VALPROIC ACID AND DERIVATIVES (DPX)

**Brands**
- Depakote, Depakote ER, Depakene, Depacon, Episenta, Epilim, Epival, Divalproex, Dicorate, Disorate, Divaa, Divalpro, Soval DX, Trend XR, Valna, Stavzor

**Generic?**
Yes, except for ER formulation

**Class**
- Antiepileptic drug (AED)

**Commonly Prescribed for**
(FDA approved in bold)
- Complex partial seizures (monotherapy and adjunctive)
- Simple and complex absence seizures (monotherapy and adjunctive)
- Adjunctive therapy for multiple seizure types, including absence seizures
- Migraine prophylaxis
- Acute mania in bipolar disorder
- Cluster headache
- Generalized tonic-clonic seizures, including juvenile myoclonic epilepsy
- Infantile spasms (West syndrome)
- Lennox-Gastaut syndrome
- Status epilepticus
- Post-hypoxic myoclonus
- Landau-Kleffner syndrome (acquired epileptic aphasia)
- Spinal muscular atrophy
- Acute migraine or status migrainosus
- Bipolar depression
- Schizophrenia/psychosis

**How the Drug Works**
Unknown but there are multiple mechanisms of action
- Activates glutamic acid decarboxylase to increase gamma-aminobutyric acid (GABA) production
- Inhibits GABA transaminase and the catabolism of GABA
- Sodium channel antagonist
- T-type calcium currents in thalamus
- May suppress NMDA excitatory neurotransmission

**How Long Until It Works**
- Seizures – 2 weeks
- Migraines – effective within a few weeks but can take up to 3 months to see full effect
- Mania – usually effective in days

**If It Works**
- Seizures – goal is the remission of seizures. Continue as long as effective and well-tolerated. Consider slowly tapering and stopping after 2 years seizure-free, depending on the type of epilepsy
- Migraine – goal is a 50% or greater reduction in migraine frequency or severity. Consider tapering or stopping if headaches remit for more than 6 months or if patient considering pregnancy

**If It Doesn’t Work**
- Increase to highest tolerated dose. Check a drug level if compliance an issue
- Epilepsy: consider changing to another agent, adding a second agent or referral for epilepsy surgery evaluation. When adding a second agent keep in mind the drug interactions
- Migraine: address other issues, such as medication-overuse, other coexisting medical disorders, such as anxiety, and consider changing to or adding a second agent

**Tests**
- Obtain liver function testing and platelet counts before starting, optional to monitor regularly for the first few months and once or twice a year after that. Test urgently if any symptoms of liver disease or new bleeding or easy bruising
- Monitor for weight gain and signs of metabolic syndrome (weight gain, hyperlipidemia, elevated fasting glucose)
Hyperammonemia may occur, even with normal liver function tests. Often asymptomatic. Check a level for any clinically significant symptoms.

**ADVERSE EFFECTS (AEs)**

**How Drug Causes AEs**

- CNS AEs may be caused by sodium or calcium channel effects or GABA effects
- DPX-associated hyperammonemia can cause delirium, tremor
- DPX-associated hepatic toxicity can cause nausea, anorexia, or jaundice

**Notable AEs**

- Sedation, tremor, dizziness, diplopia, blurred vision, cognitive problems
- Nausea, vomiting, abdominal pain, diarrhea, anorexia, constipation
- Weight gain, peripheral edema, bronchitis, pharyngitis, alopecia, carnitine depletion

**Life-Threatening or Dangerous AEs**

- Hepatotoxicity and liver disease, especially in children under 2 on multiple anti-epilepsy medications. More commonly patients have mild-moderate elevations of serum liver enzymes that are asymptomatic. Patients usually recover
- Rare pancreatitis can occur months to years after starting DPX. Most patients recover but can be fatal
- Thrombocytopenia
- Polycystic ovarian syndrome, including obesity, elevated androgen concentrations, anovulation, and hirsutism
- Significant weight gain and development of insulin resistance/metabolic syndrome (controversial)

**Weight Gain**

- Problematic
- Usually steady and associated with carbohydrate craving

**Sedation**

- Common
- May wear off with time

**What to Do About AEs**

- May be decreased with extended-release formulation
- Decrease dose
- Small elevations in liver enzymes or increased ammonia are common. If there are no symptoms, then the decision to decrease or maintain dose depends on the patient and the severity of the condition treated
- Change to another drug

**Best Augmenting Agents for AEs**

- Propranolol for tremor
- Weight gain may improve with augmentation or transition to Zonegran or topiramate
- Zinc and selenium can help alopecia

**DOSING AND USE**

**Usual Dosage Range**

- Epilepsy: 10–60 mg/kg/day, may need to increase in some patients
- Migraine: 1000 mg/day, some need a higher dose
- Cluster: 500–2000 mg/day
- Acute mania: Usually 1000 mg/day or more

**Dosage Forms**

- As valproic acid: 250 mg (Depakene) or 250 mg /5 mL syrup
- As divalproex sodium compound: 125 mg sprinkles or delayed release 125 mg, 250 mg, 500 mg, Depakote ER: 250 mg, 500 mg
- Valproate sodium solution for injection: 100 mg/mL in 5 mL vials

**How to Dose**

- Epilepsy: Start at 10–15 mg/kg/day and increase to goal dose
- Migraine: Start 250–500 qhs
- As valproic acid: tid; as delayed release divalproex sodium: bid. Depakote ER can be taken once daily
**Dosing Tips**

- Easier to rapidly increase dose than many other AEDs; IV Depacon available for emergency use to treat seizures, status migrainosis and mania
- When converting to Depakote ER, plasma levels are generally 10–20% lower than immediate release for a given dose
- Oral loading with 20–30 mg/kg per day is an alternative to IV loading
- Depakote ER has less GI AEs; avoids peak levels
- For most conditions levels 50–100 mcg/mL are effective, but in some cases higher levels are needed, i.e., cluster headache and mania

**Overdose**

- Stupor and coma, increased intracranial pressure. Fever. Respiratory insufficiency and supraventricular tachycardia. Supportive care and gastric lavage. Can be fatal

**Long-Term Use**

- Regular platelet counts and liver function testing. Optional unless patient symptomatic

**Habit Forming**

- No

**How to Stop**

- Taper slowly and keep drug interactions in mind
- Abrupt withdrawal can lead to seizures in patients with epilepsy
- Headaches may return within days to months of stopping

**Pharmacokinetics**

- Mainly hepatic metabolism. Metabolized in part by CYP450 system. Plasma half-life is 9–16 hours. 100% bioavailability and 93% protein bound

**Drug Interactions**

- DPX causes interactions by displacing other medications from plasma proteins and inhibiting hepatic metabolism. Drugs that affect the expression of hepatic enzymes such as glucuronosyltransferases can alter DPX clearance
- Increases levels of carbamazepine, lamotrigine, phenobarbital, and ethosuximide
- Increases free levels of phenytoin (which can cause toxicity even if serum levels are in a normal therapeutic range)
- DPX increases levels of warfarin, amitriptyline, nortriptyline, zidovudine, valium, cimetadine, chlorpromazine, erythromycin, and nimodipine
- Phenytoin, phenobarbital, primidone, cholestyramine, rifampin, and carbamazepine (hepatic inducers) can lower DPX levels
- Addition of salicylates, erythromycin, felbamate, and chlorpromazine can increase DPX levels

**Other Warnings/Precautions**

- CNS AEs increase when taken with other CNS depressants or with most acute or chronic illnesses
- Hepatotoxicity: nausea, vomiting, jaundice, edema
- Pancreatitis: abdominal pain, anorexia, nausea
- Teratogenic effects: neural tube defects
- Urea cycle disorders: unexplained delirium in children, mental retardation, vomiting, lethargy and hyperammonemia

**Do Not Use**

- Patients with a proven allergy to DPX. Also contraindicated in patients with thrombocytopenia, liver disease, urea cycle disorders, and pancreatitis

**SPECIAL POPULATIONS**

**Renal Impairment**

- No known effects. Highly protein bound, easier to use in patients on dialysis than most other AEDs

**Hepatic Impairment**

- Do not use

**Cardiac Impairment**

- No known effects
**Valproic Acid and Derivatives (DPX)** (continued)

**Elderly**
- Use a lower dose and watch for AEs and nutritional intake

**Children and Adolescents**
- Approved for use in children and often used in generalized seizures, such as absence and juvenile myoclonic epilepsy
- May help treat infantile spasms related to tuberous sclerosis, especially if ACTH is ineffective or cannot be used
- For infants with new-onset unexplained seizures, metabolic diseases are not rare. Consider using an alternative agent until ruled out

**Pregnancy**
- Risk category D. Increased risk of neural tube defects, cardiac defects, craniofacial abnormalities, and hepatic failure
- Women who continue taking DPX during pregnancy should be considered high-risk and take folate
- If a patient continues taking during pregnancy, consider vitamin K during the last 6 weeks of pregnancy to reduce risk of bleeding
- Patients taking DPX for conditions other than epilepsy should generally stop DPX before considering pregnancy. Migraine usually improves in the last 2 trimesters

**Breast Feeding**
- Relatively low (3%) in breast milk and safer than most other AEDs
- Monitor infant for sedation, poor feeding or irritability

**Potential Advantages**
- Highly effective for multiple types of epilepsy due to broad spectrum of action. Treats generalized seizures as well as partial and is approved as monotherapy. Effective for both migraine and cluster headache. Useful for patients with more than one condition, such as migraine and epilepsy or mania

**Potential Disadvantages**
- Weight gain. Tremor. Risk of polycystic ovarian syndrome and teratogenicity

**Primary Target Symptoms**
- Seizure frequency and severity
- Headache frequency and severity

**Pregnancy**
- Drug of choice for patients with generalized epilepsies, however may not be as effective as carbamazepine for focal seizures
- Useful in status epilepticus for patients with contraindications to phenytoin. Loading dose 20–30 mg/kg. Less respiratory depression than other AEDs
- Highly effective for migraine and cluster prophylaxis. For cluster, DPX is more likely to be effective at the upper end of the therapeutic range
- May be useful as an acute headache treatment in the emergency room or infusion setting as IV Depacon. (300–1000 mg as rapid infusion.) For use as a preventive drug after discharge, you can load the medication (15 mg/kg) and then administer 5 mg/kg every 8–12 hours. IV Depacon for acute headache is especially useful for patients who cannot tolerate or have contraindications to other medications
- As a headache prophylactic agent for patients in the emergency room, consider giving an intravenous treatment followed by an initial dose of 1000 mg/day
- For migraine patients on DPX with tremor and suboptimal headache control, propranolol may improve headaches and treat tremor
- DPX may have neuroprotective properties, such as inhibition of apoptosis and slowing of neurofibrillary tangle formation, suggesting usefulness for treatment of neurodegenerative diseases. However, studies for treatment of Alzheimer’s dementia and associated psychosis have been largely negative, with poor tolerability in this population
- Preliminary studies suggest utility in treating spinal muscular atrophy, especially in young children

**Pearls**
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Suggested Reading


