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Focus on pharmacotherapy for depression

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Abstract: Many patients are prescribed antidepressants. This article discusses depression, as well as the available first- and second-line prescription medications used to manage the disorder in adults.

Keywords: antidepressants, depression, major depressive disorder, MAOIs, MDD, monoamine oxidase inhibitors, SARIs, selective serotonin reuptake inhibitors, serotonin antagonist and reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, SNRIs, SSRIs, TCAs, tricyclic antidepressants

MAJOR DEPRESSION is one of the most common mental health disorders in the US. For some, it can result in severe impairments that interfere with major life activities.¹ Antidepressant prescriptions and usage have increased substantially over the past few decades.²

The 2018 National Survey on Drug Use and Health (NSDUH) estimated that 7.2% of all US adults, or 17.1 million individuals, had experienced at least one depressive episode in the previous year. The prevalence of major depressive episodes was highest among young adults age 18 to 25 (13.8% or 4.6 million). The NSDUH survey also estimated that

14.4% of US adolescents ages 12 to 17, or 3.5 million teenagers, had experienced at least one major depressive episode in this same time frame.¹

This article provides an overview of depression in adults, as well as the prescription medications available to manage the disorder. Psychotherapy, electroconvulsive therapy, and nonprescription and over-the-counter (OTC) products are beyond the scope of this article. Consult the pharmaceutical product information for details on each drug. These may include any contraindications or special considerations for specific patient populations such as pregnant women, older

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adults, and those with hepatic or renal dysfunction.

Diagnostic criteria

Depression is both disabling and highly recurrent.³ To be diagnosed with major depressive disorder (MDD), patients must have been experiencing one of the main symptoms, such as a depressed mood or an inability to experience pleasure, for 2 or more weeks. Additionally, patients must have at least four of the following symptoms:³

- low energy level
- poor concentration
- change in appetite or weight
- insomnia or hypersomnia
- psychomotor slowness or agitation
- thoughts of worthlessness or guilt
- recurrent suicidal ideation.

Pathophysiology

The pathophysiology of depression is multifactorial, involving a combination of genetic, biological, environmental, and psychologic factors, but clinical understanding remains rudimentary.^{3,4}

Research indicates that orexins, also called hypocretins, and their receptors are involved in the pathophysiology of depression, but the role of these neuropeptides is not well understood.⁵ Other evidence suggests that microRNAs may be a biomarker for depression and other neuropsychiatric disorders.⁴ Similarly, ceramides, a class of sphingolipids, may also play a role. These act as a physical barrier between the intracellular and extracellular environments in the brain and can affect neurotransmission by altering proteins in the cell membrane (see *Areas of the brain affected by depression*).⁶

Treatment options

Patients with depression may benefit from psychotherapy to assist with coping skills, small life changes, better relationships, insecurities, and better understanding of themselves. In some cases, psychotherapy alone is successful, but medication is often prescribed in combination.^{4,7}

Antidepressants are the most common treatment for MDD. Despite

several attempts using different drug therapies and classes, however, nearly one-third of patients experience an inadequate response to pharmacologic treatment.⁴

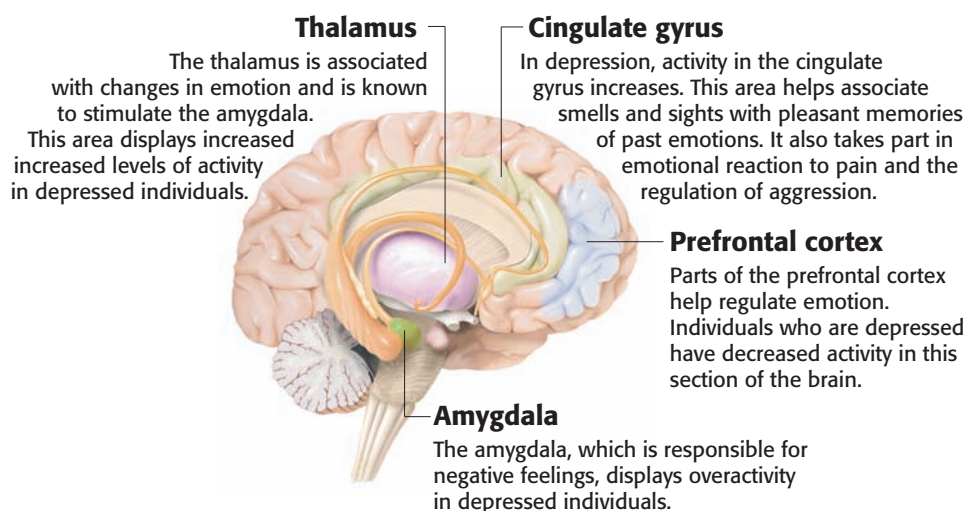
Antidepressant pharmacotherapy

Mild depression may be treated with psychotherapy and other behavioral therapies, whereas MDD generally requires one or more classes of antidepressants.⁸ In addition, many patients will not achieve remission after their initial treatment with an antidepressant.⁶ As such, two or more classes may be required to alleviate depressive symptoms. The dosage of one antidepressant should be optimized before adding a second.

First-line therapies include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and atypical antidepressants such as bupropion and mirtazapine. Of these, SSRIs or SNRIs are typically used first, with atypical agents or tricyclic antidepressants (TCAs) used as add-on therapies.⁹ Due to safety

Areas of the brain affected by depression

Several areas of the brain are involved in the emotional and physical changes seen in depression. While the brain of a depressed individual is generally underactive, certain areas display overactivity.



Source: Braun CA, Anderson CM. *Applied Pathophysiology: A Conceptual Approach to the Mechanisms of Disease*. 3rd ed. Philadelphia, PA: Wolters Kluwer Health; 2017.

concerns, monoamine oxidase inhibitors (MAOIs) and TCAs are recommended as second-line therapies. Augmentation strategies may include serotonin antagonist and reuptake inhibitors (SARIs), lithium, thyroid hormones, or second-generation antipsychotics. (See *Available antidepressants*.) Careful attention to the drug class and mechanism of action is necessary to anticipate potential adverse reactions.

Antidepressant drug regimens may improve symptoms of depression in as little as 1 to 2 weeks, but they may also take up to 8 weeks. If the patient does not improve after 8 weeks, treatment should be adjusted by switching medications, increasing dosages, or adding another medication to the regimen.

Antidepressants may put patients at risk for suicidal ideation or behavior, especially in children and young adults. This is most common in the first few months of therapy. Patients must be monitored closely and instructed to contact their provider if they experience troubling changes in mood or behavior.⁸

SSRIs have the strongest safety profile and are better tolerated than other antidepressants. They act by inhibiting the reuptake of serotonin, allowing more serotonin to be available to bind to receptors and improve mood.

Drugs such as citalopram, fluoxetine, sertraline, and escitalopram may be associated with prolongation

Available antidepressants^{10-16,18,21,23,33,34}

Drug class	Examples
Atypical antidepressants	Bupropion, mirtazapine
MAOIs	Isocarboxazid, phenelzine
SARIs	Nefazodone, trazodone, vilazodone, vortioxetine
SNRIs	Duloxetine, desvenlafaxine, levomilnacipran, venlafaxine
SSRIs	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
TCAs	Amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline

of the corrected QT interval (QTc). The QTc allows QT intervals to be evaluated objectively regardless of the patient's heart rate.¹⁰ All patient medications, including common prescriptions that prolong the QTc such as azithromycin and levofloxacin, should be evaluated to determine whether an SSRI would be a safe addition. These medications may lead to ventricular dysrhythmias such as torsades de pointes or ventricular fibrillation.¹¹ (See *Danger of QT interval prolongation*.)

The most common adverse reaction to SSRIs is nausea during the first 2 weeks of therapy. Gastrointestinal (GI) issues may be common in combination with antiplatelet or anticoagulant medications and include diarrhea, xerostomia (dry mouth), constipation, vomiting, and GI bleeding. Teach patients to maintain hydration and eat small, frequent meals that do not irritate the GI tract.

Sexual dysfunction may occur in patients starting SSRIs. This includes ejaculatory delay, decreased libido, erectile dysfunction, and orgasm dysfunction. An open, frank discussion about the possibility of these symptoms will make it easier for patients to discuss them if they occur and may help with adherence to SSRI therapies as prescribed.

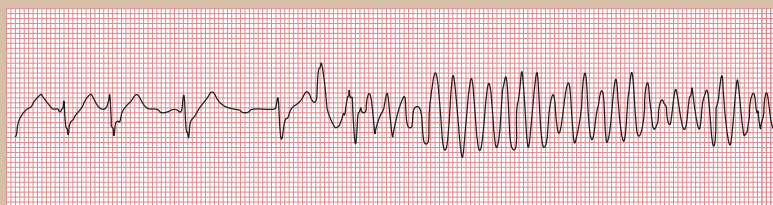
Other adverse reactions include weight gain or weight loss, agitation or insomnia, fractures, hyponatremia, fatigue, and the risk of falls. For patients with depression, adverse reactions such as weight gain that affect body image can be devastating. Communication about what to expect and how to cope with these signs and symptoms before and during patient treatment is crucial.¹²

Warn patients not to discontinue their medication without the health-care provider's guidance. Abruptly stopping an SSRI may lead to withdrawal, which presents as flu-like symptoms. Slow titration, whether increasing or decreasing dosages, is important to minimize adverse reactions.¹³

SNRIs inhibit the reuptake of both serotonin and norepinephrine and cause adverse reactions similar to those of SSRIs. Educate patients, families, and partners on the possibility of syncope or seizures, sexual dysfunction, and GI symptoms.

Danger of QT interval prolongation

This rhythm strip was recorded at the onset of torsades de pointes. Note the pause-dependent initiation of tachycardia and prolonged QT interval in the preceding beats.



Source: Herzog E. *The Cardiac Care Unit Survival Guide*. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012.

Often seen with drugs such as venlafaxine, hypertension is another common adverse reaction. Patients should know their baseline BP and monitor it regularly. Teach patients and families to monitor the patient's pulse rate and encourage them to keep a log of the results.

Noradrenergic adverse reactions include tachycardia, dilated pupils, xerostomia, diaphoresis, and constipation. Hard candy or sugarless gum may help with dry mouth, and hydration may help prevent constipation. Anticipating and preventing these signs and symptoms may help patients adhere to their medication.¹⁴

Atypical antidepressants are medications with a mode of action that differs from that of drugs in other classes. For example, bupropion and mirtazapine are each considered first-line therapies.⁹ *Bupropion* has a nondirect effect on serotonergic neurotransmitters, which is beneficial for patients experiencing adverse reactions such as sexual dysfunction. It should be avoided in those with a history of or increased risk for seizures.¹⁵ *Mirtazapine* is often prescribed for patients experiencing insomnia as a symptom of depression due to its sleep-promoting effects. It is associated with weight gain, making it less appealing to many patients. Discussing this possibility with patients and monitoring weight gain are important.

SARIs include second-line therapies that act as weak SNRIs. They are typically used in combination with an initial antidepressant. Due to sedative effects, advise patients to take them before bed.

Orthostatic hypotension, dizziness, dysrhythmias, and sexual dysfunction are other potential adverse reactions to trazodone. Patient and family education on possible adverse reactions, including syncope, chest pain, shortness of breath, and palpitations, are important before and during treatment. As with SNRIs,

Serotonin syndrome^{11-15,18,22,35}

Serotonin syndrome is an adverse reaction that can be seen with multiple antidepressant drugs and drug classes, including SSRIs, SNRIs, TCAs, buspirone, mirtazapine, and lithium. Also referred to as serotonin toxicity, it is a potentially life-threatening condition associated with increased serotonergic activity in the central nervous system. Physical assessment findings include:

- hyperthermia
- agitation
- ocular clonus
- tremor
- akathisia
- hyperreflexia
- inducible or spontaneous clonus
- muscle rigidity
- dilated pupils
- dry mucus membranes
- hyperactive bowel sounds
- flushed skin
- diaphoresis.

they should also be taught to monitor pulse and BP.¹⁶

Drugs such as nefazodone should be avoided in patients with hepatic failure. Nurses should obtain a thorough health history and ask specific questions about hepatitis.¹⁶ Some other adverse reactions include xerostomia, constipation, orthostasis, and visual alterations. For safety, patients should be educated to change position slowly to avoid orthostatic hypotension. Hard candy or sugarless gum may help to alleviate dry mouth. Hydration may help with constipation, but patients and nurses should contact the healthcare provider if it persists or becomes severe.¹⁴

MAOIs such as selegiline increase the levels of norepinephrine, serotonin, and dopamine by inhibiting the enzyme monoamine oxidase. Activation of the sympathetic nervous system, which is responsible for the body's fight-or-flight response, may lead to tachycardia, bronchodilation, and hypertension.¹⁷

Although MAOIs help to keep the levels of the norepinephrine, serotonin, and dopamine neurotransmitters high, they are older drugs that are not used as often due to potentially life-threatening adverse reactions (see *Serotonin syndrome*).¹⁹ The most serious adverse reaction is hypertensive emergency with signs or symptoms of acute, ongoing target-organ damage such as severe headache, confusion, chest pain, and dyspnea.²⁰ It can lead to stroke and death.¹⁸

In patients taking MAOIs, hypertensive emergencies may be triggered by foods with high levels of dopamine or tyramine.¹⁸ Warn patients to avoid fermented cheeses or meat products, yeast extracts, beans, red wine, draft beers, and over-ripe or spoiled foods.¹⁸ Also teach patients to read labels on herbs and OTC products and question the safe combination of MAOIs with any new drugs or herbal products, such as St. John's wort.¹⁸ Medications such as other antidepressants, triptans, dextromethorphan, linezolid, or meperidine may further increase the adverse reactions of MAOIs.¹⁸

Patient, family, and caregiver education must be repetitive, thorough, and ongoing. Because patients prescribed MAOIs often have severe depression, they may not have the focus or energy to maintain critical dietary restrictions or self-monitor for adverse reactions. Teach patients how to monitor pulse, BP, edema, and weight. Additional education on sexual symptoms such as impotence and anorgasmia, GI symptoms such as constipation and nausea, and sleep symptoms such as insomnia or excessive fatigue is imperative.¹⁸

Most important, nurses must keep lines of communication open so that patients and family caregivers will ask questions early when adverse reactions are first noticed to avoid life-threatening issues.²¹

TCAs are second-line therapies due to inferior safety and tolerability. In lower dosages, they are more commonly used for neuropathic pain and headaches than depression and are not recommended in patients with cardiovascular disease, glaucoma, urinary retention, or prostate disease.²²

Cardiovascular adverse reactions are a concern, and close monitoring for dysrhythmias, such as heart blocks, and orthostatic hypotension is important. Anticholinergic adverse reactions such as dry mouth, constipation, urinary retention, and blurred vision are also common. Other adverse reactions include weight gain, drowsiness, and seizures.²²

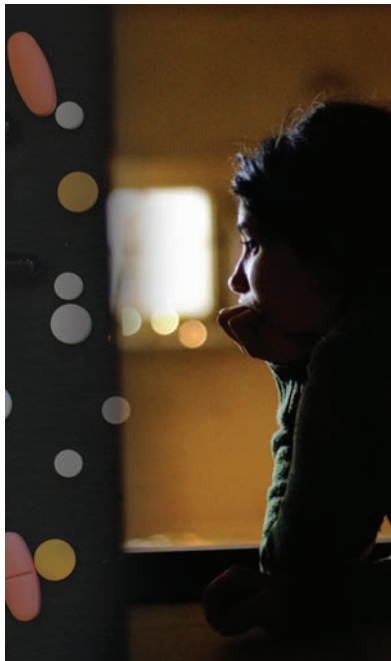
Besides assessing for contraindications, nurses should focus on patient education. Teach patients to avoid driving and doing other tasks or actions that require mental alertness until they see how these drugs affect them.²³ Similarly, patients should be advised to stay hydrated and notify their provider regarding abdominal pain and/or decreased urination, as these may indicate urinary retention.²² Most important, patients, families, and caregivers should be taught to monitor heart rate and BP, as well as to avoid changing position quickly due to possible orthostatic hypotension.²²

The role of nurses

Nurses are in a unique position to help patients understand and manage their depression. This requires them to be knowledgeable about the nature of the disorder and the available therapies. It also requires the establishment of a trusting nurse-patient and family relationship with open, honest, nonjudgmental dialogues to provide ongoing education and support.

Nurses must consider many questions when administering antidepressants and educating patients, such as:¹⁴

- What are the expected adverse reactions for this medication?



Nurses must keep lines of communication open so that patients will ask questions when adverse reactions are first noticed.

- What other medications does the patient take?
- Does the patient have any comorbidities that will affect or be affected by the medication?
- Who comprises this patient's support system, and are these individuals aware of the adverse reactions?

Suicidal ideation and action is a risk for patients with depression who are taking antidepressants, especially in the first weeks and months after initiating therapy.²⁴ Some patients may have already harbored these thoughts but lacked the energy to act on them. As the medication takes effect, these patients may have more energy while remaining depressed. The increased energy may present the means to act on impulses related to self-harm. Patients and their families must be warned to remain vigilant

of this possibility before starting antidepressant therapies.²⁵

Patient safety is always top priority, so nurses must stay in the habit of asking patients if they are thinking about hurting themselves or others and, if so, do they have a plan?⁷ Ask in an interested but nonjudgmental tone and maintain eye contact. If patients feel the question is insincere or the nurse is not truly concerned, the opportunity for a meaningful dialogue to assess intentions and the severity of the depression may be lost.

Although some nurses may worry that asking about suicidal ideation will cause patients to think about hurting themselves when it otherwise would not have crossed their minds, this assumption has been debunked.²⁶ Patients may be considering suicidal behavior, but they are often afraid to discuss it or do not know how to start the conversation.⁷ Depending on the setting, nurses may have more success in beginning these conversations than other members of the healthcare team due to their established relationships with their patients.

A trusting relationship with both patients and their families (who may catch subtle signs of worsening depression early on) is essential in developing an awareness of suicidal ideation and helping patients find effective treatments and avoid self-harm.²⁷ Healthcare providers typically limit the quantity of antidepressant medications prescribed at one time to prevent lethal doses.

Nurses should maintain caring relationships with their patients and encourage open communication.^{7,26,27} Upon learning about a patient's suicidal ideation, nurses should remain calm and obtain additional information. Asking about a plan is important. If the answer to either of the following is yes, nurses

must contact a supervisor or the healthcare provider to share these thoughts while maintaining the rules of confidentiality established by the Health Insurance Portability and Accountability Act of 1996. Questions to explore further include:

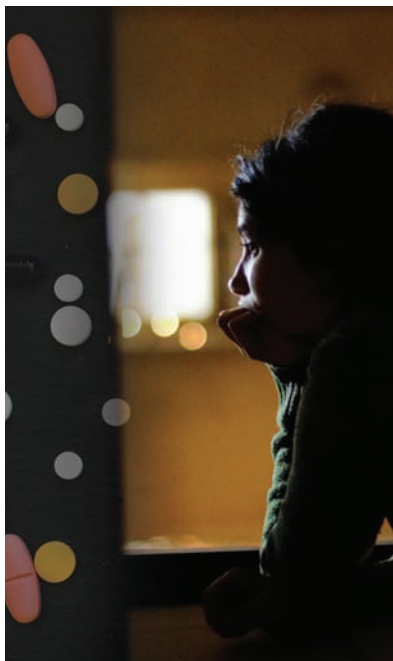
- Does the patient have access to the necessary resources such as weapons or medication?
- Do any contributing factors increase the risk of an attempted suicide, such as addiction, personal loss, or ongoing depression?

Due to barriers to care such as social stigmas surrounding mental health, as well as the relative ease and low cost of some options, some patients may consider self-medication to be a good coping strategy. Self-medication is the practice of using a substance to relieve depression or other mental health issues.²⁸ Many assume that this practice only refers to alcohol or drug use, but it may also refer to caffeinated food and drinks. Some may even expand the definition to behaviors such as emotional eating.²⁹

Self-medication provides only a quick fix, however, and prevents long-lasting symptom relief.³⁰ Moreover, alcohol and drug use have been found to cause changes in brain chemistry. One study on patients experiencing depression secondary to posttraumatic stress disorder found that self-medication with recreational drugs and alcohol increased the risk of attempted suicide.³¹ Nurses should be nonjudgmental and empathetic when discussing these behaviors and support their patients in finding the most effective treatment options.

Encouraging adherence to therapy

For many patients, adhering to prescribed drug therapy and follow-up appointments is challenging.³²



Upon learning about a patient's suicidal ideation, nurses should remain calm and obtain additional information.

The symptoms of depression may prevent them from focusing on and remembering important information about prescriptions, as well as actions to take if they experience adverse reactions or their symptoms do not resolve. If the signs and symptoms prevent patients from adhering to treatment, more action is necessary to manage the disorder.

Patients require ongoing support from the healthcare team because persistent encouragement and education may aid in the success of therapeutic interventions. With the patient's permission, social support systems such as parents, siblings, and significant others may be helpful in monitoring potential adverse reactions or ongoing symptoms.⁷ This may also help patients cope with adverse reactions and remind them of the benefits of therapy and psychotherapy.

Patient education

Many antidepressants carry adverse reactions that can affect an individual's self-image or daily activities. Weight gain and sexual dysfunction are common. Clear and individualized patient education is crucial.

Nurses should discuss potential adverse reactions and provide education based on the patient's health literacy level. For example, patients may understand that a medication may decrease their heart rate, but they may not understand that this can lead to fatigue, dizziness, and adversely affect cognition and endurance in activities of daily living. As such, patients should understand how to take their pulse and know normal pulse rates.

Additionally, nurses must ensure that patients are provided any FDA-mandated Medication Guides and understand the pharmaceutical information related to their medications. Without specific details on the effects of a drug and guidance on what to do in the event of an adverse reaction, patients may feel frustrated and stop taking their medication. In these cases, treatment may not be successful.¹⁴

More research needed

Further research will help define the pathophysiology of depression, leading to the development of newer, more successful drug therapies. Nurses must not underestimate depression. Antidepressants may not be enough to alleviate depression alone, and concurrent psychotherapy is imperative. Ongoing open communication and education are essential for nurses caring for patients with depression. ■

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