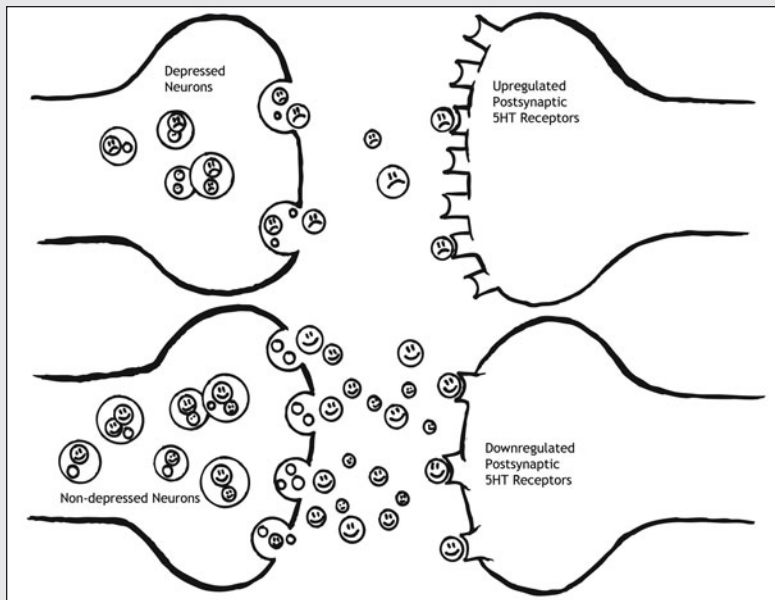


Why Do Antidepressants Take So Long to Work?

If depression is caused by low levels of NT, then you should feel better as soon as those levels return to normal. The amount of NTs starts increasing within 24-48 hours of starting medicine, but antidepressants typically take four to six weeks to work. Why should improvement take so long? One possible explanation is a phenomenon that happens to receptors called *down regulation*. Up regulation is an increase in postsynaptic receptors that occurs as NT levels drop. Down regulation is a return to a normal number of receptors when NT levels increase and takes about 4 to 6 weeks.

Down regulation is also seen with autoreceptors. Antidepressants block the presynaptic autoreceptors from determining NT



In depression, neurons respond by generating more receptors on the receiving (postsynaptic) neuron. This is called up regulation, which researchers believe may be responsible for some depression symptoms. With antidepressants, more neurotransmitters become available, and the receptor numbers return to normal. This is called down regulation. Down regulation takes four to six weeks to occur, about the time it takes antidepressants to help people feel better.

levels. In response to being tricked into thinking that there is too little NT available, the autoreceptors down regulate. With fewer autoreceptors, there is less feedback to the neuron to slow down NT production. This ultimately leads to an increase in NTs over time. Down regulation of autoreceptors also can take several weeks to occur, explaining the delayed effect of antidepressants.

Another possible explanation is that increasing NT levels triggers a series of actions that result in the depression response. One of these actions could be an increased production of neurotrophic factors, such as BDNF. This may explain how areas of the brain reduced in size and activity with depression can return to normal when depression is treated. In Chapter Five I discuss non-medicine interventions that may also increase BDNF. In the future, scientists may be able to develop new antidepressants that bypass increasing NT levels and work directly on another of these actions. Such a medication could work faster, be more effective, and have fewer side effects than those we have today.

Although I mentioned the delayed effect of antidepressants, a small number of people do feel better in a day or two. Some may experience a placebo effect in which they feel better because they convince themselves that the medicine is helping before it really does. Others may be benefiting from an increase in NTs alone. Those who improve only after several weeks on medicine may be responding when down regulation occurs or neurotrophic factors have time to take effect.

is listed by the generic name with the U.S. brand in parentheses. Appendix A “Past Medication History Form” details the mechanism of action in more detail for each medication, available forms and doses, dosing range, FDA indications, common side effects, and additional comments. There are other medicines used to treat depression outside the United States but those not approved by the FDA are not included.

Selective serotonin reuptake inhibitors (SSRIs): They work by blocking the serotonin reuptake pump, keeping the serotonin in the synapse between neurons around longer. They often affect other serotonin receptors and can lead to unintended side effects such as nausea, sleeping difficulties, and anxiety. They are the most common class prescribed because they are easy to start, usually well tolerated, and physicians are