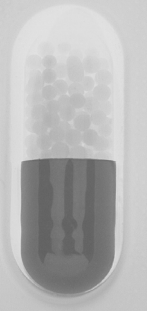


Tricyclic Antidepressants



Anafranil (clomipramine)
Elavil (amitriptyline)
Norpramin (desipramine)
Pamelor (nortriptyline)
Sinequan (doxepin)
Tofranil and Tofranil PM (imipramine)

The **tricyclic antidepressants** represent an older class of antidepressants that were once widely used in the treatment of depression. The *tricyclic* antidepressants refer to their three-ring chemical structures. For convenience, this handout shall refer to the tricyclic antidepressants as **TCAs**. These agents have been supplanted by newer antidepressants that are as effective but are much safer and have fewer side effects. They are still used to treat depression, but more frequently these agents are used to treat conditions outside of their approved indications, such as for the treatment of insomnia, chronic pain syndromes, generalized anxiety disorder, panic disorder, eating disorders (e.g., bulimia nervosa), and premenstrual dysphoric disorder. The use of a medication for its approved indication is called its *labeled use*. In clinical practice, however, physicians often prescribe medications for *unlabeled* (“off-label”) uses when published clinical studies, case reports, or their own clinical experiences support the efficacy and safety of these medications for these unapproved indications.

The TCAs are similar not only in structure but also in pharmacological effects. Presumably, these agents work by inhibiting the reuptake of **serotonin** and **norepinephrine**, two important neurotransmitters in the central nervous system, back into brain cells. *Neurotransmitters*, such as serotonin and norepinephrine, are chemicals produced by brain cells called neurons that enable them to communicate with one another. The neurotransmitters are released by one neuron into the space between that neuron and the next neuron. The neurotransmitters come into contact with specific sites on the surface membrane of neurons called receptors. From there, the chemical signal is transformed into an electrical impulse that travels down the neuron, causing further release of neurotransmitters. This process of neurotransmission is repeated along a chain of neurons. During neurotransmission, after neurotransmitters are released and the chemical signal is transferred to adjacent neurons, the neurotransmitters are recaptured back into brain cells by a process known as **reuptake**. By blocking the reuptake of neurotransmitters back into the brain cells from which they were released, the antidepressant can amplify the effects of the neurotransmitter.

The TCAs vary in their reuptake action depending on their chemical structure. One drug may have relatively greater norepinephrine reuptake blocking action, whereas another may have predominantly serotonin reuptake blocking properties. Most TCAs, however, block both serotonin and norepinephrine reuptake to varying degrees.

Depression and other mental disorders may be due to abnormally low levels of certain neurotransmitters in the brain. This abnormality may in turn produce changes in affected areas of the brain, resulting in psychiatric symptoms such as depression or anxiety. When neurotransmission is altered by the antidepressant, the affected brain areas may be restored to normal functioning, decreasing or eliminating the symptoms of the illness.

Common Side Effects

The TCAs are associated with numerous side effects and may not be tolerated by some individuals. Side effects often limit the usefulness of these agents, especially at higher dosages. Side effects can be managed sometimes by increasing the dosage slowly or by reducing the dosage. Monitoring blood drug levels for a selected TCA can also ensure the greatest benefit with the fewest side effects, because drug blood levels may identify patients with excessively high levels when toxic effects are suspected or those with low levels of drug in whom lack of absorption or rapid metabolism is suspected.

Most of the side effects from taking antidepressants usually subside greatly within 3–4 weeks, although this does not always occur. In the meantime, practical strategies may help minimize some of the side effects. Because TCAs are generally sedating, taking the prescribed medication before bedtime often results in a reduction of daytime side effects, especially drowsiness. When a medication is prescribed in divided doses, taking the larger dose at bedtime often helps. Other common side effects include feeling “spacey,” a sense of being “slowed down,” and forgetfulness.

Because the TCAs inhibit **cholinergic neurons** in the nervous system, they frequently produce a cluster of symptoms called **anticholinergic** side effects, which include dry mouth and skin, blurred vision, constipation, and difficulty urinating. Usually, individuals become tolerant to these side effects, but excessive anticholinergic effects may lead to confusion and a psychiatric disorder called delirium if not monitored closely. Sometimes the physician may prescribe another medication to counteract the anticholinergic action of the antidepressant. For example, a physician may prescribe a 1% pilocarpine eye drop to treat blurred vision and bethanechol (e.g., Urecholine), a cholinergic agent, to treat urinary difficulties. For constipation, an over-the-counter stool softener such as Colace (docusate) is usually helpful.

Individuals may experience dizziness from TCAs. Dizziness may be caused by the drugs' effect in momentarily dropping blood pressure; they block the body's compensatory response to maintain a stable blood pressure when a person moves from lying down to a sitting position or from sitting to standing. This reaction is known in medical terms as **orthostatic hypotension**. Seniors and those taking medications to lower blood pressure may be more susceptible to orthostatic hypotension from these antidepressants.

Weight gain is also another common problem, particularly with Elavil (amitriptyline), Pamelor (nortriptyline), and Sinequan (doxepin). Most individuals gain several pounds while taking TCAs. If the individual's weight does not stabilize, the physician may switch the patient's medication to one of the newer, weight-neutral antidepressants, such as the **selective serotonin reuptake inhibitors** (SSRIs).

TCAs may also produce sexual difficulties, including impotence and ejaculatory difficulty in men and decreased sexual drive in both men and women. If this is a problem, the physician may switch the patient's medication to another antidepressant, such as bupropion (Wellbutrin-SR or -XR), that does not interfere with sexual functioning.

Adverse Reactions and Precautions

As previously stated, seniors and individuals taking antihypertensive medications may be particularly susceptible to orthostatic hypotension from the TCAs. Patients taking these antidepressants should be cautious when rising suddenly to their feet. If lying down, patients should rise gradually to a sitting position before standing to avoid a sudden change in blood pressure. If lightheaded or dizzy, they should sit and wait for a minute or two to allow the blood pressure to adjust before standing up.

TCAs also may aggravate a potentially serious eye condition called **narrow-angle glaucoma**. Individuals should inform their psychiatrist if they have this condition.

In patients with a history of seizure disorder, use of the TCAs must be monitored closely because these antidepressants may lower the threshold for, and trigger, seizures. They may also slow cardiac conduction, which may result in a disturbance in heart rhythms called an arrhythmia. This side effect is more common in

seniors and in people with a history of cardiac arrhythmias. For these individuals an electrocardiogram is recommended prior to and periodically (at least annually) during antidepressant treatment.

Overdose

TCAs are extremely lethal in acute overdoses, particularly in children. Overdoses often result in death, especially when TCAs are combined with other drugs or alcohol. Disturbance of cardiac rhythm is usually the leading cause of death in fatal TCA overdoses.

Any suspected overdose should be treated as an emergency. The person should be taken to the emergency department 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 produce 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 if they do not feel better immediately.

Researchers do not fully understand the exact mechanisms by which antidepressants work, but they appear to disrupt the chain of events that produce abnormalities in how the brain deals with emotions or stress, resulting in the symptoms of depression. When an individual does not respond to a tricyclic, does it make sense for the physician to switch the patient's medication to another TCA, since TCAs 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 one agent may be effective for one person but not for another. Sometimes it takes trial and error to find the right antidepressant, or combination of antidepressants, to successfully treat the person.

The controversial issue of suicide and antidepressants has prompted the FDA to ask manufacturers of some antidepressants, particularly the SSRIs, to provide warnings in their package insert that the risk of suicide may be increased in depressed individuals (especially children) during the first several weeks after beginning an antidepressant. However, 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. Depressed individuals who are at risk for suicide should be closely watched at the outset of therapy, and any signs of suicidal or violent behavior should be immediately reported to the physician or a mental health provider.

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

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