VALPROATE

**Brands**
- Depakene
- Depacon
- Depakote, Depakote ER
- Stavzor

*see index for additional brand names*

**Generic?** Yes

**Class**
- Neuroscience-based Nomenclature: glutamate (Glu); yet to be determined
- Anticonvulsant, mood stabilizer, migraine prophylaxis, voltage-sensitive sodium channel modulator

**Commonly Prescribed for**
(bold for FDA approved)
- Acute mania (divalproex) and mixed episodes (divalproex, divalproex ER, valproic acid delayed-release)
- Complex partial seizures that occur either in isolation or in association with other types of seizures (monotherapy and adjunctive)
- Simple and complex absence seizures (monotherapy and adjunctive)
- Multiple seizure types, which include absence seizures (adjunctive)
- Migraine prophylaxis (divalproex, divalproex ER, valproic acid delayed-release)
- Maintenance treatment of bipolar disorder
- Bipolar depression
- Psychosis, schizophrenia (adjunctive)

**How the Drug Works**
- Blocks voltage-sensitive sodium channels by an unknown mechanism
- Increases brain concentrations of gamma-aminobutyric acid (GABA) by an unknown mechanism

**How Long Until It Works**
- For acute mania, effects should occur within a few days depending on the formulation of the drug
- May take several weeks to months to optimize an effect on mood stabilization
- Should also reduce seizures and improve migraine within a few weeks

**If It Works**
- The goal of treatment is complete remission of symptoms (e.g., mania, seizures, migraine)
- Continue treatment until all symptoms are gone or until improvement is stable and then continue treating indefinitely as long as improvement persists
- Continue treatment indefinitely to avoid recurrence of mania, depression, seizures, and headaches

**If It Doesn’t Work (for bipolar disorder)**
- Many patients have only a partial response where some symptoms are improved but others persist or continue to wax and wane without stabilization of mood
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider checking plasma drug level, increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider adding psychotherapy
- Consider the presence of noncompliance and counsel patient
- Switch to another mood stabilizer with fewer side effects
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)

**Best Augmenting Combos**
- Lithium
- Atypical antipsychotics (especially risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole)
- Lamotrigine (with caution and at half the dose in the presence of valproate because valproate can double lamotrigine levels)
- Antidepressants (with caution because antidepressants can destabilize mood in some patients, including induction of rapid cycling or suicidal ideation; in particular consider bupropion; also SSRIs, SNRIs, others; generally avoid TCAs, MAOIs)

**Tests**
- Before starting treatment, complete blood counts, coagulation tests, and liver function tests
Life-Threatening or Dangerous Side Effects

- Can cause tachycardia or bradycardia
- Rare hepatotoxicity with liver failure sometimes severe and fatal, particularly in children under 2 years old
- Rare pancreatitis, sometimes fatal
- Rare but serious skin condition known as Drug Reaction with Eosinophilia (DRESS)
- Rare activation of suicidal ideation and behavior (suicidality)

Weight Gain

- Many experience and/or can be significant in amount
- Can become a health problem in some

Sedation

- Frequent and can be significant in amount
- Some patients may not tolerate it
- Can wear off over time
- Can reemerge as dose increases and then wear off again over time

What to Do About Side Effects

- Wait
- Wait
- Take at night to reduce daytime sedation, especially with divalproex ER
- Lower the dose
- Switch to another agent

Best Augmenting Agents for Side Effects

- Propranolol 20–30 mg 2–3 times/day may reduce tremor
- Multivitamins fortified with zinc and selenium may help reduce alopecia
- Many side effects cannot be improved with an augmenting agent

SIDE EFFECTS

How Drug Causes Side Effects

- CNS side effects theoretically due to excessive actions at voltage-sensitive sodium channels

Notable Side Effects

- Sedation, dose-dependent tremor, dizziness, ataxia, asthenia, headache
- Abdominal pain, nausea, vomiting, diarrhea, reduced appetite, constipation, dyspepsia, weight gain
- Alopecia (unusual)
- Polycystic ovaries (controversial)
- Hyperandrogenism, hyperinsulinemia, lipid dysregulation (controversial)
- Decreased bone mineral density (controversial)

DOSING AND USE

Usual Dosage Range

- Mania: 1,200–1,500 mg/day
- Migraine: 500–1,000 mg/day
- Epilepsy: 10–60 mg/kg per day
Divalproex immediate-release formulation reduces gastrointestinal side effects compared to generic valproate

Divalproex ER improves gastrointestinal side effects and alopecia compared to immediate-release divalproex or generic valproate

The amide of valproic acid is available in Europe [valpromide (Depamide)]

Trough plasma drug levels >45 μg/mL may be required for either antimanic effects or anticonvulsant actions

Trough plasma drug levels up to 100 μg/mL are generally well tolerated

Trough plasma drug levels up to 125 μg/mL may be required in some acutely manic patients

Dosages to achieve therapeutic plasma levels vary widely, often between 750–3,000 mg/day

Overdose

Fatalities have been reported; coma, restlessness, hallucinations, sedation, heart block

Long-Term Use

• Requires regular liver function tests and platelet counts

Habit Forming

• No

How to Stop

• Taper; may need to adjust dosage of concurrent medications as valproate is being discontinued
• Patients may seize upon withdrawal, especially if withdrawal is abrupt
• Rapid discontinuation increases the risk of relapse in bipolar disorder
• Discontinuation symptoms uncommon

Pharmacokinetics

• Mean terminal half-life 9–16 hours
• Metabolized primarily by the liver, approximately 25% dependent upon CYP450 system (CYP450 2C9 and 2C19)
• Inhibits CYP450 2C9
• Food slows rate but not extent of absorption

Drug Interactions

• Lamotrigine dose should be reduced by perhaps 50% if used with valproate,
as valproate inhibits metabolism of lamotrigine and raises lamotrigine plasma levels, theoretically increasing the risk of rash

- Plasma levels of valproate may be lowered by carbamazepine, phenytoin, ethosuximide, phenobarbital, rifampin
- Aspirin may inhibit metabolism of valproate and increase valproate plasma levels
- Plasma levels of valproate may also be increased by felbamate, chlorpromazine, fluoxetine, fluvoxamine, topiramate, cimetidine, erythromycin, and ibuprofen
- Valproate inhibits metabolism of ethosuximide, phenobarbital, and phenytoin, and can thus increase their plasma levels
- No likely pharmacokinetic interactions of valproate with lithium or atypical antipsychotics
- Use of valproate with clonazepam may cause absence status
- Reports of hyperammonemia with or without encephalopathy in patients taking topiramate combined with valproate, though this is not due to a pharmacokinetic interaction; in patients who develop unexplained lethargy, vomiting, or change in mental status, an ammonia level should be measured

Other Warnings/Precautions

✽ Be alert to the following symptoms of hepatotoxicity that require immediate attention: malaise, weakness, lethargy, facial edema, anorexia, vomiting, yellowing of the skin and eyes

✽ Be alert to the following symptoms of pancreatitis that require immediate attention: abdominal pain, nausea, vomiting, anorexia

✽ Teratogenic effects in developing fetuses such as neural tube defects may occur with valproate use

✽ Somnolence may be more common in the elderly and may be associated with dehydration, reduced nutritional intake, and weight loss, requiring slower dosage increases, lower doses, and monitoring of fluid and nutritional intake

✽ Use in patients with thrombocytopenia is not recommended; patients should report easy bruising or bleeding

- Evaluate for urea cycle disorders, as hyperammonemic encephalopathy, sometimes fatal, has been associated with valproate administration in these uncommon disorders; urea cycle disorders, such as ornithine transcarbamylase deficiency, are associated with unexplained encephalopathy, mental retardation, elevated plasma ammonia, cyclical vomiting, and lethargy
- Valproate is associated with a rare but serious skin condition known as Drug Reaction with Eosinophilia (DRESS). DRESS may begin as a rash but can progress to others parts of the body and can include symptoms such as fever, swollen lymph nodes, inflammation of organs, and an increase in white blood cells known as eosinophilia. In some cases, DRESS can lead to death.
- Warn patients and their caregivers about the possibility of activation of suicidal ideation and advise them to report such side effects immediately

Do Not Use

- If patient has pancreatitis
- If patient has serious liver disease
- If patient has urea cycle disorder
- If there is a proven allergy to valproic acid, valproate, or divalproex

SPECIAL POPULATIONS

Renal Impairment
- No dose adjustment necessary

Hepatic Impairment
- Contraindicated

Cardiac Impairment
- No dose adjustment necessary

Elderly
- Reduce starting dose and titrate slowly; dosing is generally lower than in healthy adults
- Sedation in the elderly may be more common and associated with dehydration, reduced nutritional intake, and weight loss
- Monitor fluid and nutritional intake
- 1 in 3 elderly patients in long-term care who receive valproate may ultimately develop thrombocytopenia

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Children and Adolescents

- Not generally recommended for use in children under age 10 for bipolar disorder except by experts and when other options have been considered
- Children under age 2 have significantly increased risk of hepatotoxicity, as they have a markedly decreased ability to eliminate valproate compared to older children and adults
- Use requires close medical supervision

Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Use during first trimester may raise risk of neural tube defects (e.g., spina bifida) or other congenital anomalies
- Cases of developmental delay in the absence of teratogenicity associated with fetal exposure have been identified
- Increased risk of lower cognitive test scores in children whose mothers took valproate during pregnancy
- Use in women of childbearing potential requires weighing potential benefits to the mother against the risks to the fetus
- If drug is continued, monitor clotting parameters and perform tests to detect birth defects
- If drug is continued, start on folate 1 mg/day early in pregnancy to reduce risk of neural tube defects
- If drug is continued, consider vitamin K during the last 6 weeks of pregnancy to reduce risks of bleeding
- Antiepileptic Drug Pregnancy Registry: (888) 233–2334

Breast Feeding

- Some drug is found in mother’s breast milk
- Generally considered safe to breastfeed while taking valproate
- If drug is continued while breastfeeding, infant should be monitored for possible adverse effects
- If infant shows signs of irritability or sedation, drug may need to be discontinued
- Bipolar disorder may recur during the postpartum period, particularly if there is a history of prior postpartum episodes of either depression or psychosis
- Relapse rates may be lower in women who receive prophylactic treatment for postpartum episodes of bipolar disorder
- Atypical antipsychotics and anticonvulsants such as valproate if treatment of bipolar disorder is required during pregnancy
- Bipolar symptoms may recur or worsen during pregnancy and some form of treatment may be necessary

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Manic phase of bipolar disorder
- Works well in combination with lithium and/or atypical antipsychotics
- Patients for whom therapeutic drug monitoring is desirable

Potential Disadvantages

- Depressed phase of bipolar disorder
- Patients unable to tolerate sedation or weight gain
**VALPROATE (continued)**

- Multiple drug interactions
- Multiple side effect risks
- Pregnant patients

**Primary Target Symptoms**
- Unstable mood
- Incidence of migraine
- Incidence of partial complex seizures

**Pearls (for bipolar disorder)**

* Valproate is a first-line treatment option that may be best for patients with mixed states of bipolar disorder or for patients with rapid-cycling bipolar disorder
* Seems to be more effective in treating manic episodes than depressive episodes in bipolar disorder (treats from above better than it treats from below)
* May also be more effective in preventing manic relapses than in preventing depressive episodes (stabilizes from above better than it stabilizes from below)
* Only a third of bipolar patients experience adequate relief with a monotherapy, so most patients need multiple medications for best control
* Useful in combination with atypical antipsychotics and/or lithium for acute mania
* May also be useful for bipolar disorder in combination with lamotrigine, but must reduce lamotrigine dose by half when combined with valproate
* Usefulness for bipolar disorder in combination with anticonvulsants other than lamotrigine is not well demonstrated; such combinations can be expensive and are possibly ineffective or even irrational
* May be useful as an adjunct to atypical antipsychotics for rapid onset of action in schizophrenia
* Used to treat aggression, agitation, and impulsivity not only in bipolar disorder and schizophrenia but also in many other disorders, including dementia, personality disorders, and brain injury
* Patients with acute mania tend to tolerate side effects better than patients with hypomania or depression
* Multivitamins fortified with zinc and selenium may help reduce alopecia
* Association of valproate with polycystic ovaries is controversial and may be related to weight gain, obesity, or epilepsy
* Nevertheless, may wish to be cautious in administering valproate to women of childbearing potential, especially adolescent female bipolar patients, and carefully monitor weight, endocrine status, and ovarian size and function
* In women of childbearing potential who are or are likely to become sexually active, should inform about risk of harm to the fetus and monitor contraceptive status
* Association of valproate with decreased bone mass is controversial and may be related to activity levels, exposure to sunlight, and epilepsy, and might be prevented by supplemental vitamin D 2,000 IU/day and calcium 600–1,000 mg/day
* New delayed-release capsule of valproic acid (Stavzor) may be easier to swallow than other formulations
* A prodrug of valproic acid, valpromide, is available in several European countries
* Although valpromide is rapidly transformed to valproic acid, it has some unique characteristics that can affect drug interactions
* In particular, valpromide is a potent inhibitor of liver microsomal epoxide hydrolase and thus causes clinically significant increases in the plasma levels of carbamazepine-10,11-epoxide (the active metabolite of carbamazepine)
Suggested Reading


