Antidepressant Medications

An evidence-based review of the indications, adverse effects, and special considerations related to these medications.

ABSTRACT: Depression is one of the most common mental health conditions. Many nurses will care for patients who have depression and may be receiving treatment. Treatment often includes the use of medications that affect mood. This article provides a brief overview of the history, indications for use, adverse effects, and nursing considerations regarding antidepressants. This is the second in a series of articles about medications used in the treatment of mental health disorders. For the first article in this series, see "Antipsychotic Medications," June 2017.

Keywords: antidepressants, depression, mental health, mental illness, psychotropic medications

Depression is a universal phenomenon. It should come as no surprise, therefore, that nurses, regardless of the areas in which they work, are more likely than not to care for patients who have depression and who may be taking antidepressant medications. Moreover, there is a strong correlation between several medical diseases and disorders and mental health issues. For example, people with cardiac problems often have depression, and those who have depression often develop heart disease.[1] It's therefore important that nurses are aware of the history, indications for use, adverse effects, and special considerations related to antidepressants.

According to the World Health Organization (WHO), depression affects more than 300 million people worldwide. It is the leading cause of disability globally, knows no age limitation, tends to affect women more than men, and can lead to suicide.[2] Although several treatments are available, the WHO reports that fewer than 50% of people receive treatment. According to the WHO, the number of people affected by depression rose by 18% from 2005 to 2015.[3] The National Institute of Mental Health (NIMH) has reported that an estimated 16.1 million adults age 18 or older in 2015 had at least one major depressive episode in the previous year.[4] This number represented 6.7% of all U.S. adults.

Adults, however, aren't the only people experiencing symptoms of depression. In 2015, the NIMH reported that an estimated 3 million U.S. adolescents 12 to 17 years of age had at least one major depressive episode in the past year, with that number representing 12.5% of children in this age group.[4] Major depressive disorder, which is a chronic, recurring form of depression, is regarded as the most common mood disorder among Americans.[5]

UNDERSTANDING MENTAL ILLNESS: DEPRESSION

According to the fifth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, depression is classified as a mood disorder and causes problems with how a person feels, thinks, acts, and behaves.[6,7] For a diagnosis of depression, symptoms must be present for at least two consecutive weeks.[7] They can range from mild to severe and may include the following[7]:

- Feeling sad or having a depressed mood
- Loss of interest or pleasure in activities once enjoyed
- Changes in appetite—weight loss or gain unrelated to dieting
- Trouble sleeping or sleeping too much
- Loss of energy or increased fatigue
- Increase in purposeless physical activity (such as hand-wringing or pacing) or slowed movements and speech (actions observable by others)
- Feeling worthless or guilty
- Difficulty thinking, concentrating, or making decisions
- Thoughts of death or suicide

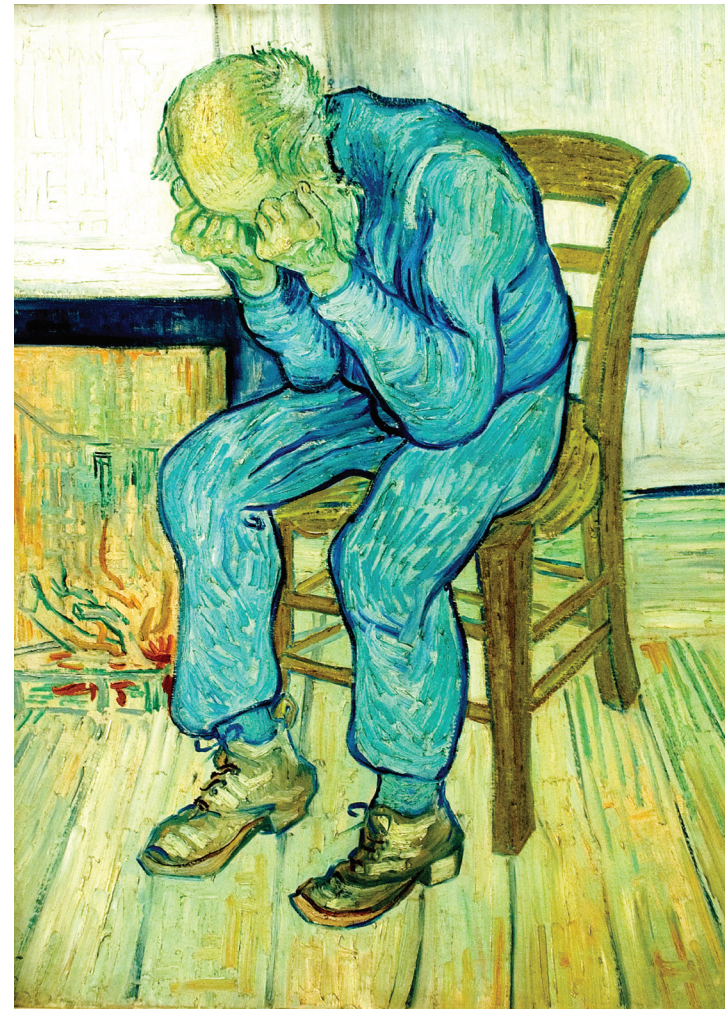
Depression is a manageable disorder, especially so since the advent of medications that affect mood.

ANTIDEPRESSANT MEDICATIONS

Several factors can put a person at increased risk for depression. These include genetic, personal, environmental, and biochemical risk factors that may occur alone or in combination.[7] Much is still unknown or poorly understood about the genetic risks for depression. It's known that there's a familial link to depression. Some genes shared by family members are responsible for the production, transport, and activity of neurotransmitters, which affect mood. Likewise, environmental or nongenetic factors, such as poor and stressful relationships with others, social isolation, and loss of employment, can also put someone at risk for depression.[8] Nurses should be aware that depression can also be caused by medical conditions and the use of certain medications or recreational drugs.[9, 10]

As researchers have developed a better understanding of the causes of mental illness over the past half century, an important theory, called the monoamine hypothesis of depression, emerged. This theory posits that depression can result from an imbalance of neurotransmitters, which are chemicals that allow cells, or neurons, to communicate with each other.[11] Essentially, neurotransmitters travel from one cell to the next by crossing the synapse between the two. Neurotransmitters can either increase or decrease the activity of the receiving cell. Those that increase or mimic the body's normal response are referred to as agonists, and those that decrease or inhibit this normal response are referred to as antagonists.[12-14] The monoamine hypothesis proposes that depression is caused by a lack of norepinephrine, serotonin, and/or dopamine, which are monoamine neurotransmitters in the brain.[10, 12, 15] It's believed that a decrease in any of these neurotransmitters plays a role in the development of the signs and symptoms of depression.

Both antipsychotics and medications to improve mood were introduced in the 1950s.[16] The discovery of the earliest medication to ease the symptoms of depression occurred after clinicians noticed that antimycobacterial agents—such as isoniazid, which is a derivative of hydrazine (a fuel used by the Germans to propel rockets during World War II), and iproniazid (withdrawn from the market in 1961)—rid patients of tuberculosis while also improving their mood and sense of well-being.[11, 12, 15, 17] These agents worked by inhibiting the monoamine oxidase enzyme, thus leading to the realization that depression had a neurochemical cause that could be managed using medications that corrected underlying neurotransmitter imbalances. The first class of antidepressants used to manage depression were monoamine oxidase inhibitors, also known as MAOIs. These were followed by tricyclic antidepressants (TCAs).



Sorrowing Old Man was painted in 1890 by Dutch artist Vincent van Gogh, who suffered for years from mental illness. Photo by Peter Horree / Alamy Stock Photo.

The most recently developed and perhaps best-known classes of antidepressants are selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs). Additional reuptake inhibitory antidepressants include norepinephrine–dopamine reuptake inhibitors (NDRIs) and serotonin-2 antagonist reuptake inhibitors (SARIs).[13, 15] As the name implies, reuptake inhibitors inhibit a given neurotransmitter from being taken back up into the presynaptic neuron, allowing for more to remain at the postsynaptic cleft to bind with the postsynaptic receptors, thus improving a person's mood.[15, 18]

Another class of medications are noradrenergic and specific serotonergic antidepressants (NaSSAs). Medications in the NaSSA class include mirtazapine (Remeron). Among other adverse effects, these drugs are known for their sedating and anticholinergic characteristics, and can cause agranulocytosis.[13]

MAOIs. Drugs in this class inhibit the release of the enzyme monoamine oxidase.[5] (See *Monoamine Oxidase Inhibitors and Their Adverse Effects*.) If the enzyme is not released, it is unable to break down the neurotransmitters serotonin and norepinephrine, thereby allowing more of those transmitters to be available to the nervous system, which improves mood.[12, 15] Today, MAOIs are rarely used, or they are the last antidepressant to be used, owing to serious and potentially fatal food and drug interactions (including with over-the-counter cold and cough medications) that can lead to hypertensive crisis.[13, 14]

Monoamine Oxidase Inhibitors and Their Adverse Effects

Medications
- Isocarboxazid (Marplan)
- Phenelzine (Nardil)
- Tranylcypromine (Parnate)

Adverse Effects
- Anticholinergic effects
- Orthostatic hypotension
- Central nervous system stimulation
- Sexual dysfunction
- Hypertensive crisis brought on by eating foods containing tyramine or tryptophan-rich foods, such as aged cheese, wine, chocolate, certain fish, and sour cream[a]

Precautions
- Avoid use with other MAOIs and antidepressants, as well as with several other medications, including over-the-counter cold remedies.
- Patients should adhere to a tyramine-free diet.
- Use cautiously in patients with diabetes, glaucoma, hyperthyroidism, or hypertension.
- A washout period of several weeks is required to clear the patient's system, after which the patient can start another antidepressant.

MAOI = monoamine oxidase inhibitor.
[a]This adverse effect can be serious and in some cases life-threatening.
PDR Network, LLC. *PDR: prescribers' digital reference*. Whippany, NJ: ConnectiveRx; 2018. www.pdr.net.

TCAs were developed as antihistamines but failed to manage allergy symptoms; instead, they successfully improved the mood of those patients who were depressed.[12] (See *Tricyclic Antidepressants and Their Adverse Effects*.) TCAs work by blocking the reuptake of two neurotransmitters: norepinephrine and serotonin. This allows for more of the neurotransmitters to be available at the receptor sites before reentering the neuron, thus having a positive effect on mood.[12] Like MAOIs, TCAs are currently not among first-line treatment options. They can have a negative impact on cardiac health, and can also cause death if taken in high doses; therefore, it's important that patients taking these medications are evaluated for suicide potential.[9, 12] TCAs can be used off label to manage, for example, pain associated with fibromyalgia and diabetic neuropathy.[14]

SSRIs. As the name implies, SSRIs work by inhibiting the reuptake of the neurotransmitter serotonin, thus allowing more of it to remain at the receptor sites to improve a person's mood. (See *Selective Serotonin Reuptake Inhibitors and Their Adverse Effects*.) Today, SSRIs are among the most commonly used medications to manage depression and are regarded as first-line treatment. People experiencing adverse effects from one SSRI may benefit by switching to another drug in this class. SSRIs are safer than MAOIs and TCAs, have fewer adverse effects, and are less likely to result in death from overdose. They are also used to manage posttraumatic stress disorder (PTSD), anxiety disorders, and obsessive–compulsive disorder (OCD).[13, 19] These and the other reuptake inhibitors have the advantage of selectively targeting the neurotransmitters commonly associated with depression (that is, serotonin, norepinephrine, and dopamine).[19]

SNRIs, NDRIs, and SARIs inhibit the reuptake of serotonin and norepinephrine, norepinephrine and dopamine, and serotonin, respectively. SARIs also inhibit serotonin 2A receptors. (See *Other Antidepressants and Their Adverse Effects*.)

OTHER INDICATIONS FOR USE

Aside from their use in managing depression, select antidepressants are also used to treat people who have other mental health issues and physical conditions, including panic disorder, OCD, PTSD, attention deficit–hyperactivity disorder, bulimia, physical pain, and premenstrual dysphoric disorder.[15, 18] Of note for smokers, bupropion (Wellbutrin and others) is used to help smoking cessation.[20]

NURSING IMPLICATIONS

There are several important points to consider and remember regarding antidepressants. First, they don't

work for everyone. There have even been questions about whether they work at all, and if so, the level of their effectiveness.[14, 15, 21, 22] In a 1996 review of then recent clinical studies, Fava and Davidson found that 29% to 46% of patients failed to fully respond to treatment with antidepressants, even when taking the proper dose for the proper duration.[23] The efficacy of antidepressants may depend on several factors, including whether patients stop the medications because of adverse effects, don't take the most effective dose, or don't take the medications for long enough.[22] Another possible factor is that the medications may result in better outcomes when they are used by people who have moderate, severe, or chronic depression rather than a milder form of the condition.[24]

When depression has not been successfully ameliorated by medication, a person may be diagnosed as having treatment-resistant depression. In such instances, electroconvulsive therapy may be considered. There remains some controversy surrounding this procedure because of past sensationalized portrayals in the movies and literature. Although electroconvulsive therapy is not without risks and requires general anesthesia, it is considered safer than in years past because of efforts undertaken to refine the process. Common but self-limiting adverse effects include headaches, nausea, and confusion; rare but more serious adverse effects include pulmonary and cerebrovascular events. In addition, memory loss after electroconvulsive therapy can be short or long term.[10, 25]

For many, monotherapy, or the use of a single antidepressant, is not effective.[10] In this case, augmentation (adding a medication from a different class) or a combination of antidepressants may be necessary.[10] When antidepressants are effective, it may still take several weeks—two to six, on average, and sometimes more—for patients to notice any significant symptom relief.[9, 14, 26] It's important that nurses inform patients about this anticipated interval and encourage them to explore other ways to improve their well-being in the meantime.

Potentially serious drug–drug interactions can occur when using most medications, including antidepressants. Interactions may occur when taking more than one antidepressant or when taking an antidepressant and another type of medication.[15, 20]

Of concern for many people who have mental health issues, and especially for those with depression, is the risk of suicide. Patients should be assessed for present and past suicidal ideation and suicide attempts. They should be monitored for signs, such as changes in mood, preoccupation with death, increased use of alcohol or drugs, reckless behavior, and giving away their belongings.[27] Nurses should also explore whether psychotherapy might benefit the patient. This type of treatment can help patients before medication takes effect, and it's also effective in combination with medications.[15] Mintz notes that numerous studies have confirmed the benefits of combining these two modalities when treating patients with depression.[28] Research suggests that medication should continue to be taken for six to 12 months after a remission of symptoms occurs.[19]

Tricyclic Antidepressants and Their Adverse Effects

Medications

- Amitriptyline (formerly available as Elavil)
- Clomipramine (Anafranil)
- Desipramine (Norpramin)
- Imipramine (Tofranil)
- Nortriptyline (Pamelor)

Adverse Effects

- Cardiac arrhythmias and QT interval prolongation
- Anticholinergic effects
- Orthostatic hypotension
- Sedation
- Elevated intraocular pressure
- Extrapyramidal effects (tardive dyskinesia, akathisia, and pseudoparkinsonism motor symptoms)
- Weight gain

Precautions

- Assess patient's cardiac status prior to initiating treatment with TCAs; this should include a pretreatment ECG.

ECG = electrocardiogram; TCA = tricyclic antidepressant.
PDR Network, LLC. *PDR: prescribers' digital reference*. Whippany, NJ: ConnectiveRx; 2018. www.pdr.net.

For many, monotherapy, or the use of a single antidepressant, is not effective.

There has been some controversy surrounding the possible connection between antidepressant use and suicide. There is concern that antidepressants heighten the risk of suicidal ideation and suicide, especially among children, adolescents, and young adults, hence

the black box warning on these medications.[14, 15, 19] It is important to regularly assess people with depression for suicidal ideation, even when they begin taking antidepressants and their condition improves; as patients' energy levels rise, they may be more capable of following through on suicidal thoughts. Nurses should also be aware that a greatly improved mood during the first several weeks of treatment can signal that the patient is considering suicide.[13, 14] Moreover, hoarding medications for a later suicide attempt is not unheard of.[19]

Although many of the adverse effects of antidepressants are not serious and lessen or resolve over time, a few are life threatening. These include hypertensive crisis, which can occur when taking MAOIs, and serotonin syndrome. Signs and symptoms of hypertensive crisis—which occurs when a patient who is taking an MAOI simultaneously eats tyramine-rich foods, such as aged cheese and meats, wine, beans, or canned or frozen soups—include excessive sweating, tachycardia, chest pain, and a sudden and explosive headache.[19] Serotonin syndrome occurs when a person's serotonin level becomes too high as a result of taking too many medications that increase serotonin levels. The person can develop a rapid increase in temperature and blood pressure, tachycardia, agitation, nausea, diarrhea, muscle twitching, tremors, rigidity, and changes in mental status.[9, 19] Both hypertensive crisis and serotonin syndrome are medical emergencies that require immediate medical attention. Patients should stop taking the medications in question and notify their prescribers.[19]

Abruptly stopping these medications, particularly those that have a short half-life and have been taken long term by the patient, can result in discontinuation syndrome. This uncomfortable condition is characterized by flu-like symptoms, headache, gastrointestinal disturbances, hyperarousal, insomnia, and electric shock sensations, among other symptoms.[9, 15, 29] Early reports referred to this as *withdrawal*, but the term *discontinuation syndrome* is now used to acknowledge that antidepressants are not addictive.[29, 30]

Nurses should also be aware that symptoms of mania—such as agitation, sleep disturbances, and excitability—can be triggered by antidepressant use in patients who haven't been properly assessed or treated for bipolar disorder but may have a history of this disorder.[18]

Precautions and contraindications. It's important to be aware of all the medications a patient is taking, even over-the-counter medications such as cold remedies or St. John's wort, which can negatively interact with prescribed antidepressants. Depending on the class of antidepressants prescribed, it's also important to assess for cardiac health, kidney and liver functioning, a history of seizure disorder, recent use of MAOIs, a history of suicide attempts and suicidal ideation, alcohol use, and the possibility of pregnancy.[31]

As with all medications, there are special concerns when prescribing antidepressants to certain patient populations. Caution should be exercised when prescribing for children, adolescents, and young adults—especially given the black box warning related to the increased risk of suicidal thoughts and behaviors among these patients.[13, 14, 18] Two antidepressants are prescribed for patients in this age range; fluoxetine (Prozac, Sarafem) and escitalopram (Lexapro) have been approved by the Food and Drug Administration (FDA) to treat children ages eight and older and 12 and older, respectively.[15, 18]

Selective Serotonin Reuptake Inhibitors and Their Adverse Effects

Medications
- Citalopram (Celexa)
- Escitalopram (Lexapro)
- Fluoxetine (Prozac, Sarafem)
- Fluvoxamine (Luvox)
- Paroxetine (Paxil and others)
- Sertraline (Zoloft)

Adverse Effects
- Nervousness and agitation
- Sedation and fatigue
- Headache
- Insomnia
- Sexual dysfunction
- Gastrointestinal upset (nausea and diarrhea)
- Weight loss or gain
- Serotonin syndrome[a]
- Discontinuation syndrome[a]

Precautions
- Avoid mixing with other antidepressants and over-the-counter medications, such as cold remedies and St. John's wort. It's especially important to avoid medications that increase serotonin levels to avoid serotonin syndrome.
- Taper patients off medications slowly to avoid discontinuation syndrome.
- Assess patients' use of blood thinners, antibiotics, lithium, and all other medications.

[a]This adverse effect can be serious and in some cases life-threatening.
PDR Network, LLC. *PDR: prescribers' digital reference*. Whippany, NJ: ConnectiveRx; 2018. www.pdr.net.

Other Antidepressants and Their Adverse Effects

Medications

SNRIs
- Duloxetine (Cymbalta)
- Desvenlafaxine (Pristiq, Khedezla)
- Venlafaxine (Effexor XR)

NDRIs
- Bupropion (Wellbutrin and others)

SARIs
- Nefazodone
- Trazodone

Adverse Effects

SNRIs
- Central nervous system depression
- Nausea
- Headache
- Decreased appetite
- Hypertension
- Insomnia
- Serotonin syndrome

NDRIs
- Anorexia
- Lower seizure threshold
- Nausea
- Blurred vision
- Central nervous system stimulation
- Hypertension

SARIs
- Anticholinergic effects
- Hepatotoxicity
- Headache
- Agitation
- Priapism
- Sedation

Precautions

SNRIs
- Use cautiously in patients with seizure disorder, hypertension, and liver or kidney problems.
- Taper medications to avoid discontinuation syndrome.

NDRIs
- Contraindicated in patients with a history of seizure disorders, anorexia nervosa, or alcoholism.
- Use with caution in those with renal, hepatic, or cardiovascular problems.
- Can be fatal when combined with MAOIs.

SARIs
- Do not use in patients who are taking MAOIs.
- Use cautiously in patients with seizure disorders.

MAOI = monoamine oxidase inhibitor; NDRI = norepinephrine–dopamine reuptake inhibitor; SARI = serotonin-2 antagonist reuptake inhibitor; SNRI = serotonin–norepinephrine reuptake inhibitor.
PDR Network, LLC. *PDR: prescribers' digital reference*. Whippany, NJ: ConnectiveRx; 2018. www.pdr.net.

Taking any medication during pregnancy and while breastfeeding requires carefully weighing the risks and benefits.[15] Although several antidepressants are considered relatively safe during pregnancy, some are known to cause birth defects. The use of paroxetine (Paxil and others), for instance, has been associated with cardiac defects in infants.[15, 18] Women should consult with their health care providers regarding the use of antidepressants both during and after pregnancy.

Likewise, antidepressant use in the elderly requires special consideration. The rule of thumb is to start at 50% of the recommended dose and slowly increase the dose, as tolerated.[15, 18, 31]

It's important to counsel all patients about the importance of tapering antidepressants, instead of stopping abruptly, to avoid discontinuation syndrome.[9, 15]

ONGOING DEVELOPMENTS

Antidepressants can be a powerful tool in combating depression in many people, but they don't work quickly, and they're not effective for everyone. In some cases, finding the right medication requires trial and error and can take a while because of the time required to obtain positive effects. Such a situation can be understandably frustrating for patients who wish to feel better sooner rather than later. Aside from medications, psychotherapy and other nonpharmacological approaches to treatment—including cognitive behavioral therapy, exercise, yoga, and dietary changes—can be utilized to improve patients' moods and symptoms.[10] Patients who have treatment-resistant depression, in which medications aren't effective, may want to consider electroconvulsive treatment, vagal nerve stimulation, or transcranial direct current stimulation.[10, 32]

RESOURCES

Websites

Informedhealth.org
Institute for Quality and Efficiency in Health Care
Depression: How effective are antidepressants?
www.informedhealth.org/depression-how-effective-are-antidepressants.2125.en.html?part=behandlung-yi

Medscape
Depression
https://emedicine.medscape.com/article/286759-overview
Depression Medication
https://emedicine.medscape.com/article/286759-medication

NAMI: National Alliance on Mental Illness
Mental Health Medications
www.nami.org/Learn-More/Treatment/Mental-Health-Medications

National Institute of Mental Health
Mental Health Medications
www.nimh.nih.gov/health/topics/mental-health-medications/index.shtml

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Some have lamented the lack of newer and more effective medications to better manage depression and treatment-resistant depression, yet research into new treatments is ongoing. For example, ketamine, which is an anesthetic (sometimes used as a party or club drug), is being studied for its ability to alleviate some of the symptoms of depression, including suicidal ideation.[33, 34] Other relatively new or novel medications approved by the FDA to manage depression include vilazodone (Viibryd), levomilnacipran (Fetzima), and vortioxetine (Trintellix).[35]

There has certainly been progress in our ability to understand and manage depression, and we have come a long way from the discovery made in the halls of tuberculosis sanitariums. Yet we still have a long way to go in improving the mood and well-being of those who are struggling to feel better. ▼

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