# VALPROIC ACID (Depakene, Depakote, others) Fact Sheet [G]

**Bottom Line:**
Valproic acid is the go-to antimanic agent for acute manic episodes, featuring faster onset of response and better adverse effect profile compared to lithium, fewer drug interactions than carbamazepine, and efficacy for rapid cycling and relapse prevention.

**FDA Indications:**
**Bipolar disorder (acute mania);** migraine prophylaxis; seizures.

**Off-Label Uses:**
Bipolar maintenance; impulse control disorders; violence and aggression.

**Dosage Forms:**
- **Capsules (valproic acid, [G]):** 250 mg.
- **Oral liquid (Depakene, [G]):** 250 mg/5 mL.
- **Delayed-release tablets (Depakote, [G]):** 125 mg, 250 mg, 500 mg.
- **Delayed-release capsules (Depakote Sprinkles, [G]):** 125 mg.
- **ER tablets (Depakote ER, [G]):** 250 mg, 500 mg.

**Dosage Guidance:**
- Acute mania: Start 250–500 mg QHS; ↑ rapidly to effective dose (serum level 50–125 mcg/mL, target 1000–1500 mg/day); max 4000 mg/day, or 60 mg/kg.
- Depakote ER is generally better tolerated in terms of side effects. When converting from regular Depakote to Depakote ER, be aware that patients will get about 20% less valproic acid with the ER formulation.

**Monitoring:** Valproic acid level, LFTs, CBC for platelets, pregnancy test, ammonia if confusion.

**Cost:** $

**Side Effects:**
- Most common: Somnolence, nausea, fatigue, dizziness, hair loss, tremor, thrombocytopenia (up to 24% of patients; dose-related; reversible).
- Serious but rare: Hepatotoxicity—rare idiosyncratic reaction, not dose related; most cases occur within three months; risk factors: age <2 years, multiple anticonvulsants, and presence of neurologic disease in addition to epilepsy. Asymptomatic elevations of liver enzymes may occur, not necessarily associated with hepatic dysfunction. Pancreatitis (rare but potentially fatal). Polycystic ovary syndrome (PCOS) in about 10% of women. Hyperammonemia, encephalopathy (sometimes fatal) reported and may present with normal liver enzymes.
- Pregnancy/breastfeeding: Avoid in pregnancy (risk of neural tube defects); safe in breastfeeding.

**Mechanism, Pharmacokinetics, and Drug Interactions:**
- Sodium channel blocker.
- Metabolized primarily by liver with only minimal (10%) role of CYP450 enzymes (2A6, 2B6, 2C9); t ½: 9–16 hours.
- VPA causes ↑ levels of lamotrigine and risk for rash. Taking with topiramate can lead to encephalopathy.

**Clinical Pearls:**
- ER tablets have 10%–20% less fluctuation in serum concentration than delayed-release (DR) tablets. Divalproex sodium ER and DR tablets are *not* bioequivalent; increase total daily dose by 10%–20% if switching from DR to ER.
- ER formulation should be dosed QAM so that peak levels and sedation occur in the evening.
- Elevations of ammonia can often occur at normal doses and serum levels of VPA. Reducing dose when clinically appropriate typically reverses ammonia elevation. Treating with L-carnitine is also effective.
- Once steady state levels reached (within two to four days of initiation or dose adjustment), trough serum levels should be drawn just before once-daily ER dose in the morning (21–24 hours post-administration) and 12-hours post dose with IR formulation. Target levels between 50–125 mcg/mL.
- Several major malformations, most notably neural tube defects, have been clearly associated with first-trimester exposure to valproic acid. Educate and exercise caution in women of childbearing age.

**Fun Fact:**
Valproic acid was first synthesized in 1882 by B.S. Burton as an analogue of valeric acid, found naturally in valerian.