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concentrations of therapeutically effective free valproate increase at serum concentrations above 50 to 100 µg/mL. The unbound portion of valproate is considered to be pharmacologically active and can cross the blood–brain barrier. The extendedrelease preparation produces lower peak

concentrations and higher minimum concentrations and can be given once a day. Valproate is metabolized primarily by hepatic glucuronidation and mitochondrial β oxidation. The biochemical basis of valproate's therapeutic effects remains poorly understood. Postulated mechanisms include enhancement of GABA activity, modulation of voltagesensitive sodium channels, and action on extrahypothalamic neuropeptides. THERAPEUTIC INDICATIONS Valproate is currently approved as monotherapy or adjunctive therapy of complex partial seizures, monotherapy and adjunctive therapy of simple and complex absence seizures, and adjunctive therapy for patients with multiple seizures that include absence seizures. Divalproex has additional indications for prophylaxis of migraine. Bipolar I Disorder Acute Mania. About two-thirds of persons with acute mania respond to valproate. The majority of patients with mania usually respond within 1 to 4 days after achieving valproate serum concentrations above 50 μg/mL. Antimanic response is generally associated with levels greater than 50 μg/mL, in a range of 50 to 150 μg/mL. Using gradual dosing strategies, this serum concentration may be achieved within 1 week of initiation of dosing, but rapid oral loading strategies achieve therapeutic serum concentrations in 1 day and can control manic symptoms within 5 days. The short-term antimanic effects of valproate can be augmented with addition of lithium, carbamazepine (Tegretol), SDAs, or DRAs. Numerous studies have suggested that the irritable manic subtype respond significantly better to divalproex than lithium or placebo. Because of its more favorable profile of cognitive, dermatologic, thyroid, and renal adverse effects, valproate is preferred to lithium for treatment of acute mania in children and elderly persons. Acute Bipolar Depression. Valproate possesses some activity as a short-term treatment of depressive episodes in bipolar I disorder, but this effect is far less pronounced than for treatment of manic episodes. Among depressive symptoms, valproate is more effective for treatment of agitation than dysphoria. In clinical practice, valproate is most often used as add-on therapy to an antidepressant to prevent the development of mania or rapid cycling. Prophylaxis. Studies suggest that valproate is effective in the prophylactic treatment of bipolar I disorder, resulting in fewer, less severe, and shorter manic episodes. In direct comparison, valproate is at least as effective as lithium and is better tolerated than lithium. It may be particularly effective in persons with rapid-cycling and

ultrarapid-cycling bipolar disorders, dysphoric or mixed mania, and mania caused by a general medical condition as well as in persons who have comorbid substance abuse or panic attacks and in persons who have not had complete favorable responses to lithium treatment. Schizophrenia and Schizoaffective Disorder Valproate may accelerate response to antipsychotic therapy in patients with schizophrenia or schizoaffective disorder. Valproate alone is generally less effective in schizoaffective disorder than in bipolar I disorder. Valproate alone is ineffective for treatment of psychotic symptoms and is typically used in combination with other drugs in patients with these symptoms. Other Mental Disorders Valproate has been studied for possible efficacy in a broad range of psychiatric disorders. These include alcohol withdrawal and relapse prevention, panic disorder, PTSD, impulse control disorder, borderline personality disorder, and behavioral agitation and dementia. Evidence supporting use in these cases is weak, and any observed therapeutic effects may be related to treatment of comorbid bipolar disorder. PRECAUTIONS AND ADVERSE REACTIONS Although valproate treatment is generally well tolerated and safe, it carries quite a few black box warnings and other warnings (Table 29.33-1). The two most serious adverse effects of valproate treatment affect the pancreas and liver. Risk factors for potentially fatal hepatotoxicity include young age (younger than 3 years); concurrent use of phenobarbital; and the presence of neurologic disorders, especially inborn errors of metabolism. The rate of fatal hepatotoxicity in persons who have been treated with only valproate is 0.85 per 100,000 persons; no persons older

than the age of 10 years have been reported to have died from hepatotoxicity. Therefore, the risk of this adverse reaction in adult psychiatric patients is low. Nevertheless, if symptoms of lethargy, malaise, anorexia, nausea and vomiting, edema, and abdominal pain occur in a person treated with valproate, the clinician must consider the possibility of severe hepatotoxicity. A modest increase in liver function test results does not correlate with the development of serious hepatotoxicity. Rare cases of pancreatitis have been reported; they occur most often in the first 6 months of treatment, and the condition occasionally results in death. Pancreatic function can be assessed and followed with serum amylase concentrations. Other potentially serious consequences of treatment include hyperammonemia-induced encephalopathy and thrombocytopenia. Thrombocytopenia and platelet dysfunction occur most commonly at high dosages and result in the prolongation of bleeding times. Table 29.33-1

Black Box Warnings and Other Warnings for Valproate There are multiple concerns regarding the use of valproate during pregnancy. Women who require valproate therapy should therefore inform their physicians if they intend to become pregnant. First trimester use of valproate has been associated with a 3 to 5 percent risk of neural tube defects, as well as an increased risk of other malformations affecting the heart and other organ systems. Multiple reports have also indicated that in utero exposure to valproate may negatively affect cognitive development in children of mothers who take valproate during pregnancy. They have lower IQ scores at age 6 years compared with those exposed to other antiepileptic drugs. Fetal valproate exposure has dose-dependent associations with reduced cognitive abilities across a range of domains at 6 years of age. Valproate exposure may also increase the risk of autistic spectrum disorder. Valproate is also associated with teratogenicity, most notably neural tube defects (e.g., spina bifida). The risk is about 1 to 4 percent of all women who take valproate during the first trimester of pregnancy. The risk of valproate-induced neural tube defects can be reduced with daily folic acid supplements (1 to 4 mg a day). All women with childbearing potential who take the drug should be given folic acid supplements. Infants breastfed by mothers taking valproate develop serum valproate concentrations 1 to 10

percent of maternal serum concentrations, but no data suggest that this poses a risk to the infant. Valproate is not contraindicated in nursing mothers. Clinicians should not administer the drug to persons with hepatic diseases. Valproate may be especially problematic for adolescent and young women. Cases of polycystic ovarian disease have been reported in women using valproate. Even when the full syndromal criteria for this syndrome are not met, many of these women develop menstrual irregularities, hair loss, and hirsutism. These effects are thought to result from a metabolic syndrome that is driven by insulin resistance and hyperinsulinemia. The common adverse effects associated with valproate (Table 29.33-2) are those affecting the GI system, such as nausea, vomiting, dyspepsia, and diarrhea. The GI effects are generally most common in the first month of treatment, particularly if the dosage is increased rapidly. Unbuffered valproic acid (Depakene) is more likely to cause GI symptoms than the enteric-coated “sprinkle” or the delayed-release divalproex sodium formulations. Other common adverse effects involve the nervous system, such as sedation, ataxia, dysarthria, and tremor. Valproate-induced tremor may respond well to treatment with β-adrenergic receptor antagonists or gabapentin. Treatment of the other neurologic adverse effects usually requires lowering the valproate dosage. Table 29.33-2 Adverse Effects of Valproate Weight gain is a common adverse effect, especially in long-term treatment, and can best be treated by strict limitation of caloric intake. Hair loss may occur in 5 to 10 percent of all persons treated, and rare cases of complete loss of body hair have been reported. Some

clinicians have recommended treatment of valproate-associated hair loss

with vitamin supplements that contain zinc and selenium. About 5 to 40 percent of persons experience a persistent but clinically insignificant elevation in liver transaminases up to three times the upper limit of normal, which is usually asymptomatic and resolves after discontinuation of the drug. High dosages of valproate (above 1,000 mg a day) may rarely produce mild to moderate hyponatremia, most likely because of some degree of the syndrome of secretion of inappropriate antidiuretic hormone, which is reversible upon lowering of the dosage. Overdoses of valproate can lead to coma and death. DRUG INTERACTIONS Valproate is commonly prescribed as part of a regimen involving other psychotropic agents. The only consistent drug interaction with lithium, if both drugs are maintained in their respective therapeutic ranges, is the exacerbation of drug-induced tremors, which can usually be treated with β-receptor antagonists. The combination of valproate and DRAs may result in increased sedation, as can be seen when valproate is added to any CNS depressant (e.g., alcohol), and an increased severity of extrapyramidal symptoms, which usually responds to treatment with antiparkinsonian drugs. Valproate can usually be safely combined with carbamazepine or SDAs. Perhaps the most worrisome interaction of valproate and a psychotropic drug involves lamotrigine. Since the approval of lamotrigine for the treatment of bipolar disorder, the likelihood that patients will be treated with both agents has increased. Valproate more than doubles lamotrigine concentrations, increasing the risk of a serious rash (Stevens-Johnson syndrome, and toxic epidermal necrolysis). The plasma concentrations of carbamazepine, diazepam (Valium), amitriptyline (Elavil), nortriptyline (Pamelor), and phenobarbital (Luminal) may also be increased when these drugs are coadministered with valproate, and the plasma concentrations of phenytoin (Dilantin) and desipramine (Norpramin) may be decreased when they are combined with valproate. The plasma concentrations of valproate may be decreased when the drug is coadministered with carbamazepine and may be increased when coadministered with guanfacine (Tenex), amitriptyline, or fluoxetine (Prozac). Valproate can be displaced from plasma proteins by carbamazepine, diazepam, and aspirin. Persons who are treated with anticoagulants (e.g., aspirin and warfarin [Coumadin]) should also be monitored when valproate use is initiated to assess the development of any undesired augmentation of the anticoagulation effects. Interactions of valproate with other drugs are listed in Table 29.33-3. Table 29.33-3 Interactions of Valproate with Other Drugs

LABORATORY INTERFERENCES Valproate may cause laboratory increase of serum-free fatty acids. Valproate metabolites may produce a false-positive test result for urinary ketones as well as falsely abnormal thyroid function test results. DOSAGE AND CLINICAL GUIDELINES When starting valproate therapy, a baseline hepatic panel, CBC and platelet counts, and pregnancy testing should be ordered. Additional testing should include amylase and coagulation studies if baseline pancreatic disease or coagulopathy is suspected. In addition to baseline laboratory tests, hepatic transaminase concentrations should be obtained 1 month after initiation of therapy and every 6 to 24 months thereafter. However, because even frequent monitoring may not predict serious organ toxicity, it is more prudent to reinforce the need for prompt evaluation of any illnesses when reviewing the instructions with patients. Asymptomatic elevation of transaminase concentrations up to three times the upper limit of normal are common and do not require any change in dosage. Table 29.33-4 lists the recommended laboratory tests for valproate treatment. Table 29.33-4 Recommended Laboratory Tests During Valproate Therapy

Valproate is available in a number of formulations (Table 29.33-5). For treatment of acute mania, an oral loading strategy of initiation with 20 to 30 mg/kg a day can be used to accelerate control of symptoms. This is usually well tolerated but can cause excessive sedation and tremor in elderly persons. Agitated behavior can be rapidly stabilized with IV infusion of valproate. If acute mania is absent, it is best to initiate drug treatment gradually to minimize the common adverse effects of nausea, vomiting, and sedation. The dose on the first day should be 250 mg administered with a meal. The dosage can be raised up to 250 mg orally three times daily over the course of 3 to 6 days. The plasma concentrations can be assessed in the morning before the first daily dose is administered. Therapeutic plasma concentrations for the control of seizures range between 50 and 150 µg/mL, but concentrations up to 200 µg/mL are usually well tolerated. It is reasonable to use the same range for the treatment of mental disorders; most of the controlled studies have used 50 to 125 µg/mL. Most persons attain therapeutic plasma concentrations on a dosage between 1,200 and 1,500 mg a day in divided doses. After a person's symptoms are well controlled, the full daily dose can be taken all at once before sleep. Table 29.33-5 Valproate Preparations Available in the United States REFERENCES Atmaca M, Ozdemir H, Cetinkaya S, Parmaksiz S, Poyraz AK. Cingulate gyrus volumetry in drug free bipolar patients and patients treated with valproate or valproate and quetiapine. J Psychiatr Res. 2007;41:821.

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Revision #1
Created 2026-01-04 19:51:53 UTC by Omar Ayman
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