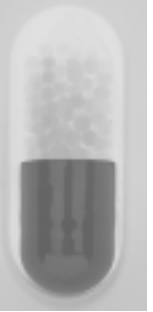


Antidepressants

Selective Serotonin Reuptake Inhibitors and Mixed-Action Antidepressants



Selective serotonin reuptake inhibitors

Celexa (citalopram)
Lexapro (escitalopram)
Luvox and Luvox CR (fluvoxamine)
Paxil and Paxil CR (paroxetine)
Prozac, Prozac Weekly, and Sarafem (fluoxetine)
Zoloft (sertraline)

Mixed-action antidepressants

Cymbalta (duloxetine)
Effexor and Effexor XR (venlafaxine)
Pristiq (desvenlafaxine)
Remeron (mirtazapine)
Wellbutrin, Wellbutrin SR, and Wellbutrin XL (bupropion)

The antidepressants known as **selective serotonin reuptake inhibitors** (SSRIs) have become widely used to treat major depression and many other psychiatric disorders, including obsessive-compulsive disorder (OCD), panic disorder, generalized anxiety disorder, social anxiety disorder, posttraumatic stress disorder, eating disorders (e.g., bulimia nervosa), and premenstrual dysphoric disorder. The antidepressants in this group are all **serotonin**-specific drugs. They work by boosting the levels of the neurotransmitter serotonin in the central nervous system. The mixed-action antidepressants increase levels of more than one neurotransmitter or have more than one mechanism of action. For instance, Cymbalta, Effexor, and Remeron increase levels of both serotonin and norepinephrine, while Wellbutrin increases levels of dopamine and norepinephrine. All these newer antidepressants are easy to prescribe and take (usually as a single dose in the morning or at bedtime); cause fewer side effects than some of the older antidepressants, such as the **tricyclic antidepressants** (TCAs), and do not require dietary restrictions, such as those required for the **monoamine oxidase inhibitors** (MAOIs). Moreover, the SSRIs and mixed-action antidepressants are usually a good choice for individuals who have medical problems, such as heart disease, hypertension, or seizures.

Neurotransmitters such as serotonin, norepinephrine, and dopamine are chemicals produced by brain cells (called neurons) that enable the neurons to communicate with each other. Serotonin, norepinephrine, and dopamine are released by one neuron into the space between that neuron and the next neuron, allowing an electrical stimulus to continue down the next neuron.

SSRIs work in the brain by inhibiting serotonin from going back to the neuron from which it was originally produced, thereby boosting the levels of serotonin available in the brain. Depression and several other psychiatric disorders, such as OCD, may be the result of abnormally low levels of serotonin in the brain. The low levels of serotonin in turn may produce changes in select areas of the brain, producing psychiatric symp-

toms such as depression or anxiety. Cymbalta and Effexor block the reuptake of both serotonin and norepinephrine, thereby boosting the levels of both neurotransmitters in the brain. Because of this dual mechanism of action, they are sometimes called **serotonin-norepinephrine reuptake inhibitors** (SNRIs). Wellbutrin blocks the reuptake of norepinephrine and dopamine, and Remeron's principal mechanism of action involves blocking presynaptic α_2 -adrenergic receptors and selected serotonin receptors.

When levels of the neurotransmitters are elevated by these antidepressants, those areas of the brain that were previously altered by the low neurotransmitter levels are restored to normal functioning. There is usually a time lag of 3–4 weeks for antidepressants to achieve their optimal effect, which may be the time needed for the brain to make the changes to restore normal functioning.

Common Side Effects

The SSRIs and mixed-action antidepressants are usually well tolerated, and they cause less sedation (except for Remeron) than older antidepressants such as the TCAs. Some individuals, however, complain of “jitters” or restlessness when taking an SSRI, SNRI, or Wellbutrin, especially with those that are more stimulating, such as Prozac, Effexor, or Wellbutrin. Caffeine can also contribute to this “hyper” feeling and should be reduced or avoided by patients taking an SSRI, an SNRI, or Wellbutrin. This side effect may be minimized by starting the antidepressant at a lower dosage and increasing it gradually.

Another frequent complaint is that SSRIs and SNRIs (Cymbalta and Effexor) cause sexual dysfunction, including retarded ejaculation in men and delayed orgasm in women, or intensify a preexisting dysfunction, such as erectile dysfunction. Such side effects may occur in about 50%–60% of individuals taking SSRI antidepressants and in a lower percentage of persons taking SNRIs. Sexual side effects may be minimized with a reduction in dosage or a change to a different SSRI, or they may be eliminated with a change to a different class of antidepressant, such as Wellbutrin (bupropion) or Remeron (mirtazapine).

Other side effects reported with SSRI and SNRI antidepressants include gastrointestinal distress, such as nausea, cramping, heartburn, and diarrhea. Patients may also experience insomnia or daytime sedation from the SSRIs and SNRIs. Taking the antidepressant in the morning may minimize insomnia, or taking it at bedtime may diminish daytime sedation. Headaches may be another bothersome side effect of SSRIs and SNRIs. Generally, patients have fewer complaints of headaches when the dosage is increased gradually.

Adverse Reactions and Precautions

SSRIs and SNRIs can increase the blood levels of other medications metabolized in the liver by inhibiting their metabolism. For example, Paxil has been reported to increase levels of the anticoagulant Coumadin (warfarin), which may increase the risk of bleeding (also refer to the handout for the given medication). Therefore, it is important for physicians to know all of the medications a patient is taking, including over-the-counter medications and herbal supplements. Patients should contact their psychiatrist when any new medications are prescribed by another physician to determine whether caution or closer monitoring is necessary with the psychiatric medications.

Patients taking other drugs that boost serotonin, such as **MAOIs**, in combination with SSRIs or SNRIs may develop a potentially hazardous condition called **serotonin syndrome**, caused by excessive serotonin stimulation in the central nervous system. Rarely, this syndrome may also occur in individuals taking a single SSRI or SNRI agent, especially at higher dosages. Early signs of serotonin syndrome are restlessness, confusion, tremors, flushing, excessive sweating, and involuntary muscle jerks. If the medications are not stopped and unremitting stimulation continues, the individual may develop more life-threatening complications resulting in muscle disorders, high fever, respiratory problems, clotting problems, and destruction of red blood cells that may lead to acute renal failure. Patients taking SSRIs or SNRIs should be alert to signs of serotonin syndrome, which require immediate medical attention and discontinuation of the serotonin-boosting medications.

Overdose

In contrast to the TCAs, overdoses of SSRIs and mixed-action antidepressants are generally much less dangerous, especially when these agents are taken alone. Overdose often involves multiple medications, and the other drugs involved may increase the risk of more serious complications.

Any suspected overdose should be treated as an emergency. The person should be taken to the emergency room for observation and treatment. The prescription bottle of medication (and any other medication suspected in the overdose) should be brought as well, because the information on the prescription label can be helpful to the treating physician in determining the number of pills ingested.

Special Considerations

Most cases of major depression can be treated successfully, usually with medication, psychotherapy, or both. The combination of psychotherapy and antidepressants is very effective in treating moderate to severe depression. The medications improve mood, sleep, energy, and appetite while therapy strengthens coping skills, deals with possible underlying issues, and improves thought patterns and behavior.

In general, antidepressants alone help about 60%–70% of those taking them. Although a few individuals may experience some improvement from antidepressants by the end of the first week, most people do not see significant benefits from their antidepressants until after 3–4 weeks, and it can sometimes take as long as 8 weeks for the medication to achieve its full effects. Thus it is critical that patients continue to take their antidepressant long enough for the medication to be beneficial and that patients not get discouraged and stop their medication prematurely.

We do not fully understand the exact mechanisms by which antidepressants work. They appear to disrupt the chain of events that produce abnormalities in how the brain deals with emotions or stress and result in the symptoms of depression. When an individual does not respond to an SSRI or mixed-action antidepressant, does it make sense for the physician to switch the patient's medication to another medication in the same class if they all have similar modes of action? In practice, patients who do not respond fully to one antidepressant often may respond to another one in the same class. This may not adequately explain the paradox. The molecular structure of an antidepressant may be effective for one individual but not for another. Sometimes it takes trial and error to find the right antidepressant, or combination, for a given individual.

In short-term studies, antidepressants were found to increase the risk of suicidal thinking and behavior in children and adolescents with major depression and other psychiatric disorders. The FDA requires the prescriber to warn of this risk in children and adolescents when starting antidepressant therapy. According to the FDA findings, the risk of suicidal thoughts and behaviors associated with antidepressants is age-related. This phenomenon tends to occur in the younger population and is most likely to occur early in the course of treatment. In adults over 24 years of age, there did not appear to be an increased risk of suicidality with antidepressants compared with placebo. In patients over age 65, the findings showed that antidepressants had a "protective effect" against suicidal thoughts and behavior. Other studies have found that when more people in a community are taking antidepressants, the suicide rate is lower.

The risk of suicide is inherent in depression and may persist until the individual responds to treatment. Closely observe children and adolescents taking antidepressants for signs of worsening, suicidal thoughts, and changes in behavior, especially early in the course of therapy and with change in dosages. Similarly, adults with depressive disorder taking antidepressants should be closely observed for any signs of clinical worsening and suicidal thoughts and behaviors, especially during the first few months of therapy.

Warning: Always let your physician or family member know if you have suicidal thoughts. Notify your psychiatrist or family physician whenever your depressive symptoms worsen or whenever you feel unable to control suicidal urges or thoughts.

For more information, refer to the bandout for the antidepressant that was prescribed for you.