VALPROIC ACID (Depakote) Fact Sheet [G]

BOTTOM LINE:
Along with lithium, valproate is a first-line antimanic agent for acute manic episodes in kids. Avoid in patients with ovaries due to risk of PCOS as well as risk of congenital malformation; if used, ensure adequate contraception (ideally IUD or depot contraceptive).

PEDIATRIC FDA INDICATIONS:
Seizures.

ADULT FDA INDICATIONS:
Seizures; bipolar disorder (acute mania); migraine prophylaxis.

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.

PEDIATRIC DOSAGE GUIDANCE:
- Start 15 mg/kg/day divided BID–TID, increase by 5–10 mg/kg/day in weekly intervals; max 60 mg/kg/day. Typical dosing range in kids is 500–2000 mg/day divided BID–TID.
- When converting from regular Depakote to Depakote ER, be aware that patients will get about 20% less valproic acid with the ER formulation. ER better tolerated when dosed once daily in the morning.

MONITORING: LFTs, CBC for platelets, lipids, pregnancy test, weight, serum drug level, ammonia in patients with confusion, and amylase and lipase when pancreatitis is suspected.

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 genetically born females. Hyperammonemia, encephalopathy (sometimes fatal) reported and may present with normal liver enzymes.

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.

EVIDENCE AND CLINICAL PEARLS:
- Significantly more data in pediatric bipolar than other agents, with eight open-label studies (average response rate: 43%) and three double-blind studies, one of which did not separate from placebo.
- Once steady-state levels reached (within two to four days of initiation or dose adjustment), trough serum levels should be drawn just before the next dose (21–24 hours post-dose for ER/DR preparations) or before the morning dose (12 hours for immediate-release preparations). Target serum level: 50–125 mcg/mL.
- Valproate often reduces available carnitine, which is needed for cell transport physiology. This results in elevated ammonia levels, creating fatigue, confusion, and other symptoms of metabolic stress. Carnitine can be very safely replaced using a minimum twice-daily dosing of carnitine in 330 mg capsules (can be opened, but contents have a strong odor) and titrating up based on repeat laboratory studies.

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