Divalproex Sodium

Brand name - Depakote

Oral dosing for adults with acute manic or mixed episodes in bipolar disorder

Divalproex sodium is an anti-epileptic drug indicated for manic and mixed episodes in bipolar disorder. Its exact therapeutic mechanism is unclear but may be mediated by increasing brain concentrations of GABA.

	Extended Release (ER)	Delayed Release (DR)
Initial Dose	25mg/kg once daily	750mg daily, divided in doses
Titration Timeline	Increase as rapidly as clinically appropriate to response or desired plasma concentration	
Max Dosage	60mg/kg daily	

Prescribing Pearls

- Swallow ER and DR tablets whole; do not crush or chew.
- **Converting from DR to ER.** ER total daily dose is generally 8%–20% higher.
- When clinically indicated, obtain a trough total valproate concentration after sufficient time for dose to approach steady state (~72-96 hours post-dose adjustment) and after clinically-meaningful dose changes. Interpret valproate level in combination with clinical response, adverse effects, serum albumin, interacting medications, and formulation. Consider consulting psychiatry or pharmacy if needed.
  - *General trough level targets from trials.* ER: 85–125 mcg/mL | DR: 50–125 mcg/mL
- **Before treatment.** Obtain liver-function testing and CBC; assess bleeding/coagulation risk, pregnancy potential, concomitant rx, and relevant hepatic/metabolic hx.
- **During treatment.** Repeat liver testing frequently for first 6 mo and thereafter as indicated. Monitor CBC/platelets and coagulation periodically and when bleeding, bruising, surgery, pregnancy, or other clinical concerns arise.
- Check ammonia level for unexplained lethargy, vomiting, cognitive change, altered mental status, or hypothermia. Valproate-associated hyperammonemia can occur even in the setting of normal LFTs.

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Prescribing Pearls, Cont'd

- **Contraindications include** significant hepatic disease/dysfunction, POLG-related mitochondrial disorders, urea-cycle disorders, & hypersensitivity to valproate/divalproex.
- **Common side effects include** nausea, GI upset, somnolence, dizziness, tremor, increased appetite, weight gain, and alopecia.
- Monitor for sedation, tremor, thrombocytopenia/bleeding, metabolic, & GI symptoms.
- **Review major interactions**, including lamotrigine (valproate reduces clearance) and topiramate (increased risk of hyperammonemia/encephalopathy).

Safety

- **Pregnancy.** Do not prescribe to patients who are pregnant or likely to become pregnant unless alternative treatments failed to adequately control symptoms or are otherwise unacceptable. Pregnancy-capable patients should use contraception and receive regular counseling about reproductive risks/alternatives. In-utero valproate exposure can cause neural-tube defects, other congenital malformations, and lower IQ & increased risk of neurodevelopmental disorders. If exposure occurs, consider enrollment in the North American Antiepileptic Drug Pregnancy Registry.
- **Lactation.** Valproate concentration in human milk is relatively low. Published data show low infant serum exposure & have **not** demonstrated adverse effects from exposure through breast milk. Monitor infant for jaundice and unusual bruising/bleeding. Consider maternal need for treatment, benefits of breastfeeding, & infant's clinical status.
- Monitor for symptom worsening, unusual behavioral change, & suicidal thoughts.
- **Hepatotoxicity.** Potentially fatal hepatic failure can occur. Obtain baseline and frequent liver testing, particularly during the first 6 mo, and evaluate symptoms such as malaise, weakness, lethargy, facial edema, anorexia, or vomiting promptly.
- **Pancreatitis.** Life-threatening hemorrhagic pancreatitis has occurred early in treatment and after years of treatment. New significant abdominal pain, nausea, vomiting, or anorexia requires prompt evaluation. Discontinue valproate upon pancreatitis diagnosis.
- **Thrombocytopenia/bleeding.** Risk related to dose/concentration. Monitor CBC/platelets, coagulation.
- **Hyperammonemic encephalopathy.** Assess ammonia with otherwise unexplained lethargy, vomiting, mental-status change, or hypothermia.

Disclaimer. CHAMP guidance is a supplement to clinician decision-making. This sheet does not constitute medical care. The clinician is responsible for ensuring appropriate application of guidance in patient care.