptake inhibitors. They may also enhance 5-$HT_{1A}$-mediated neurotransmission.[63] Trazodone blocks $\alpha_1$ and H1 receptors leading to adverse reactions (eg, dizziness and sedation) that limit its use as an antidepressant. Use of nefazodone declined after reports of hepatotoxicity and the FDA-approved labeling includes a boxed warning describing rare cases of fulminant liver failure (1 case per 300,000 treatment years) and hepatic impairment (29 cases per 100,000 treatment years).[74] Trazodone and nefazodone are effective agents in treating MDD; however, both carry risks that limit their usefulness. Immediate-release trazodone is most often used adjunctively (in low doses) with other antidepressants to treat insomnia associated with MDD.[67]

Trazodone and nefazodone have minimal anticholinergic effects and comparatively less 5-HT agonist adverse reactions (eg, sexual dysfunction), but they can cause orthostatic hypotension. Sedation, cognitive slowing, and dizziness are the most frequent dose-limiting adverse reactions associated with trazodone, although the dosage used for the treatment of depression is significantly higher than the dosage often used for the treatment of insomnia (25-200 mg).[4,67] Common adverse medication reactions associated with nefazodone include light-headedness, dizziness, orthostatic hypotension, and somnolence. Nefazodone treatment should not be initiated in individuals with active liver disease or with elevated baseline serum transaminases. A rare but potentially serious adverse reaction of trazodone is priapism, which is reported to occur in approximately 1 in 6,000 male patients. Some cases have required surgical intervention (1 in 23,000), and permanent impotence may result.[75] There have been no reports of priapism associated with nefazodone use in males, but there is a published case report of nefazodone-induced clitoral priapism.[75]

Vilazodone and vortioxetine are combination SSRI and 5-$HT_{1A}$ presynaptic receptor partial agonists approved for the treatment of MDD.[73] Presynaptic 5-$HT_{1A}$ partial agonism has previously been hypothesized as a mechanism for SSRI augmentation with pindolol, which has preferential antagonism at the presynaptic 5-$HT_{1A}$ receptor.[76] The primary dose-limiting adverse reaction of these two newer agents is nausea. Vortioxetine additionally antagonizes 5-$HT_3$ which is proposed to mitigate some of the nausea, and is also a partial agonist at 5-$HT_{1B}$, and an antagonist at 5-$HT_{1D}$ and 5-$HT_7$ receptors.[62] Preliminary data support a linkage between the 5-$HT_7$ receptor antagonism and lack of cognitive slowing and potential for improved

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cognitive symptoms with vortioxetine in patients with MDD.

Vilazodone and vortioxetine are both associated with significant dose-related GI tolerability issues (eg, diarrhea and nausea), dizziness, insomnia, and decreased libido (particularly among males) when compared to placebo.[73] Rates of sexual dysfunction appear to be lower than with SSRIs; however, in some trials comparator agents known to cause sexual dysfunction (eg, duloxetine) also had lower rates of sexual dysfunction.[62,73]

### Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)

Bupropion has no appreciable effect on the 5-HT reuptake, and inhibits both the NE and DA reuptake making it one of the most activating antidepressants.[63] This can be particularly helpful for decreased motivation, low energy, and fatigue, which are common symptoms in older adult patients. It is also FDA-approved for smoking cessation and in a combination product with naltrexone for weight loss.

Adverse medication reactions associated with bupropion include nausea, vomiting, tremor, insomnia, and dry mouth. The occurrence of seizures in patients taking bupropion appears to be strongly dose-related, and may be increased by predisposing factors such as history of prior seizure activity, severe alcohol withdrawal, head trauma, or CNS tumor. Bupropion use is contraindicated in patients with eating disorders such as bulimia and anorexia. In addition to risk for further appetite suppression, these patients are prone to electrolyte abnormalities and are therefore at higher risk for seizure activity. At daily doses of 450 mg (the FDA-approved maximum dose) or less, the incidence of seizures is 0.4%, which is similar to reported rates for clomipramine, desipramine, and citalopram.[77] Bupropion is associated with minimal sexual dysfunction compared with the SSRIs and may actually improve SSRI-induced sexual dysfunction when used as adjunctive treatment.[78]

### Serotonin and $\alpha_2$-Adrenergic Receptor Antagonists

Mirtazapine enhances central noradrenergic and serotonergic activity through the antagonism of central presynaptic $\alpha_2$-adrenergic autoreceptors and heteroreceptors.[79] Furthermore, it antagonizes postsynaptic 5-$HT_2$, 5-$HT_3$, and H1 receptors resulting in anxiolytic, anti-nausea, and sedative effects, respectively.

The most common adverse medication reactions of mirtazapine are somnolence, weight gain (>7%), likely due to relatively strong antihistaminergic properties.[67] Mirtazapine is associated with minimal sexual dysfunction.

### Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors increase the concentrations of NE, 5-HT, and DA within the neuronal synapse through inhibition of the MAO enzymes. The MAOIs isocarboxazid, phenelzine, and tranylcypromine are nonselective inhibitors of MAO-A and MAO-B. A selegiline transdermal patch allows inhibition of MAO-A and MAO-B in the brain, yet has reduced effects on MAO-A in the gut.[80]

The most common adverse reaction of oral MAOIs is postural hypotension, which is more likely to occur with phenelzine and may be minimized with divided doses. Other common adverse reactions include weight gain and sexual dysfunction (eg, decreased libido and anorgasmia).[2] Phenelzine has mild-to-moderate sedating effects, while tranylcypromine and selegiline may exert a stimulating effect and insomnia due to amphetamine-like metabolites.[61]

Hypertensive crisis, which is a potentially serious and life-threatening but rare adverse reaction, may occur when MAOIs are taken concurrently with foods containing tyramine. Tyramine is usually metabolized by MAO-A in the gut and not absorbed into systemic circulation where it acts as a potent vasoconstrictor. Oral MAOIs block gut MAO-A resulting in absorption of tyramine. In patients on MAOIs, 10 mg of tyramine can cause marked hypertension and severe headache, and 25 mg can result in hypertensive crisis, whereas the average adult can tolerate over 500 mg of tyramine without a significant impact on blood pressure.[61,81] This may also occur when MAOIs are co-ingested with medications that increase norepinephrine (eg, decongestants, stimulants, SNRIs). Symptoms of hypertensive crisis include occipital headache, stiff neck, nausea, vomiting, sweating, and sharply elevated blood pressure which may culminate in cerebrovascular accident and death. For details regarding management of hypertensive emergencies, refer to Chapter 30, "Hypertension." The other significant risk of MAOIs is serotonin syndrome with concurrent use of other medications that increase serotonin (eg, antidepressants other than MAOIs). Education of patients taking MAOIs regarding dietary and medication restrictions is extremely

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important. Examples of potentially high tyramine foods and medications that should be avoided or used with caution are provided in Table 88-5.[61,81]

TABLE 88-5

**Dietary and Medication Restrictions for Patients Taking Monoamine Oxidase Inhibitors**[a]

| Foods to Avoid Completely | Approximate Tyramine Content (mg) per Ounce |
|---|---|
| Aged cheeses (eg, cheddar, blue, Swiss, Camembert) | 25-45 |
| Chicken liver | 60 |
| Dry aged meats (eg, mortadella, salami, prosciutto) | 2-45 |
| Fava beans | Unknown |
| Kim chee | Unknown |
| Red wine | Variable |
| Sauerkraut | 1-3 |
| Smoked or pickled fish (eg, lox, caviar, pickled herring) | 0-80 |
| Soy sauce, fermented soy, miso | Varies |
| Tap beer | 20-40 |
| Yeast extract | 2-60 |
| **Foods to Eat in Moderation** | |
| American cheese, Parmesan cheese | <2 |
| Canned, filtered beer | <2 per 12 oz (355 mL) |
| Havarti, brie | Thought to be low |
| Pepperoni | <2 |
| Pizza (large commercial chains generally safe; avoid gourmet with aged cheeses and meats) | 2 slices |
| White wine | <1 per 4 oz (120 mL) |
| **Foods Without Restrictions** | |
| Fresh dairy products (cottage cheese, cream cheese, fresh milk, ice cream, ricotta, sour cream, yogurt) | |
| Fresh meats (including fresh sausage) | |
| Processed meats (eg, lunch meat, hot dogs, ham) | |
| Spirits (eg, bourbon, gin, rum, vodka) | |
| Yeast bread products | |

| Medications to Avoid Completely | | |
|---|---|---|
| Antidepressants[a] | Dopamine | Methylphenidate |
| Amphetamines | Ephedrine | Reserpine |
| Appetite suppressants | Epinephrine | Sympathomimetics |
| Asthma inhalants | Guanethidine | Tramadol |
| Buspirone | Levodopa | Tryptophan |
| Carbamazepine | Local anesthetics[b] | |
| Decongestants | Meperidine | |
| Dextromethorphan | Methyldopa | |

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[a]Tricyclic antidepressants may be used with caution by experienced clinicians in treatment-refractory populations.

[b]Those containing sympathomimetic vasoconstrictors.

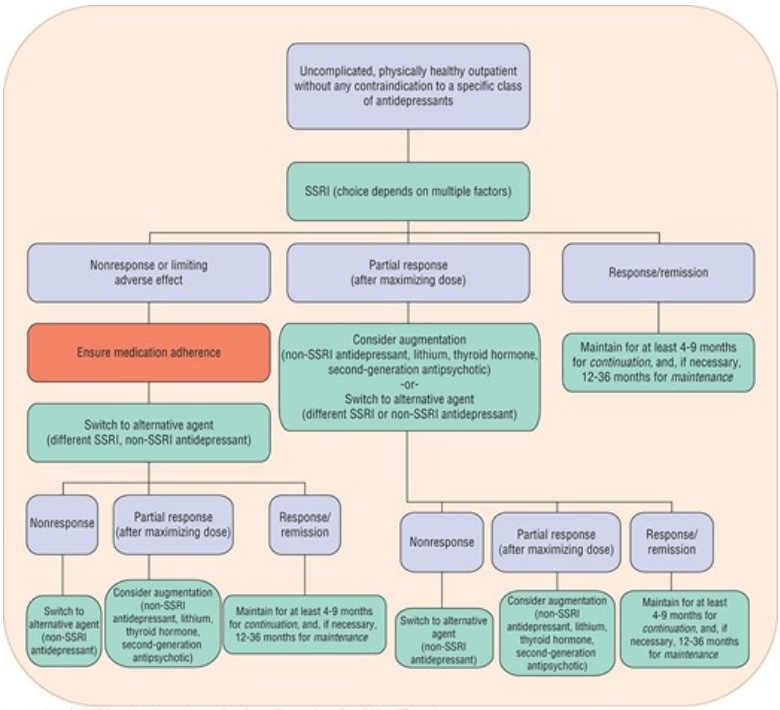
*Data from References 61 and 81.*

### Second-Generation Antipsychotics

The second-generation antipsychotics (SGAs) aripiprazole, brexpiprazole, and quetiapine have been FDA-approved for augmentation of antidepressant treatment. The combination of olanzapine/fluoxetine is FDA-approved for treatment refractory depression. Additionally, cariprazine, olanzapine, and risperidone have been studied and are recommended in some treatment guidelines for refractory symptoms.[3,4] The specific mechanisms for these medications in MDD is not fully understood, but is thought to involve modulation of 5-HT and DA activity as they have variable activity at 5-$HT_{1A}$, 5-$HT_{2A}$, $D_2$, and $D_3$ receptors.[60] While these medications may be useful in the treatment of depression they are associated with the risk of metabolic complications and movement disorders. As discussed in detail in Chapter 87, "Schizophrenia," patients taking SGAs must have baseline and follow-up monitoring of metabolic parameters (weight, glucose, lipids, blood pressure) due to the risk of metabolic syndrome. Additionally, patients should be assessed for treatment emergent extrapyramidal symptoms (eg, parkinsonism, akathisia, dystonia). See Chapter 87 for greater detail.

**FIGURE 88-3**

Suggested algorithm for treatment of uncomplicated MDD. (SSRI, selective serotonin reuptake inhibitor.) Note: Both the British Association of Pharmacology (BAP) guidelines and the STAR*D trial suggest that switching and augmentation strategies are supported by stronger evidence compared to dose increases (among poor antidepressant responders).

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### New/Investigational Agents with Novel Mechanisms

Medications with novel mechanisms have transitioned from proof of concept research to formal clinical trials and, in some cases, FDA approval (see Table 88-10). As mentioned above, while these agents do not directly alter activity of monoamines, they likely alter activity of monoamines as a

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secondary effect.

Ketamine, an older anesthetic agent, has increasingly been studied and used in the past decade for treatment resistant depression (TRD). Ketamine modulates glutamate activity via extrasynaptic *N*-methyl-*D*-aspartate (NMDA) receptor antagonism that is thought to increase synaptic glutamate activity resulting in increased BDNF activity and synaptogenesis.[30] Though not FDA-approved for MDD, ketamine has demonstrated rapid antidepressant effects in sub-anesthetic intravenous doses (typically 0.5 mg/kg) for TRD in multiple studies.[19] Esketamine, the single *s*-isomer of ketamine, has a higher affinity for the NMDA receptor than the *r*-isomer.[82] An intranasal formulation of esketamine was FDA-approved for TRD in 2019. The intranasal formulation overcomes some of the barriers associated with intravenous ketamine use, but has logistical barriers of its own. It requires supervised, in-clinic self-administration with two to six intranasal sprays per session and 2 hours of in-clinic observation after administration. In trials, patients received doses twice weekly for 4 weeks and variable dosing thereafter.[83] Overall both ketamine and esketamine appear to be relatively well tolerated at the doses used in clinical trials; however, transient psychotomimetic/dissociative effects and blood pressure elevation (10-20 mm Hg) occurred at higher rates than placebo with both agents.[19,83]

Based on research involving endogenous allopregnanolone levels and depression, specifically alterations in pregnancy and postpartum, brexanolone (exogenous allopregnanolone) was developed and FDA-approved for the indication of postpartum depression in 2019. Administration involves a 60-hour stepped dose, intravenous infusion. First-pass metabolism precludes oral administration. Brexanolone is thought to exert antidepressant effect by allosteric modulation of $GABA_A$ receptors, which may increase 5HT and NE transmission.[24,84] The most common adverse medication reactions in brexanolone trials were headache, dizziness, and somnolence. In up to 4% of patients, the infusion was stopped due to excessive sedation or loss of consciousness.[84] It has a mandatory Risk Evaluation and Mitigation Strategies (REMS) program with Elements to Ensure Safe Use (ETASU). Analogues of brexanolone with oral bioavailability, including zuranolone, are in development but not yet FDA-approved (Table 88-6).

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TABLE 88-6

**Novel Antidepressants**

| Medication | Administration | Comments |
|---|---|---|
| **Ketamine**[a]<br>10 mg/mL, 50 mg/mL, and 100 mg/mL<br>Diluted for infusion | *Not FDA-approved for MDD*<br>*Based on clinical trials*<br>Most common dose:<br>0.5 mg/kg IV infusion<br>Dose range:<br>0.1-1 mg/kg IV infusion<br>Frequency:<br>Ranges from single dose up to 3 doses per week × 2-6 weeks | Sub-anesthetic dose<br>Optimal duration of treatment not established<br>Requires IV access<br>Lower rate of dissociation compared with anesthetic doses of ketamine<br>Limited sites of care<br>May not be covered by insurance |
| **Esketamine (Spravato)** 28 mg per nasal spray device (14 mg per spray) | *FDA-approved indications: Treatment resistant depression*<br>One spray per nostril (28 mg) Repeat in 5 minutes for 56 mg and again in 5 minutes for 84 mg2×/week for 4 weeks then weekly for 4 weeks then every 1-2 weeks<br>*MDD with suicidality*<br>84 mg 2×/week for 4 weeks | Sub-anesthetic dose<br>Optimal duration of treatment not established<br>Requires in office administration and observation post-dose<br>Rate of dissociative symptoms comparable to low dose IV ketamine<br>Limited sites of care<br>Costly<br>SPRAVATO REMS program: sedation, dissociation, use and misuse |
| **Brexanolone (Zulresso)** 100 mg/20 mL | *FDA-approved for postpartum depression only*<br>Single 60-hr stepped infusion<br>0 to 4 hr 30 mcg/kg/hr<br>4 to 24 hr 60 mcg/kg/hr<br>24 to 52 hr 90 mcg/kg/hr<br>52 to 56 hr 60 mcg/kg/hr<br>56 to 60 hr 30 mcg/kg/hr | Requires hospitalization<br>ZULRESSO REMS program: excessive sedation and sudden loss of consciousness<br>Effect past 30 days not established<br>Limited sites of care<br>Costly: ~$30,000 per infusion |

[a]Not FDA-approved for treatment of MDD.

IV, intravenous; REMS, Risk Evaluation and Mitigation Strategy.

*Data from References 60, 84, and 85.*

### Additional Adverse Events

#### *Serotonin Syndrome*

Any antidepressant that increases serotonergic neurotransmission can be associated with serotonin syndrome (SS), especially in situations where interactions increase release or duration of serotonin activity. The typical triad of symptoms seen in SS includes mental status changes, autonomic instability, and neuromuscular abnormalities (eg, hyperreflexia, myoclonus) which can be lethal.[86] As SS is primarily a diagnosis of exclusion, other causes of symptoms including neuroleptic malignant syndrome, anticholinergic toxicity, and malignant hyperthermia must be ruled out, with particular attention being paid to concurrent medications to guide differential diagnosis. Prompt medical attention is needed for any patient

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suspected of having SS syndrome, to discontinue all potentially causative agents, manage blood pressure and heart rate and maintain hydration.

### Pharmacokinetics and Pharmacodynamics of Antidepressants

The PK of the antidepressants is summarized in Table 88-7.[60,73,87] The diversity of SSRIs is evident not only in their chemical structures but also in their PK profiles as the unique PK attributes of each SSRI can be used to guide treatment. For example, the long half-life of fluoxetine and its active metabolite norfluoxetine may be beneficial in instances of partial nonadherence. Conversely, caution must be taken to monitor for medication interactions prior to combining another medication with fluoxetine, fluvoxamine, or paroxetine.

TABLE 88-7

**Pharmacokinetic Properties of Antidepressants**

| Generic Name | Elimination Half-Life[a] | Plasma Protein Binding (%) | Clinically Important Metabolites |
|---|---|---|---|
| **Selective Serotonin Reuptake Inhibitors (SSRIs)** | | | |
| Citalopram | 33 hr | 80 | None |
| Escitalopram | 27-32 hr | 56 | None |
| Fluoxetine | 4-6 days[b] | 94 | Norfluoxetine[c] |
| Fluvoxamine | 15-26 hr | 77 | None |
| Paroxetine | 24-31 hr | 95 | None |
| Sertraline | 27 hr | 99[d] | None |
| **Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)** | | | |
| Desvenlafaxine | 11 hr | 30 | None |
| Duloxetine | 12 hr | 90 | None |
| Levomilnacipran | 12 hr | 22 | None |
| Venlafaxine | 5 hr | 27-30 | *O*-Desmethyl-venlafaxine |
| **TCAs** | | | |
| Amitriptyline | 9-46 hr | 90-97 | Nortriptyline |
| Desipramine | 11-46 hr | 73-92 | 2-Hydroxy-desipramine |
| Doxepin | 8-36 hr | 68-82 | Desmethyl-doxepin |
| Imipramine | 6-34 hr | 63-96 | Desipramine |
| Nortriptyline | 16-88 hr | 87-95 | 10-Hydroxy-nortriptyline |
| **Mixed Serotonergic (Mixed 5-HT)** | | | |

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| | | | |
|---|---|---|---|
| Nefazodone | 2-4 hr | 99 | *meta*-Chlorophenyl-piperazine |
| Trazodone | 6-11 hr | 92 | *meta*-Chlorophenyl-piperazine |
| Vilazodone | 25 hr | >95 | |
| Vortioxetine | 66 hr | 98 | |
| **Norepinephrine/Dopamine Reuptake Inhibitor (NDRI)** | | | |
| Bupropion | 10-21 hr | 82-88 | Hydroxy-bupropion |
| | | | Threohydro-bupropion |
| | | | Erythrohydro-bupropion |
| **Serotonin and $\alpha_2$-Adrenergic Antagonists** | | | |
| Mirtazapine | 20-40 hr | 85 | None |

[a]Biologic half-life in slowest phase of elimination.

[b]Four to 6 days with chronic dosing; norfluoxetine, 4 to 16 days.

[c]Take with food to increase area under the curve concentrations by greater than 60%.

[d]Increases 30% to 40% when taken with food.

*Data from References 60, 73, and 87.*

Bioavailability is low (30%-70%) for most TCAs as a result of first-pass metabolism, which shows great interindividual variation.[89] The TCAs have a large volume of distribution and concentrate in brain and cardiac tissue in laboratory animals. They are bound extensively and strongly to plasma albumin, erythrocytes, $\alpha_1$-acid glycoprotein, and lipoprotein.[89] The major metabolic pathways are demethylation, aromatic and aliphatic hydroxylation, and glucuronide conjugation, although enterohepatic cycling has been described.[89] Normally, the PK of TCAs is linear within the usual dosage range; however, the elimination half-lives can vary greatly among individual patients, which may be related to pharmacogenomic variability, primarily within CYP2D6 and CYP2C19.[89]

Venlafaxine is metabolized to an active metabolite, *O*-desmethylvenlafaxine, which contributes to the overall pharmacologic effect, and is also FDA-approved as an antidepressant (desvenlafaxine). Immediate release (IR) venlafaxine is generally dosed twice daily to avoid end of dose discontinuation symptoms, while extended release venlafaxine and desvenlafaxine have a longer duration of action and can be dosed once daily.[60] Bupropion is metabolized to multiple active metabolites (Table 88-7), and there are three formulations of bupropion hydrochloride (immediate release, sustained release, and extended release), which are equivalent on a total daily dose basis as well as a bupropion hydrobromide formulation that can be converted to equivalent hydrochloride doses.[90] The bupropion peak plasma concentrations are lower for the sustained-release formulation, which are believed to contribute to a lower seizure risk.[90] Mirtazapine undergoes biotransformation to several metabolites[91,92]; however, it is primarily eliminated unchanged in the urine. The mirtazapine metabolites are present at such low plasma concentrations they minimally contribute to the overall pharmacologic profile. Levomilnacipran is primarily metabolized via CYP3A4 with renal elimination of over 50% of the dose.[60]

Brexanolone undergoes extensive first-pass metabolism and is only available in intravenous formulation.[80] Ketamine (IV) and esketamine (nasal) undergo extensive oxidative metabolism and have elimination half-lives of approximately 2 hours and 7 to 12 hours, respectively.

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An important PK difference between oral selegiline (FDA-approved only for Parkinson disease) and transdermal selegiline impacts their pharmacodynamic profiles. Oral selegiline undergoes extensive first-pass metabolism resulting in bioavailability of 4% versus 73% for the transdermal formulation.[80] At the low CNS concentrations achieved with the oral formulation, selegiline selectively inhibits MAO-B resulting in increased DA levels (hence, the use for Parkinson disease). Nonselective inhibition of both MAO-A (resulting in increased NE and 5HT levels) and MAO-B, which is thought to be important to achieve an antidepressant effect, occurs at the higher CNS concentrations only achieved with the transdermal formulation.[80]

#### Antidepressant Altered Pharmacokinetics

Antidepressants may have significantly altered PK in patients with hepatic or renal disease; however, the data regarding the altered PK parameters are often derived from small, single-dose studies. Changes are variably reported as decreased clearance, increased area under the curve (AUC) or increased half-life.[91,92] In patients with chronic liver disease, clearance may be decreased 30% (citalopram, mirtazapine) to over 70% (duloxetine, sertraline) and half-life may be increased twofold (citalopram, paroxetine) to threefold (duloxetine, fluoxetine). The AUC of TCAs and bupropion have been reported to increase threefold in cirrhosis.[92] Duloxetine is not recommended in patients with significant hepatic impairment.

Renal impairment and end-stage renal disease (ESRD) do not significantly alter antidepressant PK, with notable exceptions. The half-life of citalopram, escitalopram, and paroxetine may increase 30% to 40%.[91] The AUC of bupropion desvenlafaxine, duloxetine, mirtazapine, and venlafaxine may increase twofold.[91] Duloxetine labeling recommends against use in patients with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 $m^2$.[91] Bupropion metabolites have also demonstrated accumulation in ESRD. Renal failure does not alter nortriptyline metabolism, but the 10-hydroxy metabolite may accumulate, and protein binding may be diminished, with resulting enhanced sensitivity to the medication.[89]

In patients with significant renal or hepatic impairment, it is reasonable to initiate treatment with 50% lower dose and titrate to 50% to 75% of maximum dose based on tolerability and response. Patients should be monitored for electrolyte abnormalities and low platelets that can increase risk of arrhythmias and bleeding. Additionally, lower doses and cautious monitoring are prudent when patients are on concomitant medications with overlapping toxicity profiles.

#### Plasma Concentration and Clinical Response

For the newer antidepressants, a strong correlation between plasma concentration and clinical response or tolerability has not been established, while this has been established for some TCAs (eg, amitriptyline, nortriptyline, desipramine, and imipramine). However, the best established therapeutic range is for nortriptyline (50-150 ng/mL [mcg/L; 190-570 nmol/L]),[89] which appears to demonstrate a curvilinear plasma concentration-response relationship.

Clinical response, not plasma concentration, should dictate dosage adjustments, as some patients with plasma concentrations outside the suggested therapeutic range respond to treatment, whereas others are nonresponsive even with “therapeutic” plasma concentration.

#### Plasma Concentration Monitoring

Because of interindividual variations in plasma concentrations achieved by a given dose, interpretation of plasma concentrations can be very difficult for the TCAs.[89] Although plasma concentration monitoring is not performed routinely, some indications include inadequate response, relapse, serious or persistent adverse medication reactions, use of higher-than-standard doses, suspected toxicity, older adult patients, pregnant patients, cardiac disease, suspected nonadherence, and suspected PK interactions. If plasma concentration monitoring is used to detect nonadherence, a cutoff as low as 30 ng/mL (mcg/L; ~110 nmol/L) for the TCAs has been suggested to avoid confusion with low bioavailability or unusually rapid metabolism. Blood samples for plasma concentration determinations should be obtained at steady state, usually after a minimum of 1 week at constant dosage. Sampling should be performed during the elimination phase, usually in the morning, 12 hours after the last dose. Samples collected in this manner are comparable for patients on once-, twice-, or thrice-daily regimens.[89]

### Medication Interactions

Interactions fall into two broad categories: PK and PD medication interactions, with the PK interactions being the most common. Antidepressants are

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primarily substrates for cytochrome P450 enzymes and variably act as inhibitors of the enzymes (see Table 88-8).[60,88]

TABLE 88-8

**Antidepressants and Cytochrome (CYP) P450 Enzyme Inhibitory Potential**

| | CYP Enzyme Inhibition | | | |
|---|---|---|---|---|
| **Medication** | **1A2** | **2C** | **2D6** | **3A4** |
| Bupropion | 0 | 0 | +++ | 0 |
| Citalopram | 0 | 0 | + | NA |
| Duloxetine | 0 | 0 | +++ | 0 |
| Escitalopram | 0 | 0 | + | 0 |
| Fluoxetine | 0 | ++ | ++++ | ++ |
| Fluvoxamine | ++++ | ++ | 0 | +++ |
| Mirtazapine | 0 | 0 | 0 | 0 |
| Nefazodone | 0 | 0 | 0 | ++++ |
| Paroxetine | 0 | 0 | ++++ | 0 |
| Sertraline | 0 | ++ | + | + |
| (des)-Venlafaxine | 0 | 0 | 0/+ | 0 |
| Vilazodone | 0 | 0 | 0 | 0 |
| Vortioxetine | 0 | 0 | 0 | 0 |

++++, high; +++, moderate; ++, low; +, very low; 0, absent.

*Data from References 60 and 88.*

### Pharmacokinetic Interactions

Interactions may occur when an antidepressant is coadministered with another medication metabolized through the cytochrome P450 system. Two of the cytochrome P450 system isoenzymes, CYP2D6 and CYP3A4, are responsible for the metabolism of most currently marketed medications.[88] The ability of an antidepressant to inhibit the activity of these enzymes will be a significant contributory factor in determining its capability to cause a PK interaction when administered concomitantly. Table 88-8 shows the cytochrome P450 enzyme inhibitory potential of antidepressant agents. Patients taking substrates of these enzymes should be monitored closely if started on an antidepressant with inhibitory potential. Select examples can be found in Table 88-9.

TABLE 88-9

**Select Pharmacokinetic Interactions of Antidepressants**

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| Antidepressant | Interacting Medication/Medication Class | Effect |
|---|---|---|
| **Selective Serotonin Reuptake Inhibitors** | | |
| Citalopram and escitalopram | Omeprazole | Increased concentrations of citalopram and escitalopram |
| Fluoxetine | Alprazolam | Increased concentrations and half-life of alprazolam; increased psychomotor impairment |
| | Antipsychotics (eg, aripiprazole, haloperidol) | Increased antipsychotic concentrations; increased extrapyramidal symptoms |
| | β-Adrenergic blockers | Increased metoprolol concentrations; increased bradycardia; possible heart block |
| | Carbamazepine | Increased concentrations of carbamazepine; symptoms of carbamazepine toxicity |
| | Phenytoin | Increased concentrations of phenytoin; symptoms of phenytoin toxicity |
| | Tamoxifen | Decreased conversion of tamoxifen to active metabolites |
| | TCAs | Markedly increased TCA concentrations; symptoms of TCA toxicity |
| | Thioridazine | Thioridazine $C_{max}$ increased; prolonged QTc interval |
| Fluvoxamine | Alosetron | Increased alosetron AUC (sixfold) and half-life (threefold) |
| | Alprazolam | Increased AUC of alprazolam by 96%, increased alprazolam half-life by 71%; increased psychomotor impairment |
| | β-Adrenergic blockers | Fivefold increase in propranolol concentration; bradycardia and hypotension |
| | Carbamazepine | Increased concentrations of carbamazepine; symptoms of carbamazepine toxicity |
| | Clozapine | Increased clozapine concentrations; increased risk for seizures and orthostatic hypotension |
| | Diltiazem | Bradycardia |
| | Methadone | Increased methadone plasma concentrations; symptoms of methadone toxicity |
| | Ramelteon | Increased AUC (190-fold) and $C_{max}$ (70-fold) |
| | TCAs | Increased TCA concentration; symptoms of TCA toxicity |
| | Theophylline and caffeine | Increased concentrations of theophylline or caffeine; symptoms of theophylline or caffeine toxicity |
| | Thioridazine | Thioridazine $C_{max}$ increased; prolonged QTc interval |

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| | | |
|---|---|---|
| | Warfarin | Increased effect of warfarin |
| Paroxetine | Antipsychotics (eg, aripiprazole, haloperidol) | Increased antipsychotic concentrations; increased CNS and extrapyramidal symptoms |
| | β-Adrenergic blockers | Increased metoprolol concentrations; increased bradycardia; possible heart block |
| | Tamoxifen | Decreased conversion of tamoxifen to active metabolites |
| | TCAs | Markedly increased TCA concentrations; symptoms of TCA toxicity |
| | Thioridazine | Thioridazine $C_{max}$ increased; prolonged QTc interval |
| Sertraline | Methadone | Increased methadone levels |
| **Serotonin–Norepinephrine Reuptake Inhibitors** | | |
| Venlafaxine and desvenlafaxine | CYP3A4 inhibitors | May increase levels of venlafaxine and *O*-desmethylvenlafaxine especially in CYP2D6 poor metabolizers |
| Duloxetine | Metoprolol | May increase metoprolol levels twofold |
| | Tamoxifen | Decreased conversion of tamoxifen to active metabolites |
| | Thioridazine | Thioridazine $C_{max}$ increased; prolonged QTc interval |
| Levomilnacipran | CYP3A4 inhibitors | Clinically relevant increases in levomilnacipran concentrations may occur |
| **Mixed Serotonergic (Mixed 5-HT)** | | |
| Vilazodone | CYP3A4 inhibitors | Maximum vilazodone dose 20 mg with coadministration of potent CYP3A4 inhibitor |
| Vortioxetine | CYP2D6 inhibitors | May need to reduce vortioxetine dose by half with coadministration of potent CYP2D6 inhibitor |
| **Serotonin and α-2-Adrenergic Antagonist** | | |
| Mirtazapine | Carbamazepine | Mirtazapine concentration decreased (60%) |
| **Norepinephrine and Dopamine Reuptake Inhibitor** | | |
| Bupropion | Tamoxifen | Decreased conversion of tamoxifen to active metabolites |

AUC, area under the time concentration curve; $C_{max}$, maximum concentration; MAOI, monoamine oxidase inhibitor.

Note: Any medication that augments serotonergic function may impact bleeding risk and should be used with caution in patients receiving NSAIDs or other medications with hematologic effects.

*Data from References 2, 60, 73, and 88.*

Because the TCAs are metabolized in the liver through the cytochrome P450 system, they may interact with other medications that modify hepatic

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enzyme activity or hepatic blood flow. TCAs are also extensively protein bound, which can result in interactions through displacement from protein-binding sites. Many commonly used medications can interact when given concurrently with TCAs.

As nefazodone use has been severely limited due to its potential to induce liver toxicity, and trazodone is primarily used as a non-FDA-approved hypnotic at low doses, neither of these agents is likely to be involved in clinically significant medication interactions. However, nefazodone is a potent inhibitor of CYP3A4.[88] Vilazodone is primarily metabolized via CYP3A4 and vortioxetine is primarily metabolized via CYP2D6 and both require dose adjustment with inhibitors.[60,62]

#### Pharmacodynamic Medication Interactions

Certain PD medication interactions that may occur with antidepressants are concerning and require close monitoring. For example, concurrent use of serotonergic antidepressants with other medications that augment serotonergic function can increase the risk of SS with some combinations conferring a higher risk than others.[86]

Tramadol presents as an example of a PK interaction increasing the risk of a PD interaction. When tramadol is coadministered with strong CYP2D6 inhibitors, the decrease in metabolism may result in higher levels of tramadol, which also exhibits SNRI effects. Therefore, high doses of the combination have been reported to cause serotonin syndrome.[86,93]

See Table 88-10 for key examples of PD interactions.[60,86,93-96]

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TABLE 88-10

**Select Pharmacodynamic Medication Interactions of Antidepressants**

| Medication/Medication Class | Antidepressants/Antidepressant Class | Effect and Management |
|---|---|---|
| NSAIDs<br>Aspirin<br>Anticoagulants<br>Antiplatelet agents | SSRIs, SNRIs, TCAs, trazodone, vilazodone, vortioxetine | • FDA warning for increased risk of bleeding<br>• Number needed to harm with NSAIDs = 82 vs >700 with SSRI alone<br>• Assess for baseline bleeding risk and monitor closely<br>• Educate at risk patients regarding signs of bleeding<br>• Consider histamine-2 ($H_2$) antagonist in high-risk patients |
| Triptans | MAOIs, SSRIs, and SNRIs | • FDA warning in labeling<br>• Very low risk<br>• Monitor for signs of serotonin syndrome when frequent high doses are used<br>• Triptan toxicity possible when almotriptan, rizatriptan, sumatriptan, or zolmitriptan are combined with MAO inhibitors |
| Linezolid | All serotonergic antidepressants | • Linezolid is weak, reversible, nonselective, MAOI<br>• FDA labeling recommends against use with other MAOIs and recommends discontinuing antidepressants if linezolid is started<br>• Actual rate of serotonin syndrome with combination reported at <1%<br>• Abrupt discontinuation of antidepressants can have negative consequences<br>• If linezolid is indicated and patient is already on an antidepressant, monitor for signs of serotonin syndrome upon initiating combination<br>• If patient is on short course of linezolid and in need of treatment for depression, consider postponing antidepressant initiation until course is complete |
| Tramadol | Bupropion, duloxetine, fluoxetine, paroxetine | • Decreased metabolism results in increased SNRI activity of tramadol<br>• Rare cases of high dose tramadol combined with CYP2D6 inhibitors resulting in serotonin syndrome have been reported<br>• Monitor for increased signs of serotonin syndrome and decreased analgesic response when combination is used |

*Data from References 60, 86, and 93-96.*

There are two types of PD medication interactions that may occur between antidepressant medications and NSAIDs. An increased risk for abnormal bleeding (eg, upper GI and intracranial hemorrhage) associated with combined antidepressants and NSAID use is a potentially very serious pharmacodynamic interaction.[94] This interaction is likely mediated by serotonergic mechanisms that occur at the platelet level. Additionally, NSAIDs may lessen the efficacy of SSRIs; however, the evidence is insufficient to draw firm conclusions.[95] However, given the volume of prescriptions for both NSAIDs and SSRIs, this is an area of pharmacotherapy that certainly deserves further research and thoughtful prescribing practices.

Lastly, refer to the section "Monoamine Oxidase Inhibitors" above and Table 88-5 regarding the hypertensive crisis that may result following coadministration of MAOIs and other medications that increase vasopressor response (eg, amphetamines). Notably, MAOIs and TCAs have been coadministered safely in TRD patients with apparent increased efficacy compared with monotherapy; however, severe reactions (eg, hypertensive

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crisis) and fatalities have occurred.[2,89] Therefore, this combination should be used sparingly by experienced clinicians and monitored extremely carefully.

## Alternative Pharmacotherapy

The APA Task Force on Complementary and Alternative Medicine (CAM) as well as CANMAT guidelines include evidence-based and consensus-based recommendations on the use of CAM for the treatment of MDD.[59,97] While these recommendations are not the focus of this chapter, clinicians treating patients with MDD should be cognizant of them.

### Omega-3 Fatty Acids

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) omega-3 fatty acids are generally low-risk and demonstrate variable benefit as augmentation in the treatment of MDD. Use of EPA alone or the combination of EPA/DHA is likely more effective than DHA alone. As these agents may increase bleeding risk, their use should be carefully considered in patients taking SSRIs and other concomitant medications associated with bleeding risk (eg, NSAIDs, anticoagulants).

### St. John's Wort

There is a lack of consensus regarding St. John's wort for the treatment of MDD. Furthermore, St. John's wort induces hepatic metabolic enzymes and is associated with significant interactions. The APA Task Force conservatively states that St. John's wort may be reasonable for some individuals with mild-to-moderate MDD while CANMAT considers it to have level 1 evidence as first-line therapy for mild-to-moderate MDD.[2,4] Further, the BAP guidelines state a "standardized" preparation of St. John's wort "could be considered" in patients with mild-to-moderate MDD, if other first-line medications are not an option.[3]

### *S*-Adenosyl-L-Methionine (SAMe)

The use of SAMe received a favorable review by the APA Task Force. However, the final consensus was that more rigorous studies need to confirm the efficacy of SAMe for treating MDD. The CANMAT guidelines consider SAMe as a second-line augmentation strategy while the BAP guidelines state that evidence is developing for use of SAMe as an augmentation strategy in the treatment of MDD.[3]

### Folate

The three compounds in this category are (a) folic acid, (b) folinic acid, and (c) 5-methyltetrahydrofolate (5-MTHF) as these compounds are involved in the synthesis of key neurotransmitters such as 5-HT. The APA Task Force states that augmentation with these compounds is reasonable, but more work is needed to clarify which subgroup of patients may achieve the greatest response.[59] For example, in one study, only females responded to folic acid augmentation of fluoxetine treatment. Regardless, CANMAT guidelines consider folate supplementation a third-line augmentation strategy.[4]

## Special Populations

### Older Adult Patients

Depression in older adults is a major public health problem as many older adult patients with depression are inadequately treated, or have their depression missed or mistaken for another disorder, such as dementia. In these patients, depressed mood, the typical signature symptom of depression, may be less prominent than other depressive symptoms such as loss of appetite, cognitive impairment, sleeplessness, anergia, and anhedonia. Previous research supports that somatic (physical) complaints (eg, pain, fatigue, gastrointestinal symptoms) present more frequently in older adults with depression. However, there are many confounders that may account for this (eg, higher rates of physical illness).[34] Appropriate recognition and treatment of depression in older adults is extremely important as individuals 65 years of age and older have a high rate of suicidality. Increased suicide attempts in older adults with depression have been associated with access to firearms, diminished cognitive functioning, sleep disruptions, poor social interactions, and inattention among primary caregivers.[98]

Before initiating antidepressant treatment, a complete physical examination should be performed. When prescribed antidepressants, older adults may

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be either overtreated or under-treated. Overtreatment occurs when age-related PK and PD factors are overlooked and under-treatment results from an overly conservative approach as a result of the patient's advanced age or concurrent medical problems. In older adults, SSRIs are usually selected as first-line treatment, and this may enable the clinician to avoid some of the problematic intolerances commonly associated with TCAs (eg, sedative, anticholinergic, and cardiovascular adverse reactions). Furthermore, there is evidence to suggest that the long-term use of antidepressants such as SSRIs in older adults, administered with either psychotherapy or clinical management, may prevent a depressive relapse.[34,35] Hyponatremia is more common in elderly females, especially in those taking concomitant diuretics. Mirtazapine has been shown to be an effective antidepressant in adults older than 65 years of age and better tolerated than the SSRI paroxetine. Furthermore, secondary measures of anxiety and sleep were improved following mirtazapine administration.[99] In addition to sleep benefits, mirtazapine can be helpful in improving appetite which is commonly diminished in older adults with depression. For those patients whose depressive symptoms include lack of overall energy, use of bupropion may capitalize on the stimulant effect of this medication. Regardless of the specific antidepressant chosen, the effect sizes for antidepressants as a pharmacological class, compared to placebo, may be smaller in older adult patients than in younger adult populations.[3]

#### Pediatric Patients

Accumulating evidence indicates that childhood depression occurs quite commonly and symptoms of depression in the young may vary from accepted diagnostic criteria to include several nonspecific symptoms such as boredom, anxiety, somatic complaints (eg, stomach ache), and impulsivity.[100]

Data collected under controlled conditions that support the efficacy of antidepressants in children and adolescents are sparse, and only fluoxetine and escitalopram are FDA-approved for depression in patients younger than 18 years of age, although other antidepressants (eg, sertraline) have been studied in this population.[100] The Treatment of Adolescent Depression Study (TADS) found that the combination of fluoxetine and CBT was superior to fluoxetine monotherapy or CBT alone in adolescents 12 to 17 years of age.[101] The Treatment of Resistant Depression in Adolescents (TORDIA) study switched adolescents 12 to 18 years of age with SSRI-resistant depression to venlafaxine or sertraline with or without CBT after nonresponse to antidepressant. Overall this study found no difference in outcomes between the two medications and also found no difference in outcomes when CBT was added to medication.[102] Additionally, the Adolescent Depression Antidepressant and Psychotherapy Trial (ADAPT) did not find a benefit of adding CBT to SSRI therapy in adolescents 11 to 17 years of age.[103]

The use of antidepressants in children and adolescents was complicated when the FDA issued a boxed warning in the product labeling for antidepressant medications warning clinicians and patients of the increased risk for suicidal ideation and behavior when antidepressants are used in this population. Results of subsequent studies attempting to elucidate the risk of antidepressants in young patients have varied. A meta-analysis of published and unpublished clinical trials supported an increased risk; however, the study was impeded by limited data access. In contrast, several retrospective longitudinal reviews of antidepressant use in children refute the increased risk of suicide attempts or deaths.[104] Furthermore, studies demonstrated a decreased rate of prescribing antidepressants and an increase in deaths by suicide after the warning appeared in labeling.[105]

The treatment of depression in children remains challenging, as depression can be difficult to diagnose and, once identified, treat. Furthermore, differences in efficacy between medication and placebo may be small and not significant in children below the age of 13 years.[3] However, antidepressants (in particular, the SSRIs) remain viable treatment options when prescribed and monitored appropriately.

#### Pregnant and Lactating Patients

The crucial decision as to whether to use antidepressants during pregnancy continues to be debated and must always include a risk-benefit analysis based upon the available evidence at the time of treatment. Approximately 14% of pregnant individuals develop clinically significant depression during pregnancy.[106] Furthermore, it has been documented that those who discontinued antidepressant therapy before or during pregnancy were five times more likely to have a relapse than those who continued treatment.[107] While numerous studies, reviews, and meta-analyses have been published over the last decade, the absolute risk of antidepressants in pregnancy is still not clear due to methodological issues and confounding factors (eg, prenatal care, continued depressive symptoms during treatment, medical and psychiatric comorbidities, and substance use).[108] An approximate 25% relative increase in congenital heart defects associated with SSRIs is the most consistent finding; however, the increase in risk ranges from 10% to a twofold increase across studies.[108] Other findings have included increased risk of low birth weight and newborn respiratory distress.[106] An oft-cited study reported a sixfold greater likelihood of persistent pulmonary hypertension of newborn infants exposed to an SSRI after the 20th week of gestation;

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however, the degree of this risk has been debated.[109] These are selected examples of studies assessing both risks and benefits of antidepressants in pregnancy. A full exploration of the conflicting literature on this topic is beyond the scope of this chapter.

Four therapeutic principles have been proposed to guide the clinician in treating pregnant individuals or individuals who desire pregnancy: (a) Pregnancy does not protect against the occurrence of depression, and the likelihood of relapse is very high in untreated individuals with recurrent illness. (b) Depression during pregnancy adversely affects child development, and prenatal depression may adversely affect the offspring. (c) When attempting to balance benefit and risk, transient postnatal behavioral abnormalities in the offspring of pregnant individuals receiving pharmacotherapy must not be assumed to portend long-term compromise. (d) SSRIs, the most commonly used and best-tolerated treatment for depression, carry a small but significant risk for a serious medical consequence.[110]

The APA and the American College of Obstetricians and Gynecologists have a report discussing the treatment of depression during pregnancy. One of the prominent conclusions of this report was that *both* antidepressant treatment and untreated depression have been associated with potential problems during pregnancy. However, studies to date have not been able to adequately control for all the necessary variables involved in birth outcomes (eg, maternal depressive disorder) and more work needs to be done.[111]

In summary, the risks and benefits of medication therapy during pregnancy must always be weighed, and concerns about the risks of untreated depression during pregnancy should be considered. These include the possibility of low birth weight secondary to poor pregnancy weight gain, suicidality, potential for hospitalization, potential for relationship discord, inability to engage in appropriate obstetric care, and difficulty caring for other children. Several different approaches exist for dealing with pregnancy and antidepressant use. First, discontinuation of an antidepressant before conception is an option for individuals who are stable and appear likely to remain well while not taking antidepressant medication (eg, no history of recurrence upon discontinuation, no history of severe symptoms or suicidality, stable psychosocial supports). Second, continuation of the antidepressant until conception may be reasonable and one with the lowest risk for the fetus should be chosen in individuals of child bearing potential or those trying to conceive. For those who have a history of depressive relapse after medication discontinuation, the antidepressant should be continued throughout pregnancy. There is a great deal of uncertainty regarding long-term antidepressant exposure in infants exposed through human milk due to the lack of data. However, sertraline is recommended and appears in relatively low concentrations in human milk and in samples taken from infants.[112] The risks of not treating depression in a patient who is pregnant or providing milk to an infant should not be underestimated or minimized. Additional information can be found in Chapter 99, “Pregnancy and Lactation.”

### Relative Resistance and Treatment-Resistant Depression

The majority of patients with TRD likely have had inadequate (low dose, short duration) therapy (relative resistance). This theory is supported by data from the National Institute of Mental Health (NIMH) Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which is generally considered to be one of the premier antidepressant trials among patients with depressive disorders.[56,113] According to this study, one in three patients with depression who previously did not achieve remission with an antidepressant (citalopram) became symptom free with an additional medication (bupropion SR or buspirone) and one in four achieved remission after switching to a different antidepressant (bupropion SR, sertraline, or venlafaxine XR). Furthermore, patients can be switched to another medication within the same class.[114] For example, patients in the STAR*D study not responding to an initial SSRI were shown to be as likely to respond to another SSRI as they were to a medication from a different class.[115] Other key findings of STAR*D include the importance of maximizing dose (higher doses associated with higher remission rates) and adequate trial duration of at least 8 to 12 weeks before deeming a medication ineffective.[56] The BAP guidelines place a higher level of confidence in both augmentation and switching strategies, compared to dosage increase approaches.[3]

Although several different definitions for TRD have been proposed, the most widely accepted is depression that has not achieved remission after two optimal antidepressant trials, which represents more than 40% of patients with MDD treated with antidepressants.[115] Three pharmacologic approaches that have been used with success for TRD include the following:

1. The current antidepressant may be stopped and another agent initiated (ie, switching). For example, the STAR*D trial compared switching to mirtazapine (up to 60 mg/day) versus nortriptyline (up to 200 mg/day) after two consecutive ineffective medication treatments.[115] In the mirtazapine group, 12.3% of patients met the remission criterion of a score of 7 or less on the Hamilton Rating Scale for Depression (HAM-D), while 19.8% of nortriptyline patients met this criterion at the end of 14 weeks.

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2. The current antidepressant can be augmented by the addition of another agent such as lithium, or another antidepressant (ie, combination antidepressant treatment). For example, the STAR*D trial evaluated the addition of lithium or triiodothyronine ($T_3$) to current antidepressant treatment. After approximately 10 weeks, $T_3$ augmentation resulted in higher remission rates (24.7%) compared with lithium (15.9%). However, the differences between these two augmentation strategies were modest and not statistically significant.[116] Although T3 and lithium demonstrated similar remission rates in this seminal trial, the BAP guidelines provide a stronger recommendation rating for lithium (ie, "A") compared to T3-based approaches (ie, "B").[116] In contrast, the CANMAT guidelines consider both agents second-line for augmentation with level 2 evidence.[4]
3. The use of SGAs to augment the antidepressant response is increasing. Aripiprazole, brexpiprazole, and quetiapine are FDA-approved for adjunctive treatment for MDD. Aripiprazole and quetiapine have been recommended as first-line agents to augment an antidepressant medication.[4] In a predominantly male population in the Veterans Health Administration, augmentation with aripiprazole was found to be more effective than switching to bupropion but no different from bupropion augmentation.[117]

The APA practice guideline for the treatment of patients with MDD offers direction for managing patients whose symptoms are refractory to medications. These guidelines advise that if patients are still symptomatic after 6 to 8 weeks of medication, a reappraisal of the treatment regimen should be considered.[2] Those with partial response should consider changing the dose, augmenting the antidepressant, or adding psychotherapy or ECT. For those with no response, options include changing to a different antidepressant or adding psychotherapy or ECT. Again, the BAP guidelines suggest that stronger evidence exists for switching or augmentation strategies compared to dose increases in patients with inadequate antidepressant response.[3] Comorbid medical or psychiatric conditions should be identified and treated because they may complicate treatment.

6 Before changing a patient's treatment, the clinician is advised to evaluate the adequacy of the medication dosage and adherence with the prescribed regimen. Issues to be addressed in assessing the patient who has not responded to treatment include the following:

1. Is the diagnosis correct?
2. Does the patient have a psychotic depression?
3. Has the patient received an adequate dose and adequate duration of treatment?
4. Do adverse medication reactions preclude adequate dosing?
5. Is patient adherence to the prescribed regimen appropriate?
6. Was a stepwise approach to treatment used?
7. Was treatment outcome adequately measured?
8. Is there a coexisting or preexisting medical or psychiatric disorder?
9. Are there other factors that interfere with treatment?

### Personalized Pharmacotherapy

7 Pharmacogenetic (PGx) applications in psychiatry have been explored for some time. Multiple commercially available PGx tests are now available and in patients who present with the testing already completed or for whom a test is ordered, evidence-based guidelines produced by the Clinical Pharmacogenomics Implementation Consortium (CPIC) can help determine test interpretation (www.cpic.org). CPIC does not specifically recommend testing in patients, but rather serves as a resource for clinicians who are presented with PGx testing results and are looking for assistance in their interpretation. Therefore, while this testing may, one day, be routinely used to guide pharmacotherapy, it is not utilized routinely in practice for several reasons.[118] Included on several of the commercially available test are genes associated with PK parameters that have long been one of the primary considerations when choosing among the antidepressants, particularly within a medication class.[2] For example, PK parameters help the clinician choose a particular SSRI (eg, longer fluoxetine half-life for partial nonadherence). The data regarding the interpretation of PGx testing results for the PK genes is more concrete than that associated with PD genes.

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A clinician can use other aspects of a medication's pharmacological profile to tailor the treatment to a particular patient. For example, antidepressants can generally be classified as either activating or sedating based upon their mechanism of action, and this is often a major consideration in antidepressant choice. Medications that promote noradrenergic activity (eg, bupropion, venlafaxine) or serotonin (eg, SSRIs) may be activating upon initiation and therefore poor choices for a patient suffering from significant insomnia. In contrast, mirtazapine and trazodone have been shown to improve sleep, likely due to antagonism of $H_1$ and 5-$HT_{2A}$ receptors.[67] Furthermore, doxepin is FDA-approved (in lower doses compared to those used for depression) as pharmacotherapy for primary insomnia.[60]

## EVALUATION OF THERAPEUTIC OUTCOMES

Several monitoring parameters, in addition to plasma or serum concentrations, are useful in managing patients (Tables 88-3 and 88-11).[2,60] Patients must be monitored for adverse medication reactions, such as sedation and anticholinergic effects, and for remission of previously documented target symptoms. The presence of adverse medication reactions does not necessarily indicate adequate or excessive dosage. In addition, changes in social and occupational functioning should be assessed. Patients receiving SNRIs should have their blood pressure monitored at regular intervals. Patients older than 40 years of age should receive a pretreatment ECG before starting TCA therapy, and follow-up ECGs should be performed periodically to assess for arrhythmias. Patients should be monitored for the emergence of suicidal ideation after initiation or discontinuation of any antidepressant, especially if other risk factors for death by suicide (eg, sleep disturbances) are present. If significant activation or insomnia occurs upon antidepressant initiation, a short-term anxiolytic or hypnotic may be appropriate.[67] Weight gain and sexual dysfunction, common adverse reactions associated with most antidepressants, may increase nonadherence and should be monitored and discussed with the patient (Table 88-11).

TABLE 88-11

**Adverse Medication Reactions and Monitoring Parameters Associated with Select Antidepressants**

| Medication | Adverse Medication Reaction | Monitoring | Comments |
|---|---|---|---|
| **Antidepressants from Each Pharmacologic Class** | | | |
| **Common to all antidepressants** | | | |
| | Suicidality | Behavioral changes | (US boxed warning) for all antidepressants; caregivers should be alerted to monitor for acute changes in behavior (especially early in treatment) |
| | | Mental status | |
| **Selective Serotonin Reuptake Inhibitors (SSRIs)** | | | |
| **Common to all** | | | |
| | Anxiety or nervousness | Assess severity and impact on patient functioning and quality of life | Most prominent on initial treatment; lower initial doses recommended in patients with prominent anxiety |
| | Hyponatremia | Serum sodium | More likely in older adult females; sodium may decrease within 72 hours of initiating antidepressant |
| | Nausea | Frequency and severity | May improve with slower dose titration |
| | Sleep changes | Sleep patterns | Among SSRI class: fluoxetine may be more activating; paroxetine may be |

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| | | | |
|---|---|---|---|
| | (insomnia and somnolence) | | more sedating |
| | Sexual dysfunction | Assess severity and impact on patient functioning and quality of life | Spontaneous self-reporting may be low; clinician should assess symptoms; reversible on medication discontinuation |
| **SSRI-Specific** | | | |
| Citalopram (possibly escitalopram) | QTc interval prolongation | Electrocardiogram; electrolytes (eg, potassium, magnesium) | Caution use in "at-risk" patients (eg, electrolyte disturbance); discontinue if QTc persistently >500 ms or increased >50 ms over baseline |
| Paroxetine | Anticholinergic effects | Symptoms: dry mouth, constipation, urinary retention, mental status | Avoid in older adults |
| **Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)** | | | |
| **Common to all** | | | |
| | Cardiovascular changes | Increases in blood pressure; heart rate | Possibly less likely with duloxetine; may need to lower/discontinue dose |
| | Insomnia | Sleep patterns | Possibly less likely with duloxetine |
| | Nausea | Frequency and severity | May improve with slower dose titration |
| | Sexual dysfunction | Assess severity and impact on patient functioning and quality of life | Spontaneous self-reporting may be low; clinicians should assess symptoms; reversible on medication discontinuation |
| | Sweating | Frequency and severity | May require change in therapy |
| **SNRI-Specific** | | | |
| Desvenlafaxine | Dose-related hyperlipidemia | Lipid profile | Elevations in total cholesterol, low-density lipoproteins, and triglycerides |
| Duloxetine | Liver toxicity | Liver function tests | May be transient upon initiation or sustained |
| **Mixed Serotonergic Effects (Mixed 5-HT)** | | | |
| Nefazodone | Liver toxicity | Liver function tests | Nefazodone boxed warning in the United States for hepatotoxicity |
| Trazodone | Orthostatic hypotension | Blood pressure, pulse | May be more severe as compared with other antidepressants; rate-limiting adverse medication reactions |
| | Priapism | Patient report of sexual dysfunction, especially painful | Patient should seek medical attention for prolonged erection (ie, >4 hr) |

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| | | | |
|---|---|---|---|
| | | erection | |
| Vilazodone and vortioxetine | Nausea | Frequency and severity | Most common dose limiting adverse reaction |
| **Serotonin and $\alpha_2$-Adrenergic Antagonist** | | | |
| Mirtazapine | Weight gain | Body weight | Frequently occurring and significant (>7% over baseline) weight gain among adults; diet mediated |
| **Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)** | | | |
| Bupropion | Seizure activity | Electroencephalogram if indicated | See Table 88-3 for proper dosing, which can help decrease seizure risk; caution use in patients with eating disorders or alcohol use disorders |

*Data from References 2,60,62,73,74, and 80.*

In addition to the clinical interview, psychometric rating instruments (such as those highlighted earlier in this chapter and in Chapter e81) allow for rapid and reliable measurement of the nature and severity of depressive and associated symptoms. It is helpful to administer the rating scales prior to treatment, 2 to 4 weeks and 8 to 12 weeks after initiation of therapy, and periodically thereafter. It is important to note that lack of robust response at 2 to 4 weeks does not necessarily predict lack of response at 8 to 12 weeks.[56] Interviewing a family member or friend (with the patient's permission) regarding symptoms and daily functioning also can assist in assessment of progress, as they may notice symptom improvements before the patient. Patients should be monitored at more frequent intervals early in treatment, particularly for suicidality. Monitoring is then continued at regular intervals throughout the continuation and maintenance phases of treatment and assessing for reemergence of target symptoms continued for several months after antidepressant therapy is discontinued.

Finally, one useful set of criteria that can be used with a variety of psychometric scales uses the following definitions: (a) *nonresponse* is less than a 25% decrease in baseline symptoms, (b) *partial response* is a 26% to 49% decrease in baseline symptoms, and (c) *partial remission or response* is greater than a 50% decrease in baseline symptoms.[53] Consistent with other recommendations, *remission* is a return to baseline functioning with no symptoms present.[2]

## CONCLUSION

Depression is a highly pervasive and complex disease state that can be impacted by comorbid medical and psychiatric conditions, psychosocial factors, as well as medications. While the precise pathophysiology of MDD is still elusive, antidepressant medications have directly targeted monoamine systems for the past half-century, and our understanding is evolving to include other complementary mechanisms. Additionally, research is revealing more about the complexity of the disease and the impact of genetic polymorphisms (both on pathophysiology and impact on pharmacotherapy outcomes). Individual patient characteristics should be considered when selecting antidepressant therapy and monitoring treatment. The goals of treatment should include remission (complete resolution of symptoms) and improved functioning.

## ABBREVIATIONS

| | |
|---|---|
| AHRQ | Agency for Healthcare Research and Quality |
| APA | American Psychiatric Association |
| BAP | British Association of Psychopharmacology |

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| | |
|---|---|
| BDI | Beck Depression Inventory |
| BDNF | brain-derived neurotrophic factor |
| CAM | complementary and alternative medicine |
| DA | dopamine |
| DHA | docosahexaenoic acid |
| *DSM-5* | *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition |
| ECG | electrocardiogram |
| ECT | electroconvulsive therapy |
| EPA | eicosapentaenoic acid |
| 5-HT | serotonin |
| GI | gastrointestinal |
| HAM-D | Hamilton Rating Scale for Depression |
| HPA | hypothalamic–pituitary–adrenal |
| KKW | kilocalories per kilogram per week |
| 5-MTHF | 5-methyltetrahydrofolate |
| MADRS | Montgomery-Åsberg Depression Rating Scale |
| MAOI | monoamine oxidase inhibitor |
| MDD | major depressive disorder |
| NDRI | norepinephrine and dopamine reuptake inhibitor |
| NE | norepinephrine |
| NIMH | National Institute of Mental Health |
| NT | neurotransmitter |
| PD | pharmacodynamic |
| PK | pharmacokinetic |
| rTMS | repetitive transcranial magnetic stimulation |
| SAMe | *S*-adenosyl-L-methionine |

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| | |
|---|---|
| SNRI | serotonin–norepinephrine reuptake inhibitor |
| SS | serotonin syndrome |
| SSRI | selective serotonin reuptake inhibitor |
| STAR*D | Sequenced Treatment Alternatives to Relieve Depression |
| $T_3$ | triiodothyronine |
| TADS | Treatment for Adolescents with Depression Study |
| TCA | tricyclic antidepressant |
| TORDIA | Treatment of Resistant Depression in Adolescents |
| TRD | treatment resistant depression |
| TREAD | Treatment with Exercise Augmentation for Depression |

## REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. Arlington, VA: American Psychiatric Association; 2013.

2. American Psychiatric Association. *Practice Guideline for the Treatment of Patients With Major Depressive Disorder.* 3rd ed. Arlington, VA: American Psychiatric Association; 2010.

3. Cleare A, Pariante CM, Young AH, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. *J Psychopharmacol.* 2015;29(5):459–525. [PubMed: 25969470]

4. Kennedy SH, Lam RW, McIntyre RS, et al. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 3. Pharmacological treatments. *Can J Psych.* 2016;61(9):540–560.

5. Iranpour S, Sabour S, Koohi F, Saadati HM, et al. The trend and pattern of depression prevalence in the U.S.: Data from National Health and Nutrition Examination Survey (NHANES) 2005 to 2016. *J Affect Disord.* 2022;298(Pt A):508–515. 10.1016/j.jad.2021.11.027 [PubMed: 34785265] .

6. Centers for Disease Control and Prevention. National VitalStatistics Report. 2017, May 17; 70(4) Available at: https://www.cdc.gov/nchs/data/nvsr70/nvsr70-04-508.pdf. Accessed October 7, 2021.

7. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. *Lancet*. 2021;398(10312):1700–1712. 10.1016/S0140-6736(21)02143-7 [PubMed: 34634250] .

8. Centers for Disease Control and Prevention. Vital Signs: Suicide rising across the US. Available at: https://www.cdc.gov/vitalsigns/suicide/index.html. Accessed November 27, 2018.

9. Substance Abuse and Mental Health Services Administration. 2017 National Survey on Drug Use and Health: Major Depressive Episode in the Past

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Year. Available at: https://www.samhsa.gov/data/report/2017-nsduh-annual-national-report. Accessed Novemeber 27, 2018.

10. Weissman MM, Gershon ES, Kidd KK, et al. Psychiatric disorders in the relatives of probands with affective disorders. The Yale University—National Institute of Mental Health Collaborative Study. *Arch Gen Psychiatry*. 1984;41(1):13–21. [PubMed: 6691780]

11. Stewart SL, Van Dyke JN, Poss JW. Examining the mental health presentations of treatment-seeking Transgender and Gender Nonconforming (TGNC) Youth. *Child Psychiatry Hum Dev.* 2021 10.1007/s10578-021-01289-1 [PubMed: 34860314] .

12. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: Review and meta-analysis. *Am J Psychiatry*. 2000;157(10):1552–1562. [PubMed: 11007705]

13. Belmaker RH, Agam G. Mechanisms of disease major depressive disorder. *N Engl J Med.* 2008;358:55–68. [PubMed: 18172175]

14. Baumeister AA, Hawkins MF, Uzelac SM. The myth of reserpine-induced depression: Role in the historical development of the monoamine hypothesis. *J Hist Neurosci.* 2003;12(2):207–220. [PubMed: 12953623]

15. Yohn CN, Gergues MM, Samuels BA. The role of 5-HT receptors in depression. *Mol Brain.* 2017;10(1):1–12. [PubMed: 28052764]

16. Pehrson AL, Sanchez C. Altered γ-aminobutryic acid neurotransmission in major depressive disorder: A critical review of the supporting evidence and the influence of serotonergic antidepressants. *Drug Des Devel Ther.* 2015;9:603–624. [PubMed: 25653499]

17. Taylor GT, Manzella F. Kappa opioids, salvinorin A and major depressive disorder. *Curr Neuropharmacol.* 2016;14(2):165–176. [PubMed: 26903446]

18. Schüle C, Nothdurfter C, Rupprecht R. The role of allopregnanolone in depression and anxiety. *Prog Neurobiol.* 2014;113:79–87. [PubMed: 24215796]

19. Newport DJ, Carpenter LL, McDonald WM. Ketamine and other NMDA antagonists: Early clinical trials and possible mechanisms in depression. *Am J Psychiatry*. 2015;172:950–966. [PubMed: 26423481]

20. Koopman M, El Aidy S; MIDtrauma consortium. Depressed gut? The microbiota-diet-inflammation trialogue in depression. *Curr Opin Psychiatry*. 2017;30(5):369–377. [PubMed: 28654462]

21. Bender A, Hagan K, Kinston N. The association of folate and depression: A meta-analysis. *J Psychiatr Res.* 2017;95:9–18. [PubMed: 28759846]

22. Farioli-Vecchioli S, Sacchetti S, di Robilant NV, et al. The role of physical exercise and omega-3 fatty acids in depressive illness in the elderly. *Curr Neuropharmacol.* 2018;16(3):308–326. [PubMed: 28901279]

23. Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. *Arch Gen Psychiatry*. 2007;64:327–337. [PubMed: 17339521]

24. Taylor C, Fricker AD, Devi L, et al. Mechanisms of action of antidepressants: From neurotransmitter systems to signaling pathways. *Cell Signal.* 2005;17(5):549–557. [PubMed: 15683730]

25. Niciu MJ, Ionescu DF, Mathews DC, et al. Second messenger/signal transduction pathways in major mood disorders—moving from membrane to mechanism of action, part I: Major depressive disorder. *CNS Spectrums.* 2013;18:231–241. [PubMed: 23462230]

26. Feighner JP. Mechanism of action of antidepressant medications. *J Clin Psychiatry*. 1999;60(suppl 4):S4–S11; discussion 12–13.

27. Rivero G, Gabilondo AM, García-Sevilla JA, et al. Increased α2- and β1-adrenoreceptor densities in post-mortem brain of subjects with depression:

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Differential effect of antidepressant treatment. *J Affective Disorders.* 2014;167:343–350.

28. Kanes S, Colquhoun H, Gunduz-Bruce H, et al. Brexanolone (SAGE-547 injection) in post-partum depression: A randomised controlled trial. *Lancet*. 2017;390:480–489. [PubMed: 28619476]

29. Björkholm C, Monteggia LM. BDNF: A key transducer of antidepressant effects. *Neuropharmacology*. 2016;102:72–79. [PubMed: 26519901]

30. Strasburger SE, Bhimani PM, Kaabe JH, et al. What is the mechanism of ketamine's rapid-onset antidepressant effect? A concise overview of the surprisingly large number of possibilities. *J Clin Pharm Ther.* 2017;42(2):147–154. [PubMed: 28111761]

31. Coryell W, Schlesser M. The dexamethasone suppression test and suicide prediction. *Am J Psychiatry*. 2001;158(5):748–753. [PubMed: 11329397]

32. Wan L, Yuhong L, Zhang Z, et al. Methylenetetrahydrofolate reductase and psychiatric diseases. *Transl Psychiatry*. 2018;8:242. [PubMed: 30397195]

33. Bousman CA, Dunlop BW. Genotype, phenotype, and medication recommendation agreement among commercial pharmacogenetic-based decision support tools. *Pharmacogenomics J.* 2018;18(5):613–622. [PubMed: 29795409]

34. Haigh E, Bogucki O, Sigmon S, et al. Depression among older adults: A 20-year update on five common myths and misconceptions. *Am J Geriatr Psychiatry*. 2018;26(1):107–122. [PubMed: 28735658]

35. Kok RM, Reynolds CF. Management of depression in older adults: A review. *JAMA.* 2017;317(20):2114–2122. [PubMed: 28535241]

36. Voinov B, Richie WD, Bailey RK. Depression and chronic diseases: It is time for a synergistic mental health and primary care approach. *Prim Care Companion CNS Disord.* 2013;15(2):pii: PCC.

37. Qato DM, Ozenberger K, Olfson M. Prevalence of prescription medications with depression as a potential adverse effect among adults in the United States. *JAMA.* 2018;319(22):2289–2298. [PubMed: 29896627]

38. Gorton HC, Webb RT, Kapur N, et al. Non-psychotropic medication and risk of suicide or attempted suicide: A systematic review. *BMJ.* 2016;6:e009074.

39. Gibbons RD, Mann JJ. Varenicline, smoking cessation, and neuropsychiatric adverse events. *Am J Psychiatry*. 2013;170(12):1460–1467. [PubMed: 24030388]

40. Risk evaluation and mitigation strategy (REMS) The iPLEDGE Program. Available at https://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM234639.pdf. Accessed November 20, 2018.

41. Hesdorffer DC, Kanner AM. The FDA alert on suicidality and antiepileptic drugs: Fire or false alarm? *Epilepsia.* 2009;50(5):978–986. [PubMed: 19496806]

42. Skovlund CW, Mørch LS, Kessing LV, et al. Association of hormonal contraception with depression. *JAMA Psychiatry*. 2016;73(11):1154–1162. [PubMed: 27680324]

43. Solmi M, Pigato G, Kane JM, et al. Treatment of tardive dyskinesia with VMAT-2 inhibitors: A systematic review and meta-analysis of randomized controlled trials. *Drug Des Devel Ther.* 2018;12:1215–1238. [PubMed: 29795977]

44. Ranchord AM, Spertus JA, Buchanan DM, et al. Initiation of β-blocker therapy and depression after acute myocardial infarction. *Am Heart J.* 2016;174:37–42. [PubMed: 26995368]

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45. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382–389. [PubMed: 444788]

46. Beck AT, Ward CH, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961;4:561–571. [PubMed: 13688369]

47. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: Validity of a brief depression severity measure. *J Gen Intern Med.* 2001;16(9):606–613. [PubMed: 11556941]

48. Hill RM, Rufino K, Kurian S, et al. Suicide ideation and attempts in a pediatric emergency department before and during COVID-19. *Pediatrics*. 2021;147(3 10.1542/peds.2020-029280
[PubMed: 33328339] .

49. Jacobs DG, Baldessarini RJ, Fawcett JA, et al. Practice guidelines for the assessment and treatment of patients with suicidal behaviors. *Am J Psychiatry*. 2003;160(11 suppl):S1–S60.

50. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry*. 2011;168(12):1266–1277. [PubMed: 22193671]

51. Fawcett JA, Baldessarini RJ, Coryell WH, et al. Defining and managing suicidal risk in patients taking psychotropic medications. *J Clin Psychiatry*. 2009;70(6):782–789. [PubMed: 19573477]

52. Sharma T, Guski LW, Freund N, et al. Suicidality and aggression during antidepressant treatment: Systematic review and meta-analyses based on clinical study reports. *BMJ.* 2016;352:i65. [PubMed: 26819231]

53. Mann JJ. The medical management of depression. *N Engl J Med.* 2005;353(17):1819–1834. [PubMed: 16251538]

54. Fava GA, Benasi G, Lucente M. Withdrawal symptoms after serotonin-noradrenalin reuptake inhibitor discontinuation: Systematic review. *Psychother Psychosom.* 2018;87:195–203. [PubMed: 30016772]

55. Weitz ES, Hollon SD, Twisk J, et al. Baseline depression severity as moderator of depression outcomes between cognitive behavioral therapy vs pharmacotherapy: An individual patient data meta-analysis. *JAMA Psychiatry*. 2015;72(11):1102–1109. [PubMed: 26397232]

56. Gaynes BN, Rush AJ, Trivedi MH, et al. The STAR*D study: Treating depression in the real world. *Cleve Clin J Med.* 2008;75(1):57–66. [PubMed: 18236731]

57. Brunoni AR, Chaimani A, Moffa AH, et al. Repetitive transcranial magnetic stimulation for the acute treatment of major depressive episodes: A systematic review with network meta-analysis. *JAMA Psychiatry*. 2017;74(2):143–153. [PubMed: 28030740]

58. Trivedi MH. The link between depression and physical symptoms. *Prim Care Companion J Clin Psychiatry*. 2004;6(suppl 1):S12–S16.

59. Freeman MP, Fava M, Lake J, et al. Complementary and alternative medicine in major depressive disorder: The American Psychiatric Association Task Force report. *J Clin Psychiatry*. 2010;71(6):669–681. [PubMed: 20573326]

60. Lexicomp Online. Lexi-Comp, Inc (Copyright 1978–2018). Available at: http://online.lexi.com. Accessed November 15, 2021.

61. Wimbiscus M, Kostenko O, Malone D. MAO inhibitors: Risks, benefits, and lore. *Cleve Clin J Med.* 2010:77(12):859–882. [PubMed: 21147941]

62. Al-Sukhni M, Maruschak NA, McIntyre RS. Vortioxetine: A review of efficacy, safety and tolerability with a focus on cognitive symptoms in major depressive disorder. *Expert Opin Drug Saf.* 2015;14(8):1291–1304. [PubMed: 26022537]

63. O'Donnell JM, Bies RR, Shelton RC. Drug therapy of depression and anxiety disorders. In: Brunton LL, Hilal-Dandan R, Knollmann BC, eds. *Goodman & Gilman: The Pharmacological Basis of Therapeutics*. 13th ed. McGraw Hill; 2018.

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64. Walsh BT, Seidman SN, Sysko R, Gould M. Placebo response in studies of major depression: Variable, substantial, and growing. *JAMA.* 2002;287(14):1840–1847. [PubMed: 11939870]

65. Cipriani A, Forukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: A systematic review and network meta-analysis. *Lancet*. 2018;391:1357–1366. [PubMed: 29477251]

66. Goldstein BJ, Goodnick PJ. Selective serotonin reuptake inhibitors in the treatment of affective disorders—III. Tolerability, safety and pharmacoeconomics. *J Psychopharmacol.* 1998;12(3 suppl B):S55–S87. [PubMed: 9808079]

67. Wichniak A, Wierzbicka A, Walecka M, et al. Effect of antidepressants on sleep. *Curr Psychiatry*. 2017;19:63.

68. La Torre A, Giupponi G, Duffy D, Conca A. Sexual dysfunction related to psychotropic drugs: A critical review—part I: Antidepressants. *PharmacoPsychiatry*. 2013;46(5):191–199. [PubMed: 23737245]

69. Howland RH. A critical evaluation of the cardiac toxicity of citalopram part 1. *J Psychosocial Nursing.* 2011;49(11):13–16.

70. Rector TS, Adabag S, Cunningham F, et al. Outcomes of citalopram dosage risk mitigation in a veteran population. *Am J Psychiatry*. 2016;173:896–902. [PubMed: 27166093]

71. Settle EC. Antidepressant drugs: Disturbing and potentially dangerous adverse effects. *J Clin Psychiatry*. 1998;59(Suppl 16):S25–S30.

72. Glassman AH, Roose SP, Bigger JT. The safety of tricyclic antidepressants in cardiac patients risk benefit reconsidered. *JAMA.* 1993;269(20):2673–2675. [PubMed: 8487453]

73. McIntyre RS. The role of new antidepressants in clinical practice in Canada: A brief review of vortioxetine, levomilnacipran ER, and vilazodone. *Neuropsychiatr Dis Treat.* 2017;13:2913–2919. [PubMed: 29238196]

74. Sedky K, Nazir R, Joshi A. Which psychotropic medications induce hepatotoxicity. *Gen Hosp Psychiatry*. 2012;34:53–61. [PubMed: 22133982]

75. Stimmel GL, Gutierrez MA. Counseling patients about sexual issues. *Pharmacotherapy*. 2006;26(11):1608–1615. [PubMed: 17064206]

76. Rabiner EA, Gunn RN, Castro ME, et al. β-Blocker binding to human 5-$HT_{1A}$ receptors *in vivo* and *in vitro*: Implications for antidepressant therapy. *Neuropsychopharmacol.* 2000;23:285–293.

77. Steinert T, Fröscher W. Epileptic seizures under antidepressive drug treatment: Systematic review. *PharmacoPsychiatry*. 2018;51:121–135. [PubMed: 28850959]

78. Taylor MJ, Rudkin L, Bullemor-Day P, Lubin J, Chukwujekwu C, Hawton K, et al. Strategies for managing sexual dysfunction induced by antidepressant medication. *Cochrane Database Syst Rev.* 20135):CD003382–CD003382. 10.1002/14651858.CD003382.pub3 [PubMed: 23728643] .

79. Gorman JM. Mirtazapine: Clinical overview. *J Clin Psychiatry*. 1999;60(suppl 17):S9–S13.

80. Azzaro AJ, Ziemnia J, Kemper E, et al. Pharmacokinetics and absolute bioavailability of selegiline following treatment of healthy subjects with selegiline transdermal system (6 mg/24 h): A comparison with oral selegiline capsules. *J Clin Pharmacol.* 2007;47:1256–1267. [PubMed: 17715422]

81. Shulman KI, Walker SE, MacKenzie S, et al. Dietary restriction, tyramine and the use of monoamine oxidase inhibitors. *J Clin Psychopharmacol.* 1989;9:397–402. [PubMed: 2592589]

82. Daly EJ, Singh JB, Fedgchin M, et al. Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: A randomized clinical trial. *JAMA Psychiatry*. 2018;75(2):139–148. [PubMed: 29282469]

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83. Canuso CM, Singh JB, Fedgchin M, et al. Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: Results of a double-blind, randomized, placebo-controlled study. *Am J Psychiatry*. 2018;175(7):620–630. [PubMed: 29656663]

84. Walkery A, Leader LD, Cooke E, VandenBerg A, et al. Review of allopregnanolone agonist therapy for the treatment of depressive disorders. *Drug Des Devel Ther.* 2021;15:3017–3026. 10.2147/DDDT.S240856
[PubMed: 34267503] .

85. Bahji A, Vazquez GH, Zarate CA Jr. Comparative efficacy of racemic ketamine and esketamine for depression: A systematic review and meta-analysis. *J Affect Disord.* 2021;278:542–555. 10.1016/j.jad.2020.09.071
[PubMed: 33022440] .

86. Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med.* 2005;352(11):1112–1120. [PubMed: 15784664]

87. DeVane CL. Metabolism and pharmacokinetics of selective serotonin reuptake inhibitors. *Cell Mol Neurobiol.* 1999;19(4):443–466. [PubMed: 10379420]

88. Drug interactions Flockhart Table. Available at https://drug-interactions.medicine/iu.edu/MainTable.aspx. Accessed November 15, 2021.

89. Wells BG. Tricyclic antidepressants. In: Taylor WJ, Caviness MHD, Taylor WJ, Caviness MHD, eds. *A Textbook for the Clinical Application of Therapeutic Drug Monitoring.* Irving, TX: Abbott Laboratories; 1986:449–465.

90. Jefferson JW, Pradko JF, Muir KT. Bupropion for major depressive disorder: Pharmacokinetic and formulation considerations. *Clin Ther.* 2005;27(11):1685–1695. [PubMed: 16368442]

91. Mullish BH, Kabir MS, Thursz MR, et al. Review article: Depression and the use of antidepressants in patients with chronic liver disease or liver transplantation. *Ailment Pharmacol Ther.* 2014;40:880–892.

92. Eyler RF, Unruh ML, Quinn DK, et al. Psychotherapeutic agents in end-stage renal disease. *Semin Dial.* 2015;28(4):417–426. [PubMed: 25857865]

93. Rickli A, Liakoni E, Hoener MC, et al. Opioid-induced inhibition of the human 5-HT and noradrenaline transporters *in vitro*: Link to clinical reports of serotonin syndrome. *Br J Pharmacol.* 2018;175(3):532–543. [PubMed: 29210063]

94. Bixby AL, VandenBerg A, Bostwick JR. Clinical management of bleeding risk with antidepressants. *Ann Pharmacother.* 2018; [Epub ahead of print].

95. Köhler O, Petersen L, Mors O, et al. Inflammation and depression: Combined use of selective serotonin reuptake inhibitors and NSAIDs or paracetamol and psychiatric outcomes. 2015;5(8):e00338.

96. Lorenz RA, VandenBerg AM, Canepa EA. Serotonergic antidepressants and linezolid: A retrospective chart review and presentation of cases. *Int J Psychiatry Med.* 2008;38(1):81–90. [PubMed: 18624020]

97. Ravindran AV, Balneaves LG, Faulkner G, et al. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder. Section 5. Complementary and alternative medicine treatments. *Can J Psychiatry*. 2016;61(9):576–587. [PubMed: 27486153]

98. Turvey CL, Conwell Y, Jones MP, et al. Risk factors for late-life suicide: A prospective, community-based study. *Am J Geriatr Psychiatry*. 2002;10(4):398–406. [PubMed: 12095899]

99. Schatzberg AG, Kremer C, Rodriguez HE, et al. Double-blind, randomized comparison of mirtazapine and paroxetine in elderly depressed patients. *Am J Geriatr Psychiatry*. 2002;10(5):541–550. [PubMed: 12213688]

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100. Mullen S. Major depressive disorder in children and adolescents. *Ment Health Clin.* 2018;8(6):275–283. [PubMed: 30397569]

101. March J, Silva S, Petrycki S, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for adolescents with depression study (TADS) randomized controlled trial. *JAMA.* 2004;292(7):807–820. [PubMed: 15315995]

102. Emslie GJ, Mayes T, Porta G, et al. Treatment of resistant depression in adolescents (TORDIA): Week 24 outcomes. *Am J Psychiatry*. 2010;167:782–791. [PubMed: 20478877]

103. Goodyer I, Dubicka B, Wilkinson P, et al. A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. The ADAPT trial. *Health Technol Assess.* 2008;12(14):iii–iv,ix-60. [PubMed: 18462573]

104. Gibbons RD, Brown CH, Hur K, et al. Suicidal thoughts and behavior with antidepressant treatment. *Arch Gen Psychiatry*. 2012;69(6):580–587. [PubMed: 22309973]

105. Gibbons RD, Brown CH, Hur K, et al. Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. *Am J Psychiatry*. 2007;164:1356–1363. [PubMed: 17728420]

106. Oberlander TF, Warburton W, Misri S, et al. Neonatal outcomes after prenatal exposure to selective serotonin reuptake inhibitor antidepressants and maternal depression using population-based linked health data. *Arch Gen Psychiatry*. 2006;63(8):898–906. [PubMed: 16894066]

107. Cohen LS, Altshuler LL, Harlow BL, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *JAMA.* 2006;295(5):499–507. [PubMed: 16449615]

108. Gao SY, Wu QJ, Zhang TN, et al. Selective serotonin reuptake inhibitor use during early pregnancy and congenital malformations: A systematic review and meta-analysis of cohort studies of more than 9 million births. *BMC Medicine*. 2018;16:205. [PubMed: 30415641]

109. Chambers CD, Hernandez-Diaz S, Van Marter LJ, et al. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med.* 2006;354(6):579–587. [PubMed: 16467545]

110. Rubinow DR. Antidepressant treatment during pregnancy: Between Scylla and Charybdis. *Am J Psychiatry*. 2006;163(6):954–956. [PubMed: 16741191]

111. Yonkers KA, Wisner KL, Stewart DE, et al. The management of depression during pregnancy: A report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. *Gen Hosp Psychiatry*. 2009;31(5):403–413. [PubMed: 19703633]

112. Freeman MP. Breastfeeding and antidepressants: Clinical dilemmas and expert perspectives. *J Clin Psychiatry*. 2009;70(2):291–292. [PubMed: 19265645]

113. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: Implications for clinical practice. *Am J Psych.* 2006;163:28–40.

114. Rush AJ, Trivedi MH, Wisniewski SR, et al. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med.* 2006;354(12):1231–1242. [PubMed: 16554525]

115. Fava M, Rush AJ, Wisniewski SR, et al. A comparison of mirtazapine and nortriptyline following two consecutive failed medication treatments for depressed outpatients: A STAR*D report. *Am J Psychiatry*. 2006;163(7):1161–1172. [PubMed: 16816220]

116. Nierenberg AA, Fava M, Trivedi MH, et al. A comparison of lithium and T(3) augmentation following two failed medication treatments for depression: A STAR*D report. *Am J Psychiatry*. 2006;163(9):1519–1530. [PubMed: 16946176]

117. Mohamed S, Johnson GR, Chen P, et al. Effect of antidepressant switching vs augmentation on remission among patients with major depressive

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disorder unresponsive to antidepressant treatment. The VAST-D randomized clinical trial. *JAMA.* 2018;318:132–145.

118. Rosenblat JD, Lee Y, McIntyre RS. Does pharmacogenomics testing improve clinical outcomes for major depressive disorder. A systematic review of clinical trials and cost-effectiveness studies. *J Clin Psychiatry*. 2017;78(6):720–729. [PubMed: 28068459]

## SELF-ASSESSMENT QUESTIONS

1. Which of the following statements is correct when considering the addition of an SSRI to a medication regimen that includes a chronic NSAID prescription?

   A. Combination must be avoided and is contraindicated

   B. Use this combination with caution and monitor patient closely

   C. Combination is associated with enhanced antidepressant efficacy

   D. Combination is associated with increased risk for clot formation

2. Multiple agents with novel mechanisms of action are under investigation or approved for depression. The agent FDA approved for treatment of postpartum depression is:

   A. Brexpiprazole

   B. Samidorphan

   C. Esketamine

   D. Brexanolone

3. Which of the following antidepressants does NOT inhibit reuptake of serotonin?

   A. Mirtazapine

   B. Vilazodone

   C. Vortioxetine

   D. Trazodone

4. According to the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which of the following are associated with increased remission rates?

   A. Use of concurrent cognitive behavioral therapy

   B. Achieving high dose

   C. Partial response at 4 days

   D. Switching to different class

5. Choose the most appropriate option for a 68-year-old patient with a history of coronary artery disease taking metoprolol and simvastatin?

   A. Fluoxetine

   B. Fluvoxamine

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C. Sertraline

D. Nortriptyline

6. In a patient who has successfully achieved remission following the acute phase of treatment, which of the following is the most important factor to consider regarding the decision as to how long treatment should be continued?

A. Prescription copayment cost

B. Risk of depressive recurrence

C. Brand name product availability

D. Caregiver preference

7. For a patient with history of antidepressant induced sexual dysfunction, which agent is least likely to cause this medication adverse reaction?

A. Bupropion

B. Paroxetine

C. Amitriptyline

D. Phenelzine

8. In a patient experiencing a treatment refractory major depressive episode, which of the following steps should be confirmed prior to concluding their symptoms are not responding to treatment?

A. Adequate dose for adequate duration

B. Adherence to prescribed regimen

C. Proper monitoring of response

D. All the above

9. To meet criteria for a major depressive episode (MDE), the patient must exhibit the following symptoms according to the *DSM-5*:

A. Depressed mood most of the day every day for at least 1 week

B. At least four of the symptoms as listed in the *DSM-5* for MDE

C. Impairment in some area of functioning (eg, social, occupational)

D. History of “switch” into mania following antidepressant treatment

10. Which of the following scenarios is considered a pharmacokinetic medication interaction, instead of a pharmacodynamic medication interaction?

A. Fluoxetine taken with tamoxifen decreases active metabolite levels

B. Fluoxetine taken with phenelzine leads to serotonin syndrome

C. Fluoxetine taken with ibuprofen increases risk of bleeding

D. Fluoxetine taken with hydrochlorothiazide increases risk of hyponatremia

11. If serotonin syndrome is suspected in a patient being treated with antidepressants, which of the following is the most likely symptom that should be identified?

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A. Clonus

B. Asterixis

C. Priapism

D. None of the above

12. When considering next-step antidepressant treatment in a patient who has not achieved full remission, which of the following approaches are supported by the evidence, according to the British Association of Psychopharmacology (BAP) guidelines and the STAR*D trial?

A. Switch antidepressant

B. Augment antidepressant

C. All the above

D. None of the above

13. A patient taking tranylcypromine should completely avoid which of the following?

A. Cheese pizza from commercial chains

B. Apple juice

C. Sour cream

D. Prosciutto

14. Which of the following antidepressants have been associated with sustained elevated blood pressure that requires close monitoring during treatment and possible dose adjustments?

A. Desvenlafaxine

B. Venlafaxine

C. Levomilnacipran

D. All the above

15. When assessing a patient with new onset symptoms of depression, which of the following medications has a clear mechanism as well as evidence to support a high rate of treatment associated depression?

A. Varenicline

B. Tetrabenazine

C. Metoprolol

D. Sumatriptan

## SELF-ASSESSMENT QUESTION-ANSWERS

1. **B.** Use of NSAIDs with antidepressants is not contraindicated with antidepressants. Use of chronic daily NSAIDs should be approached with caution and monitoring due to increased risk of bleeding. NSAIDs may be associated with a higher rate of depression. NSAIDs do not increase risk of clot formation, rather increase risk of bleeding (see Tables 88-10 and 88-11).

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2. **D.** Brexpiprazole is a second-generation antipsychotic approved for adjunctive treatment of MDD. Samidorphan is an opioid receptor antagonist. Esketamine is approved for treatment resistant depression. Only brexanolone is seeking FDA approval for treatment of postpartum depression (see Table 88-6).

3. **A.** Mirtazapine does not inhibit the serotonin transporter. Vilazodone, vortioxetine, and trazodone all inhibit the reuptake of serotonin via the transporter in addition to other mechanisms (see Table 88-4).

4. **B.** Patients who achieved remission in STAR*D were on higher average doses of medication. Outcomes regarding cognitive behavioral therapy were limited due to lack of power to analyze this group. Partial response at 2 weeks (not 4 days) was predictive of remission. There were no differences between agents in the switch arm regarding response rates.

5. **C.** Fluoxetine may significantly increase metoprolol levels due to inhibition of CYP2D6 resulting in bradycardia or hypotension. Fluvoxamine may significantly increase levels of simvastatin due to inhibition of CYP3A4. Sertraline does not have significant interactions with metoprolol or simvastatin. Nortriptyline and other TCAs are not recommended in patients over 65 years of age due to anticholinergic effects and may have negative cardiac effects in patients post-MI (see Tables 88-9 and 88-10).

6. **B.** Prescription cost may negatively impact adherence, but should not be a factor in considering continuation of antidepressant treatment. Cost of medication should be considered when initiating treatment to ensure a feasible plan for a patient. Risk of recurrence is the most important factor when determining whether to continue treatment. Caregiver input regarding severity of illness and resolution of symptoms is important in determining response to treatment. Brand name products are no more beneficial than generic products and should not drive treatment decisions.

7. **A.** Bupropion is the only agent listed that is not associated with sexual adverse effects.

8. **D.** All listed factors are important to assess prior to adjusting therapy due to nonresponse.

9. **C.** Depressed mood for most of the day must last for at least 2 weeks. At least five symptoms must be present. History of switch into mania would be suggestive of bipolar disorder not MDE. Patients must have impairment in functioning (see Table 88-2).

10. **A.** Fluoxetine has a pharmacokinetic interaction with tamoxifen as it inhibits metabolism of CYP2D6 that prevents conversion of tamoxifen to its active metabolite. When taken with phenelzine, both agents increase serotonin levels via different mechanisms. When taken with ibuprofen, both agents increase risk of bleeding via different mechanism. When taken with hydrochlorothiazide, both agents can cause hyponatremia via different mechanisms (see Tables 88-9 and 88-10).

11. **A.** Only clonus is associated with serotonin syndrome. Asterixis would be associated with liver failure. Priapism is a rare side effect of trazodone. Trazodone does increase serotonin; however, priapism is not associated with serotonin syndrome.

12. **C.** There were no statistically significant differences between the switch arm and the augmentation arm in the STAR*D trial. Patients with partial response were more likely to choose augmentation. BAP guidelines recommend switching antidepressants if there are troublesome side effects or no improvement in symptoms and augmenting for partial/insufficient response.

13. **D.** Pizza from most commercial chains have low levels of tyramine along with apple juice and sour cream. Prosciutto and other dry aged meats have high tyramine levels and should be avoided completely (see Table 88-5).

14. **D.** All SNRIs are associated with sustained elevated blood pressure and all agents listed are SNRIs.

15. **B.** Varenicline, metoprolol, and sumatriptan have been inconsistently associated with increased risk of depression. Risk is confounded by other variables in studies and has not been clearly linked to mechanism for all agents. Tetrabenazine depletes presynaptic vesicles of monoamines and has a black box warning for treatment associated depression.

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