

Valproate

Valproate (depakote, divalproex sodium, valproic acid) is a mood stabilizer which helps mania, agitation, irritability, depression, and anxiety in bipolar disorder. It is particularly helpful manic or mixed states, which can make people feel agitated, impulsive, irritable, anxious, restless, and distracted. Valproate usually takes 2-4 weeks to work. People who respond well to it often report that it improves racing thoughts and emotional reactivity so that they can think before they act.

Valproate is also FDA-approved for migraine-prevention and seizures. It has small studies suggesting it may be beneficial in alcoholism and alcohol withdrawal, panic, post-traumatic stress disorder, borderline personality and problems of anger management and impulsive control. Off-label medical uses of valproate include restless legs, certain kinds of nerve pain (e.g. post-herpetic neuralgia).

How it works

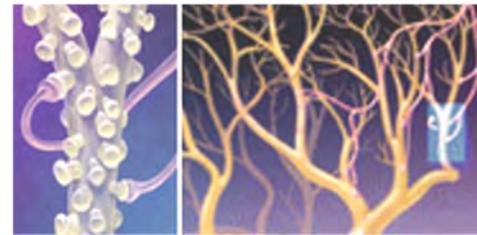
Valproate can break cycles of mood swings by stabilizing the electrical firing of brain cells. The brain can become locked in repetitive mood cycles through a process called *kindling*. The same cycles have been observed in the brains of people with repetitive seizures, which is why many seizure medications like valproate are helpful for mood swings. Valproate also helps brain cells to grow and strengthen so they have stronger connections, as shown below:



Before treatment: the effects of depression and stress have caused this nerve cell to shrink back like a tree with few branches.

Key Points

1. Take with vitamins (Centrum silver + 1,000mcg folate)
2. Best to take at night; take with food if stomach upset
3. We will check labs while on valproate
4. Be aware of drug interactions and warnings (liver problems, low blood count, pancreatitis)
5. Avoid if pregnant or carrying hepatitis C or HIV virus



After treatment: valproate has strengthened the roots and connections of the brain cell. The result is better moods and stress management.

When brain cells grow like this it helps people manage stress better and prevents mood problems for the long-term. Of all psychiatric medications, valproate and lithium have the most benefits on brain growth.

How should I take it?

Valproate can be taken 2-3 times per day or all at night depending on the dose. The capsules tend to be large. If it is hard to swallow try taking with thick liquids or consider another form of valproate (it is available as a liquid, as sprinkles and an XR version; do not break or chew the XR form).

Most people prefer to take the larger portion of their dose at night, as it can cause drowsiness, but it is fine to take in the morning if that works better for you. Valproate is better tolerated when taken with food, but can be taken on an empty stomach as well. Valproate levels peak in the blood 3-4 hours after taking it.

Valproate tends to work better and have fewer side effects if taken with a multivitamin that contains folate (at least 1mg; taking up to 3mg can help depakote work better), selenium, zinc, B6 and B12. This can be achieved by taking certain multivitamins (e.g. Centrum Silver, Puritan's Pride one-a-day) with additional folate (usually 800mcg; read the multivitamin label to determine how much).

Valproate is one medicine where we can scientifically determine your optimal dose by measuring the level in your blood. The ideal level ranges from 50-125, and the higher range (above 90) is often necessary to treat active mania.

Valproate is stabilized in its capsule by binding it to a salt. This can be done in different ways so it is available in three forms: divalproex sodium, valproate sodium, and valproic acid. Of these, the divalproex sodium form tends to be the best tolerated.

It is also available in a delayed release (XR) capsule which is easier on the stomach and may have less weight gain. If you are taking another form and switch to the XR, you will need to raise your dose by 10-20% to achieve the same blood levels (because some of the XR does not get absorbed).

What if I forget a dose?

Take the missed dose as soon as you remember it. However, if it is almost time for the next dose, skip the missed dose and continue your regular dosing schedule. Do not take a double dose to make up for a missed one. Do not take more than the prescribed daily amount in 24 hours.

How long do I need to take it?

Whether or not you can safely come off valproate depends on your diagnosis and which other medications you are taking. Most people with bipolar disorder need to stay on at least one mood stabilizer for the long term in order to prevent mood swings. If valproate helped, it is best to stay on it for at least 6 months before considering going off it. That gives the brain time to build up habits of stability.

What happens if I stop it?

Valproate is not addictive and does not cause withdrawal symptoms. You may read that stopping valproate can cause seizures; this warning only applies to people who take it for seizures. If you plan to come off valproate, it is best to do so slowly as that will lower the chance of sudden mood swings returning.

Checking labs

You will need to have labs checked a 1-2 times per year while on valproate to monitor the level of the medicine and ensure it is not impacting your liver or blood count. If you take the medicine during the day, make sure to get the labs drawn before taking your daytime dose.

Side effects

Common side effects (many of these improve by lowering the dose):

Nausea (10-30%), vomiting (5-20%), indigestion (5%), diarrhea (5%), stomach pain (5-15%), headache (10%), fatigue (5-20%), tremor (10-20%), sensory changes (10%), dizziness (5%), double vision (5%), blurred vision (5%), hair loss (5%), weight gain (5-10%), poor concentration (5%), menstrual abnormalities.

Valproate may increase bleeding and should not be taken with aspirin.

Rare but serious side effects:

- *Liver failure:* this is a rare side effect of valproate. If it occurs, it is most likely during the first 6 months. It is also more common in children and those with neurologic problems such as mental retardation and severe epilepsy. To reduce this risk, we will monitor your liver enzymes while taking valproate. Rarely, valproate will impact only the liver's ability to detoxify ammonia, causing symptoms of lethargy and confusion.
- *Pancreatitis:* rare cases of severe pancreatitis have been reported (rate approximately 1 in 1,000).
- *Thrombocytopenia (drops in platelet count):* very rarely, valproate can cause seriously impair the blood's ability to clot.
- *Polycystic Ovarian Disease:* although valproate has been rarely associated with this condition in women, it is not yet clear that it causes it. The

symptoms include irregular or no menstrual periods, facial and other hair growth, acne, changes in body shape and obesity.

Contact us if you have... *Flu-like feelings, extreme fatigue, confusion, loss of consciousness, yellowing of the skin or eyes, swelling of the face, vomiting, no appetite, belly pain, increased or unusual bleeding.*

An allergic reaction is possible with any medication. Symptoms include the following; stop the medication and call me if these occur: Pounding heartbeat; swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, or lower legs; hoarseness; difficulty swallowing or breathing; hives; rash.

Pregnancy: You should call me and plan to come off valproate if you are planning to become pregnant. There are many safer options for managing bipolar during pregnancy that we can talk about. Serious birth defects have been caused by taking valproate while pregnant (e.g. neurotube defects, where the spinal cord does not close), especially if taken during the first trimester.

Women of childbearing age should take vitamins with valproate (see page 1 "How should I take it?") to reduce the risk of these defects in the event of unexpected pregnancy while on valproate.

Valproate comes out in breast milk and should be avoided while breast feeding. Valproate will not affect future pregnancies after you stop taking it and will not affect fertility in men.

For people who are HIV+ or hepatitis C+: there is a small risk that valproate can increase the replication of the virus. Talk to us about other options for bipolar (e.g. lithium, N-acetylcysteine) which have some evidence for reducing the HIV infection.

For people with thyroid disease: there are rare reports of valproate altering thyroid levels.

Interactions (partial list)

Recreational drugs: Alcohol can increase the dizziness and dyscoordination of valproate. Alcohol and recreational drugs can also prevent valproate from working.

Valproate can lower levels of:

Oxcarbazepine (Trileptal, by 18%), amitriptyline (Elavil), nortriptyline, calcium-channel blockers (verapamil, flamlodipine; by 30%).

Valproate can raise levels of:

Diazepam (Valium), lamotrigine (also increase risk of lamotrigine-induced rashes), ethosuximide, phenobarbital, phenytoin, tolbutamide, warfarin (Coumadin), zidovudine.

Drugs that can lower valproate levels:

Phenytoin, carbamazepine (by 20%), phenobarbital, meropenem, rifampin

Drugs that can raise valproate levels:

Aspirin (valproate also can increase the risk of bleeding with aspirin), felbamate (by 30-50%)

Drugs that may increase the risk of liver problems with valproate:

High-dose or long-term acetaminophen (Tylenol), disulfiram (Antabuse), naltrexone, certain seizure medications, plicamycin (Mithracin).

Other drugs that may interact with valproate:

Acetaminophen (Tylenol: long term or high-dose use may increase risk of liver problems), amiodarone (Cordarone), anabolic steroids (nandrolone, Anabolin, oxandrolone, Anavar, oxymetholone, Anadrol, stanozolol, Winstrol), androgens (male hormones), anticoagulants (heparin, coumadin), carmustine (BiCNU), dantrolene (Dantrium), daunorubicin (Cerubidine), estrogens (female hormones), etretinate (Tegison), gold salts (medicine for arthritis), mercaptopurine (Purinethol), methotrexate (Mexate), methyl dopa (Aldomet), phenothiazines (acetophenazine, Tindal, chlorpromazine, Thorazine, fluphenazine, Prolixin, mesoridazine Serentil, perphenazine, Trilafon, prochlorperazine, Compazine, promazine, Sparine, promethazine, Phenergan, thioridazine, Mellaril, trifluoperazine, Stelazine, triflupromazine, Vesprin, trimeprazine), Tamaril, carbenicillin by injection (Geopen), dipyridamole (Persantine), pentoxifylline (Trental), sulfapyrazone (Anturane), ticarcillin (Ticar), mefloquine.

Overdose

An overdose of valproate should be assessed and treated in the emergency room. A toxic overdose can cause extreme fatigue, slowing or failure of the heart, changes in consciousness or coma.

How to store and dispose of medication

- Keep out of the reach of children.
- Store away from heat, direct light and damp places.
- To safely dispose of unwanted pills: Do not pour in the toilet or sink (it will enter the water supply). To prevent children or pets from eating it, mix unwanted pills in a bag with a little water and inedible trash (such as coffee grounds or kitty litter) and throw in the trash.

—Chris Aiken, MD, updated 6/28/2025

Valproate

Brand names	Depakote, Depakote-ER, Depakene (liquid), Stavzor Generics: Divalproex sodium, valproic acid, valproate
Dose range	Dosing is based on your blood level, which can range from 50-125 mcg/ml. A rapid starting dose can be estimated based on your body size (weight in lbs * 9): 120 lb: 1,000mg/day; 150 lb: 1,250mg/day 180 lb: 1,500mg/day; 200 lb: 1,750mg/day 250 lb: 2,250mg/day; 300 lb: 2,750mg/day The maximum dose can also be estimated as weight in pounds times 27.2: 120 lb: 3,250mg/day; 150 lb: 4,000mg/day 180 lb: 4,900mg/day; 200 lb: 5,450mg/day 250 lb: 6,800mg/day; 300 lb: 8,150mg/day

	(above doses may need to be raised by 10-20% if taking the ER form)
Sizes	> Tabs: 125, 250m 500mg (generic) > ER*: 250, 500mg (generic) > Sprinkles: 125mg (sprinkle on food) > Liquid: 50mg/ml > IV or injection (depacon) *do not crush or chew XR tabs
Release date	1/28/1978
FDA-approval	Bipolar disorder, epilepsy (seizures), migraine-prevention