



How Different Antidepressants Work

If you have treatment-resistant depression, you might have already picked up some of the antidepressant drug lingo -- you know your SSRIs, your SNRIs and your MAOIs. But do you really know *how* these drugs help?

If you don't, you're not alone. The truth is that even experts aren't completely sure how antidepressants work. There's just a lot we don't know about how the brain functions.

The most important thing you need to know when you're living with treatment-resistant depression is that antidepressants often can help. To help you understand all your medication options, here are the facts about different types of antidepressants -- along with some tips on how to use them most effectively.

Understanding Antidepressants: Basic Brain Chemistry

If you've read up on antidepressants -- in newspapers and magazines, or on the Web -- you might see depression explained simply as a "chemical imbalance" or a "serotonin deficiency." Unfortunately, it's not that simple. We really don't know what causes depression or how it affects the brain. We don't exactly know how antidepressants improve the symptoms.

That said, many researchers believe that the benefits of antidepressants stem from how they affect certain brain circuits and the chemicals (called neurotransmitters) that pass along signals from one nerve cell to another in the brain. These chemicals include serotonin, dopamine, and norepinephrine. In various ways, different antidepressants seem to affect how these neurotransmitters behave. Here's a rundown of the main types of antidepressants.

Reuptake Inhibitors: SSRIs, SNRIs, and NDRIs

Some of the most commonly prescribed antidepressants are called reuptake inhibitors. What's reuptake? It's the process in which neurotransmitters are naturally reabsorbed back into nerve cells in the brain after they are released to send messages between nerve cells. A reuptake inhibitor prevents this from happening. Instead of getting reabsorbed, the neurotransmitter stays -- at least temporarily -- in the gap between the nerves, called the synapse.

What's the benefit? The basic theory goes like this: keeping levels of the neurotransmitters higher could improve communication between the nerve cells -- and that can strengthen circuits in the brain which regulate mood.

Different kinds of reuptake inhibitors target different neurotransmitters. There are three types:

- **Selective serotonin reuptake inhibitors (SSRIs)** are some of the most commonly prescribed antidepressants available. They include Celexa, Lexapro, Luvox, Paxil,

Prozac, and Zoloft. Another drug, Symbyax, is approved by the FDA specifically for treatment-resistant depression. It's a combination of the SSRI antidepressant fluoxetine (Prozac) and another drug approved for bipolar disorder and schizophrenia called olanzapine (Zyprexa). Aripiprazole (Abilify), quetiapine (Seroquel), and brexpiprazole (Rexulti) have been FDA approved as add-on therapy to antidepressants for depression. Plus, doctors often use other drugs in combination for treatment-resistant depression. Also, the drugs vilazodone (Viibryd) and vortioxetine (Trintellix - formerly called Brintellix) are among the newest antidepressants that affect serotonin. Both drugs affect the serotonin transporter (like an SSRI) but also affect other serotonin receptors to relieve major depression.

- **Serotonin and norepinephrine reuptake inhibitors (SNRIs)** are among the newer types of antidepressant. As the name implies, they block the reuptake of both serotonin and norepinephrine. They include duloxetine (Cymbalta), venlafaxine (Effexor), desvenlafaxine ER (Khedezla), levomilnacipran (Fetzima), and desvenlafaxine (Pristiq).
- **Norepinephrine and dopamine reuptake inhibitors (NDRIs)** are another class of reuptake inhibitors, but they're represented by only one drug: bupropion (Wellbutrin). It affects the reuptake of norepinephrine and dopamine.

Other Antidepressants: Tetracyclics and SARIs

- **Tetracyclics** are another class of antidepressant with drugs such as asamoxapine (Asendin), maprotiline (Ludomil), and mirtazapine (Remeron). Although it affects neurotransmitters, Remeron doesn't prevent reuptake in the same way. Instead, it seems to stop neurotransmitters from binding with specific receptors on the nerves. Because the norepinephrine and serotonin don't bind to the receptors, they seem to build up in the areas between the nerve cells. As a result, the neurotransmitter levels rise.
- **Serotonin antagonist and reuptake inhibitor (SARIs)** appear to act in two ways. They prevent the reuptake of serotonin. But they also prevent serotonin particles that are released in a synapse from binding at certain undesired receptors and redirect them instead to other receptors that can help nerve cells within mood circuits function better. Examples include nefazodone (Serzone) and trazodone.

Older Antidepressants: Tricyclics and MAOIs

These drugs were among the first to be used for depression. Although they're effective, they can have serious side effects and can be especially dangerous in overdose. Nowadays, many doctors only turn to these drugs when newer -- and better tolerated -- medicines haven't helped. Tricyclics and MAOIs might not be the best approach for someone who was just diagnosed. But they can sometimes be very helpful for people with treatment-resistant depression, or certain forms of depression (such as depression with anxiety).

- **Tricyclic antidepressants (TCAs)** include amitriptyline (Elavil), desipramine (Norpramin), imipramine (Tofranil), and nortriptyline (Pamelor). Like reuptake inhibitors, tricyclics seem to block the reabsorption of serotonin and epinephrine back into nerve

cells after these chemicals are released into a synapse. Because of the potential side effects, your doctor might periodically check your blood pressure, request an EKG, or recommend occasional blood tests to monitor the level of tricyclics in your system. These medicines might not be safe for people with certain heart rhythm problems.

- **Monoamine oxidase inhibitors (MAOIs)** include selegiline (Emsam), isocarboxazid (Marplan), phenelzine (Nardil), and tranylcypromine (Parnate). These drugs seem to work a little differently. Monoamine oxidase is a natural enzyme that breaks down serotonin, epinephrine, and dopamine. MAOIs block the effects of this enzyme. As a result, the levels of those neurotransmitters might get a boost. The downside is that MAOIs also prevent the body's ability to break down other medicines metabolized by this enzyme (such as Sudafed, or stimulants) -- raising the risk for high blood pressure -- as well as an amino acid called tyrosine, which is found in certain foods like aged meats and cheeses. MAOIs also shouldn't be combined with other medicines that can raise serotonin (such as certain migraine medicines, or other antidepressants), because that can cause a buildup of excessive serotonin (called "serotonin syndrome"), which could be life threatening.
- **Nutraceuticals or "medical food"** which includes l-methylfolate (Deplin). This is a prescription strength form of folate, also known as one of the essential B vitamins, B9. Depression is often related to low levels of folate which affect the neurotransmitters that control moods and l-methylfolate has proven to be effective in stimulating the production of neurotransmitters.

Treatment-Resistant Depression: Getting the Most from Your Antidepressants

It's worth remembering that a lot of what we think about antidepressants is still speculative. We don't really know if low levels of serotonin or other neurotransmitters "cause" depression, or if raising those levels will resolve it. We don't know enough about brain chemistry to say what's "balanced" or "unbalanced." It's possible that antidepressants have other unknown effects, and that their benefits don't have as much to do with neurotransmitter levels as they might with other effects, such as regulating genes that control nerve cell growth and function.

This might not sound very reassuring, especially if you're relying on antidepressants to help you feel better. But remember: even though experts don't have all the answers about *how* they work, we do know that they *can* work. Studies have established that antidepressants can help many people feel better, and that's what's really important.

We also have a lot of research into how people with depression -- including treatment-resistant depression -- can get the most of their medicine.

When taking an antidepressant for treatment-resistant depression, you have to be patient. Some people start an antidepressant and expect that it will work right away. After all, when you drink a few cups of coffee, or a few glasses of wine, you feel it pretty fast. People naturally expect the same kind of instant results with antidepressants.

But that's just not how antidepressants work. No one knows exactly why, but they can take weeks or months before they gain their full effect. When you're taking an antidepressant, it's important to adjust your expectations and to try to be patient.

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