MOOD STABILIZER

Divalproex Sodium

Depakote, Depakote ER, Depakote Sprinkle, Depakene, Depacon

Broad-spectrum anticonvulsant and first-line antimanic agent, limited chiefly by hepatic, pancreatic, and severe reproductive toxicity.

USUAL ADULT RANGE	TARGET TROUGH	HALF-LIFE	METABOLISM
750-2500 mg/day PO divided	50-125 mcg/mL for mania	9-16 h; longer in liver dz	Glucuronidation, oxidation

⚠ FDA BOXED WARNING

Hepatotoxicity including fatal hepatic failure, with highest risk under age 2 and in mitochondrial POLG disorders; fetal risk including neural tube defects, other major malformations, and decreased IQ after in utero exposure; and life-threatening pancreatitis, which can occur at any point in treatment.

INDICATIONS

- FDA-approved for acute manic and mixed episodes of bipolar I disorder in adults, with the extended-release form dosed once daily.
- FDA-approved for migraine prophylaxis in adults, though it is contraindicated in pregnancy for this indication because risk exceeds benefit.
- FDA-approved for complex partial seizures as monotherapy or adjunct from age 10, and for simple and complex absence seizures.
- Off-label maintenance treatment of bipolar I disorder, widely used and guideline-endorsed despite the absence of a maintenance indication.
- Off-label use for impulsive aggression and for alcohol withdrawal, though evidence in dementia-related agitation shows harm without benefit.
- Often preferred over lithium for mixed episodes, rapid cycling, and mania with comorbid substance use or head injury.

DOSING & TITRATION

- For acute mania start delayed-release **750 mg/day** in divided doses, or extended-release **25 mg/kg/day** once daily, then titrate rapidly.
- Increase every 1 to 3 days to clinical response and a trough level of **50-125 mcg/mL**; the labeled maximum is **60 mg/kg/day**.
- Migraine prophylaxis starts at **250 mg** twice daily or extended-release **500 mg** daily, with a usual ceiling of **1000 mg/day**.
- Extended-release tablets deliver about 10 to 20 percent less valproate than delayed-release, so raise the total dose when converting.
- Reduce the dose in hepatic impairment and avoid valproate entirely in significant liver disease; no adjustment is needed for renal impairment.
- Taper over weeks when stopping in seizure disorders; abrupt withdrawal can precipitate status epilepticus or mood destabilization.

MECHANISM OF ACTION

- Increases brain GABA availability by inhibiting GABA transaminase and succinic semialdehyde dehydrogenase, raising inhibitory tone.
- Blocks voltage-gated sodium channels and attenuates T-type calcium currents, which dampens high-frequency repetitive neuronal firing.
- Inhibits histone deacetylase and modulates extracellular signal-regulated kinase pathways, effects proposed to underlie mood stabilization.
- Reduces glutamatergic excitability and stabilizes kindling phenomena, consistent with its efficacy in mixed and rapid-cycling presentations.
- The antimanic effect appears within 3 to 5 days at therapeutic levels, faster than lithium and comparable to antipsychotic monotherapy.

PHARMACOKINETICS

- Divalproex dissociates to valproate in the gut; delayed-release peaks at 3 to 8 hours and the extended-release form at 4 to 17 hours.
- Protein binding is about 90 percent but saturable, so free valproate rises disproportionately at total levels above 100 mcg/mL.
- Elimination half-life is 9 to 16 hours in adults, shorter in patients taking enzyme-inducing anticonvulsants such as carbamazepine.
- Metabolism is mainly glucuronidation and mitochondrial beta-oxidation, with minor CYP2C9, CYP2C19, and CYP2A6 contributions.
- Valproate inhibits CYP2C9, UGT enzymes, and epoxide hydrolase, which drives its most important drug interactions.

ADVERSE EFFECTS

- Nausea, dyspepsia, and diarrhea are common early and are reduced by the delayed-release or extended-release formulations taken with food.
- Weight gain affects up to half of patients, and dose-related tremor, sedation, and cognitive slowing are frequent reasons for discontinuation.
- Hair thinning occurs in roughly 10 percent and often responds to a zinc and selenium supplement while the dose is maintained.
- Thrombocytopenia is dose-dependent and common above 100 mcg/mL; asymptomatic hyperammonemia may progress to encephalopathy.
- Polycystic ovary features, hyperandrogenism, and menstrual irregularity develop in a substantial minority of young women on valproate.
- Fatal hepatotoxicity and hemorrhagic pancreatitis are rare but can occur at any time and demand immediate discontinuation.

MONITORING

- Obtain liver enzymes and CBC with platelets at baseline, then every 1 to 2 months for the first 6 months and periodically thereafter.
- Check a trough valproate level 3 to 5 days after each dose change, aiming for 50 to 125 mcg/mL in mania and 50 to 100 mcg/mL in epilepsy.
- Measure serum ammonia when lethargy, confusion, vomiting, or unexplained encephalopathy appears, even with normal liver enzymes.
- Confirm a negative pregnancy test before starting in anyone who can become pregnant, and document effective contraception in the chart.
- Track weight, menstrual regularity, and signs of hyperandrogenism at each visit, plus amylase and lipase if abdominal pain develops.

INTERACTIONS & CAUTIONS

- Valproate roughly doubles lamotrigine concentrations by inhibiting glucuronidation, so lamotrigine starting and target doses must be halved.
- Carbapenem antibiotics can drop valproate levels by more than 50 percent within days, causing breakthrough seizures or mania.
- Enzyme inducers including carbamazepine, phenytoin, phenobarbital, and rifampin substantially lower valproate concentrations.
- Valproate raises free phenytoin and inhibits CYP2C9, increasing warfarin effect; aspirin displaces it from protein and raises free drug.
- Contraindicated in hepatic disease, urea cycle disorders, known mitochondrial POLG mutations, and pregnancy for migraine prophylaxis.

SPECIAL POPULATIONS

- Valproate should not be used in anyone who can become pregnant unless other treatments are unacceptable, given a 1 to 2 percent neural tube defect rate.
- In utero exposure lowers childhood IQ by about 8 to 10 points relative to lamotrigine, an effect that persists at school age.
- Milk concentrations are low and breastfeeding is generally considered compatible, with infant platelet and liver monitoring if prolonged.
- Children under 2 years have the highest risk of fatal hepatotoxicity, especially on polytherapy or with metabolic disease.
- Older adults show reduced clearance and higher free fraction; start at lower doses and watch closely for sedation and dehydration.

PRESCRIBING PEARLS

- Add valproate to lamotrigine and you must halve the lamotrigine dose or risk Stevens-Johnson syndrome.
- Unexplained lethargy on a normal valproate level is hyperammonemia until an ammonia level says otherwise.
- Document contraception and pregnancy counseling at every visit for patients who can become pregnant.

Verify against the current FDA label and your formulary before prescribing. Educational reference only.

References

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NOTE

References follow APA 7th edition style. Dosing, boxed warnings, and interaction data change; confirm every clinical decision against the current FDA prescribing information (DailyMed) and your institution's formulary. This sheet is an educational quick reference and does not replace the full label or clinical judgment.