although differences in certain animal models have been observed and additive effects appear to occur when the drug is combined with these anticonvulsants.

Although the precise mechanism of action of topiramate is unknown, data from electrophysiologic and biochemical studies have revealed 4 properties that may contribute to the drug's efficacy for seizure disorders and migraine prophylaxis. At pharmacologically relevant concentrations, topiramate blocks voltage-dependent sodium channels; augments the activity of γ-aminobutyric acid (GABA) at some subtypes of the GABA-A receptor; antagonizes the AMPA/kainate subtype of the glutamate receptor; and inhibits carbonic anhydrase (particularly CA-II and CA-IV isoenzymes). In general, anticonvulsant drugs are thought to act by one or more of the following mechanisms: modulating voltage-dependent ion (e.g., sodium) channels involved in action potential propagation or burst generation, enhancement of GABA inhibitory activity, and/or inhibition of excitatory amino acid neurotransmitter (e.g., glutamate, aspartate) activity.

Topiramate exhibits effects on cultured neurons similar to those observed with phenytoin and carbamazepine, and such effects are suggestive of an inactive state-dependent block of voltage-dependent sodium channels. Topiramate reduces the duration of epileptiform bursts of neuronal firing and decreases the number of action potentials in studies of cultured rat hippocampal neurons with spontaneous epileptiform burst activity. Topiramate also decreases the frequency of action potentials elicited by depolarizing electric current in cultured rat hippocampal neurons. Depolarization and firing of an action potential results from the rapid inflow of sodium ions through voltage-dependent sodium channels in the neuronal cell membrane. After firing, a neuron enters a period of inactivation during which it is unable to fire again even if the sodium channel is open. A slow action potential firing rate allows the neuron sufficient time to recover from inactivation, and the normal period of inactivation has a minimal effect on low-frequency firing. During a partial seizure, neurons characteristically undergo high-frequency depolarization and firing of action potentials which is uncommon during normal physiologic neuronal activity. Some anticonvulsant drugs (e.g., phenytoin, carbamazepine) preferentially bind to voltage-dependent sodium channels during their inactivated state, slow the rate of recovery of sodium channels from their period of inactivation, and limit the ability of the neuron to depolarize and fire at high frequencies.

Topiramate enhances the activity of the inhibitory neurotransmitter GABA at a nonbenzodiazepine site on $GABA_A$ receptors. Activation of the postsynaptic $GABA_A$ receptor by GABA causes inhibition by increasing the inward flow of chloride ions, resulting in hyperpolarization of the postsynaptic cell; in chloride ion-depleted murine cerebellar granule cells, therapeutic concentrations of topiramate (in combination with GABA) enhance GABA-evoked inward flux of chloride ions in a concentration-dependent manner. Benzodiazepines act at $GABA_A$ receptors to enhance GABA-evoked inward flow of chloride ions, but the benzodiazepine antagonist flumazenil does not appear to inhibit topiramate enhancement of GABA-evoked currents in $GABA_A$ cortical neuronal receptors. Topiramate also does not appear to increase duration of chloride ion channel opening. Therefore, topiramate may potentiate $GABA_A$-evoked chloride ion flux by a mechanism other than $GABA_A$-receptor modulation.

Topiramate antagonizes a non-*N*-methyl-d-aspartate (NMDA) glutamate receptor and the kainate/α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor subtype. Although topiramate had no apparent effect on glutamate receptors of the NMDA subtype in cultured rat hippocampal neurons, topiramate antagonized the ability of kainate to activate the kainate/AMPA glutamate receptor subtype, and these effects were shown to be concentration dependent. Glutamate, the principal excitatory neurotransmitter amino acid in the brain, interacts with specific neuronal membrane receptors, including ion channel coupled (ionotropic) (e.g., NMDA, kainate/AMPA, kainate) receptor subtypes and with G-protein coupled (metabotropic) receptors that modulate intracellular second-messengers. Glutamate is responsible for a variety of neurologic functions, including cognition, memory, movement, and sensation, and excessive activation of glutamate receptors may mediate injury or destruction of neurons in some acute neurologic disorders and chronic neurodegenerative diseases. The pathogenesis of seizures is thought to be mediated at least in part through excessive stimulation of glutamate receptors. In spontaneously epileptic rats, topiramate has reduced extracellular hippocampal concentrations of both glutamate and aspartate, and a correlation existed between reduction in glutamate concentrations and suppression of tonic seizures.

In animals, topiramate exhibits anticonvulsant activity in the maximal electroshock seizure (MES) test, suggesting that, like phenytoin, it may be effective in the management of partial and tonic-clonic (grand mal) seizures in humans. Topiramate also exhibited dose-dependent inhibition of absence-like seizures, which was antagonized by pretreatment with haloperidol. In animals, topiramate was ineffective or weakly effective in blocking clonic seizures induced by pentylenetetrazole, indicating that the drug may not enhance GABA inhibitory activity substantially.

Although the precise mechanism(s) of action of topiramate in the management of alcohol dependence is unclear, topiramate enhances GABA-mediated inhibitory neurotransmission and inhibits glutamatergic stimulatory neurotransmission; such changes appear to decrease dopaminergic activity in the mesocorticolimbic areas of the brain, which have been associated with alcohol dependence.

Topiramate inhibits carbonic anhydrase CA-II and CA-IV isoenzymes and, like other carbonic anhydrase inhibitors (e.g., acetazolamide, dichlorphenamide), the drug may promote the formation of renal calculi by increasing urinary pH and decreasing the excretion of urinary citrates. In premarketing studies, renal calculi were reported to occur in 1.5% of patients receiving topiramate, an incidence 2–4 times that expected in a similar untreated population, but most patients who developed calculi elected to continue therapy with the drug. Use of topiramate with other carbonic anhydrase inhibitors may increase the risk of renal calculi and therefore should be avoided.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Topiramate

Oral		
Capsules	15 mg	**Topamax® Sprinkle, Ortho-McNeil**
	25 mg	**Topamax® Sprinkle, Ortho-McNeil**
Tablets, film-coated	25 mg	**Topamax®, Ortho-McNeil**
	50 mg	**Topamax®, Ortho-McNeil**
	100 mg	**Topamax®, Ortho-McNeil**
	200 mg	**Topamax®, Ortho-McNeil**

†Use is not currently included in the labeling approved by the US Food and Drug Administration.

Valproate Sodium — Sodium Dipropylacetate, Sodium α-Propylvalerate, DPA Sodium
Valproic Acid — Dipropylacetic Acid, 2-Propylvaleric Acid, DPA
Divalproex Sodium — Valproate Semisodium

■ Valproic acid, valproate sodium, and divalproex sodium are carboxylic acid-derivative anticonvulsants that also are used to treat acute manic episodes or for prophylaxis of migraine headache as well as certain other psychiatric disorders.

Uses

■ **Seizure Disorders** Valproic acid, valproate sodium, or divalproex sodium is used alone or with other anticonvulsants (e.g., ethosuximide) in the prophylactic management of simple and complex absence (petit mal) seizures. The drugs also may be used in conjunction with other anticonvulsants in the management of multiple seizure types that include absence seizures. Valproic acid is considered a drug of choice for absence or atypical absence seizures.

Valproic acid, valproate sodium, or divalproex sodium is used alone or with other anticonvulsants (e.g., carbamazepine, phenytoin) in the prophylactic management of complex partial seizures that occur either by themselves or in association with other seizure types. Some clinicians state that valproic acid may be considered a drug of choice for the management of complex partial seizures. Two randomized, placebo-controlled trials, one of valproic acid as monotherapy and one of valproic acid as adjunctive therapy, demonstrated that the drug decreased the frequency of seizures in patients inadequately controlled by other therapies (e.g., carbamazepine, phenytoin, phenobarbital).

Valproic acid has been used and is considered by some clinicians as a drug of choice for management of other generalized seizures, including primary generalized tonic-clonic seizures†, atypical absence†, myoclonic†, or atonic seizures†, especially for those patients with more than one type of generalized seizure. In addition, some clinicians state that valproic acid may be used as a drug of choice for the management of simple partial seizures†. Valproic acid also has been administered rectally† or by intragastric drip† with some success in the management of status epilepticus refractory to IV diazepam†. A parenteral formulation of valproic acid has been studied and has been effective when administered IV† in the management of status epilepticus.

Valproic acid has been used with some success in the treatment of Lennox-Gastaut syndrome and infantile spasms.

■ **Bipolar Disorder** Divalproex sodium is used in the treatment of manic episodes associated with bipolar disorder; valproic acid† and valproate sodium† also have been used. Because there are only minor differences in the pharmacokinetics of the formulations, and because all forms of the drug circulate in plasma as valproic acid, the term "valproic acid" will be used in the following discussion.

Valproic acid has been used as monotherapy or as part of combination therapy (e.g., with lithium, antipsychotic agents [e.g., olanzapine], antidepressants, carbamazepine) in the treatment of acute manic episodes. The American Psychiatric Association (APA) currently recommends combined therapy with valproic acid plus an antipsychotic agent or with lithium plus an antipsychotic agent as first-line drug therapy for the acute treatment of more severe manic or mixed episodes and monotherapy with one of these drugs for less severe episodes. For mixed episodes, valproic acid may be preferred over lithium. Valproic acid or lithium also is recommended for the initial acute treatment of rapid cycling.

A manic episode is a distinct period of abnormally and persistently elevated, expansive, or irritable mood. Typical symptoms include pressure of speech, motor hyperactivity, reduced need for sleep, flight of ideas, grandiosity, poor judgment, aggressiveness, and possible hostility. Efficacy of valproic acid in

the treatment of manic episodes was established in short-term, placebo-controlled, parallel-group trials in patients hospitalized with bipolar disorder, manic (DSM-IIIR); response to therapy was assessed using objective rating scales such as the Young Mania Rating Scale (YMRS), an augmented Brief Psychiatric Rating Scale (BPRS-A), the Mania Rating Scale (MRS), and the Global Assessment Scale (GAS). One study specifically enrolled patients who were intolerant of or unresponsive to previous lithium therapy. Up to 40% of patients fail to respond to or are intolerant of lithium therapy for manic episodes; such patients may demonstrate a response to valproic acid, although response to valproic acid appears to be independent of prior response to lithium therapy. Valproic acid therapy appears to be about as effective as lithium for the treatment of manic episodes. In one placebo-controlled trial, 48% of patients receiving valproic acid demonstrated a response to the drug as measured by changes in the Manic Syndrome subscale of the MRS; 49% of patients receiving lithium responded to therapy, while 25% of patients receiving placebo responded. Antimanic response to valproic acid typically occurs within 1–2 weeks of initiating therapy. Valproic acid therapy also appears to be effective in specific types of mania, including rapid-cycling mania and dysphoric mania, which have been reported to be poorly responsive to lithium.

Although the manufacturer states that safety and efficacy of long-term (i.e., longer than 3 weeks) valproic acid therapy have not been established in the treatment of manic episodes, valproic acid also has been used, alone or in combination therapy, for long-term or maintenance antimanic therapy†, and APA currently considers the best empiric evidence to support the use of valproic acid or lithium for maintenance therapy. Antimanic efficacy has been maintained from several months to more than 10 years, and such long-term therapy appears to decrease the frequency and severity of bipolar episodes over extended periods of time; however, further study is required to establish the efficacy of valproic acid as maintenance therapy of manic episodes. Valproic acid does not appear to be as effective for the management of the depressive component of bipolar disorder†; although some evidence suggests that long-term valproic acid therapy may be moderately effective in the prophylaxis of depressive episodes, its acute effects on depression appear to be limited. Some clinicians recommend that valproic acid therapy be used in patients with bipolar disorder or schizoaffective disorder, bipolar type, who have responded inadequately to or have been unable to tolerate treatment with lithium salts or other therapy (e.g., carbamazepine), particularly if the patient displays residual manic symptoms, or in the presence of rapid cycling, dysphoric mania or hypomania, associated neurologic abnormalities, or organic brain disorder.

■ **Migraine** ***Prophylaxis of Chronic Attacks*** Divalproex sodium is used in the prophylaxis of migraine headache, with or without associated aura; valproic acid† and sodium valproate† also have been used. Because there are only minor differences in the pharmacokinetics of the formulations, and because all forms of the drug circulate in plasma as valproic acid, the term "valproic acid" will be used in the following discussion. Because valproic acid may pose a hazard to the fetus (see Cautions: Pregnancy, Fertility, and Lactation), it should be considered for women of childbearing potential only after this risk has been discussed thoroughly with the patient and weighed against the potential benefits of treatment. Some clinicians state that effective contraception during valproic acid therapy should be strongly encouraged.

The US Headache Consortium states that there is good evidence from multiple well-designed clinical trials that valproic acid has medium to high efficacy for the prophylaxis of migraine headache. Valproic acid was demonstrated to be effective in the prophylaxis of migraine headache in 2 randomized, double-blind, placebo-controlled trials in patients with at least a 6-month history of migraine, with or without associated aura. Patients also had to experience at least 2 migraines per month in the 3 months prior to enrollment in the studies; patients were excluded if they had cluster headaches. Although women of childbearing potential were excluded from one study because of the teratogenic properties of valproic acid, they were included in the other, provided that they were practicing an effective form of contraception. In both studies, after a 4-week single-blind placebo baseline period, patients were randomized to receive either valproic acid or placebo during a 12-week treatment period consisting of a 4-week titration period and an 8-week maintenance period. Assessment of treatment outcome was based on 4-week migraine headache rates during the 12-week treatment period. In the first study, dosage titration was guided by the use of actual or sham trough total serum valproate concentrations for patients receiving valproic acid or placebo, respectively. The mean dosage of valproic acid was 1087 mg daily (range: 500–2500 mg daily), with dosages of more than 500 mg being given in 3 divided doses daily. Patients receiving valproic acid experienced a substantial decrease in the mean 4-week migraine headache rate compared with those receiving placebo (3.5 versus 5.7, respectively). In the second study, patients were randomized to receive (after titration from an initial dosage of 250 mg daily) 500, 1000, or 1500 mg of valproic acid daily or placebo, administered as 2 daily doses. Efficacy of valproic acid in the second study was to be determined by comparing the 4-week migraine headache rate in the combined groups of patients receiving 1000 and 1500 mg of valproic acid to that of patients receiving placebo. However, the manufacturer reports that the mean 4-week migraine headache rates in patients receiving valproic acid 500, 1000, or 1500 mg daily were 3.3, 3, or 3.3, respectively, compared to a rate of 4.5 in patients receiving placebo, and that the rate in the combined groups of patients receiving 1000 or 1500 mg daily was substantially lower than that of the placebo group.

In addition, valproic acid (given once daily as an extended-release tablet) was demonstrated to be effective in the prophylaxis of migraine headache in a 12-week, multicenter, double-blind, placebo-controlled clinical trial in patients with a history of migraine headaches with or without associated aura.

Other studies also have shown valproic acid to be effective in the prophylaxis of migraine. In one comparative single-blind, placebo-controlled, crossover study, valproic acid was shown to be as effective in migraine prophylaxis as propranolol.

Acute Attacks IV† valproate sodium has been used for the acute† management of migraine headache; however, the role of the drug relative to other acute therapies (selective serotonin type 1-like receptor agonists ["triptans"], ergot alkaloids, antiemetics, nonsteroidal anti-inflammatory agents [NSAIAs], butalbital-containing analgesics, opiate analgesics) requires further elucidation. Results of several studies, including open-label, comparative, randomized, prospective, retrospective, and/or double-blind, studies and at least one placebo-controlled study, as well as case reports, indicate that IV valproate sodium may alleviate acute migraine attacks in patients with or without aura and generally appears to be well tolerated. Efficacy generally was evaluated in terms of a reduction in headache severity as rated by the patient (i.e., a reduction in pain from severe or moderately severe to mild or absent usually using a 3- or 4-point scale) or by a visual analog pain score (VAS). Limited data indicate that 300-mg to 1-g IV valproate sodium doses (some of which were repeated at the same initial dose or less) were associated with relief of migraine headache, usually within 1 to several hours.

IV valproate sodium also has been used in the management of chronic daily headache† in a limited number of patients some of whom have had an inadequate response to dihydroergotamine or when dihydroergotamine was contraindicated.

Further study and experience are needed to more clearly define the role of IV valproate sodium in the management of acute migraine attacks and other headaches.

For further information on management and classification of migraine headache, see Vascular Headaches: General Principles in Migraine Therapy, under Uses, in Sumatriptan 28:32.28.

■ **Schizophrenia** Valproic acid or divalproex sodium has been used as an adjunct to antipsychotic agents in the symptomatic management of schizophrenia† in patients who fail to respond sufficiently to an adequate trial of an antipsychotic agent alone. The American Psychiatric Association (APA) and some clinicians state that anticonvulsant agents such as valproic acid or divalproex sodium may be useful adjuncts in schizophrenic patients with prominent mood lability or with agitated, aggressive, hostile, or violent behavior. In general, for such adjunctive therapy, valproic acid or divalproex sodium is administered in the same dosage and with the same resulting therapeutic plasma concentrations as that in the management of seizure disorders. The APA states that, with the exception of patients with schizophrenia whose illness has strong affective components, valproic acid or divalproex sodium alone has not been shown to be substantially effective in the long-term treatment of schizophrenia.

While some evidence suggested potential benefit of valproic acid in relieving tardive dyskinesia in patients receiving long-term antipsychotic drug therapy†, recent systematic review of randomized controlled trials with nonbenzodiazepine γ-aminobutyric acid (GABA) agonists such as valproic acid found the evidence for such benefit unconvincing, and indicated that any possible benefit may be outweighed by adverse effects. For additional information on the management of schizophrenia, see Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

■ **Other Uses** Some experts recommend use of valproic acid for the treatment of aggressive outbursts in children with ADHD. For a more detailed discussion on the management of ADHD, see Uses: Attention Deficit Hyperactivity Disorder, in Methylphenidate 28:20.04.

Valproic acid used alone or in conjunction with GABA was ineffective in the treatment of chorea† (including Huntington's chorea). Valproic acid has been effective in a limited number of patients with organic brain syndrome†.

Dosage and Administration

■ **Administration** Valproate sodium can be administered orally or by IV infusion and valproic acid and divalproex sodium are administered orally. Valproic acid also has been administered rectally by enema or in wax-based suppositories.

Patients who are currently receiving or beginning therapy with valproic acid, valproate sodium, or divalproex sodium and/or any other anticonvulsant for any indication should be closely monitored for the emergence or worsening of depression, suicidal thoughts or behavior (suicidality), and/or any unusual changes in mood or behavior. (See Cautions: Nervous System Effects and Cautions: Precautions and Contraindications.)

Oral Administration Valproic acid, valproate sodium, and divalproex sodium are administered orally. Valproic acid capsules should be swallowed whole; not chewed, in order to prevent local irritation to the mouth and throat. If GI irritation occurs, the drug may be administered with food. Patients who are unable to tolerate the GI effects of valproic acid or valproate sodium may tolerate divalproex sodium. When switching to divalproex sodium delayed-release tablets in patients receiving valproic acid, the same daily dose and schedule should be used. After stabilization with divalproex sodium therapy, the daily dose may be divided and administered 2 or 3 times daily in selected patients. Extended-release tablets of divalproex sodium are administered once daily; patients should be advised that the extended-release tablets must be swallowed intact and not chewed or crushed. Valproate sodium oral solution should not be administered in carbonated drinks because valproic acid will be liberated and may cause local irritation to the mouth and throat as well as an unpleasant taste.

The commercially available capsules containing coated particles of divalproex sodium (Depakote®) may be swallowed intact or the entire contents of

the capsule(s) may be sprinkled on a small amount (about 5 mL) of semisolid food (e.g., applesauce, pudding) immediately prior to administration. The mixture containing coated particles from the capsules should not be chewed. The mixture of coated particles and semisolid food should not be stored for future use. Patients receiving divalproex sodium capsules containing coated particles should be instructed not to be concerned if they notice coated particles in their stool, because these particles do not completely dissolve and may be passed in the stool.

The manufacturer states that although the extent of GI absorption of valproic acid from capsules containing coated particles or delayed-release tablets of divalproex sodium is equivalent, peak and trough plasma concentrations achieved with these dosage forms may vary (e.g., higher peak valproic acid concentrations generally are achieved with the delayed-release tablets). Although these differences are unlikely to be clinically important, increased monitoring of plasma valproic acid concentrations is recommended if one dosage form is substituted for the other.

The manufacturer states that although it is agreed that pharmacologic treatment beyond an initial response in patients with manic episodes is desirable, both for the maintenance of initial response and for prevention of new manic episodes, the safety and efficacy of long-term (i.e., longer than 3 weeks) valproic acid therapy for manic episodes have not been established in controlled clinical trials and that clinicians who elect to use such therapy for extended periods (i.e., longer than 3 weeks) should continually reevaluate the usefulness of valproic acid therapy in the individual patient. The manufacturer states that the safety of valproic acid for longer-term antimanic therapy is supported by data from record reviews involving approximately 360 patients treated for longer than 3 months.

IV Administration Valproate sodium injection is intended for IV use only.

For IV use, the manufacturer states that the appropriate dose of valproate sodium injection should be diluted with at least 50 mL of a compatible IV solution (e.g., 5% dextrose injection, 0.9% sodium chloride injection, lactated Ringer's injection). Diluted IV solutions of the drug should be infused IV over 60 minutes.

Rapid IV infusion of valproate sodium has been associated with an increased risk of adverse effects and is not currently included in the manufacturer's labeling. However, rates exceeding 20 mg/minute or infusion periods less than 60 minutes have been studied in a limited number of patients with seizure disorders and in patients with acute migraine headaches, and such administration generally appeared to be well tolerated. In a study of the safety of initial 5- to 10-minute IV infusions of valproate sodium (1.5–3 mg/kg per minute of valproic acid), patients generally tolerated such rapid infusions of the drug; the study was not designed to assess the efficacy of the regimen. The drug also appeared to be well tolerated in studies evaluating efficacy in the management of acute migraine attacks† when valproate sodium doses of 300 mg to 1 g were infused IV at rates ranging from 17–250 mg/minute or occasionally by direct rapid ("bolus") IV injection (100-mg doses).

Use of rapid infusions in patients receiving the IV preparation as a parenteral replacement for oral valproic acid has not been established.

Valproate sodium injection and diluted solutions of the drug should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

■ **Dosage** Dosage of valproate sodium and divalproex sodium is expressed in terms of valproic acid. Dosage must be carefully and slowly adjusted according to individual requirements and response.

Seizure Disorders **IV Dosage.** IV valproate sodium therapy may be employed in patients in whom oral therapy is temporarily not feasible, but therapy should be switched to oral administration as soon as clinically possible. IV administration of the drug can be used for monotherapy or as adjunctive therapy in the management of seizure disorders. The manufacturer states that the usual total daily dosages of valproic acid are equivalent for IV or oral administration, and the doses and frequency of administration employed with oral therapy in seizures disorders are expected to be the same with IV therapy, although plasma concentration monitoring and dosage adjustment may be necessary. The use of IV therapy for longer than 14 days has not been studied to date. The manufacturer also states that the use of IV valproate sodium for initial monotherapy has not been systematically studied; however, usual dosages and titration employed with oral therapy can be employed with parenteral therapy. Patients receiving dosages near the maximum recommended dosage of 60 mg/kg daily should be monitored closely, particularly when enzyme-inducing drugs are not used concomitantly.

Oral Dosage. Various valproic acid dosage regimens have been used in published studies. A correlation between plasma valproic acid concentration and therapeutic effect has not been established; however, a therapeutic range of 50–100 mcg/mL has been suggested.

For the management of complex partial seizures, the manufacturers state that the usual initial dosage of valproic acid as monotherapy or as adjunctive therapy, when being added to a current therapeutic regimen, for adults and children 10 years of age and older is 10–15 mg/kg daily. For the management of simple or complex absence seizures, the manufacturer states that the usual initial dosage of valproic acid is 15 mg/kg daily. Dosage may be increased by 5–10 mg/kg daily at weekly intervals until seizures are controlled or adverse effects prevent further increases in dosage. The manufacturers state that the maximum recommended dosage is 60 mg/kg daily. These dosage recommendations also apply when anticonvulsant therapy is being initiated with divalproex sodium as delayed- or extended-release formulations.

When converting a patient from a current anticonvulsant to valproic acid therapy for the treatment of complex partial seizures, valproic acid therapy should be initiated at usual starting doses. The dose of the current anticonvulsant may be decreased by 25% every 2 weeks, either starting concomitantly with the initiation of valproic acid therapy or delayed by 1–2 weeks if there is a concern that seizures are likely to occur with a reduction. The speed and duration of withdrawal of the current anticonvulsant can be highly variable, and patients should be monitored closely during this period for increased seizure frequency. In order to prevent adverse GI effects, the manufacturers state that the drug should be administered in 2 or more divided doses when the dosage exceeds 250 mg daily. When divalproex sodium delayed-release tablets are administered, a twice-daily dosing regimen is suggested whenever feasible and appears to adequately maintain plasma valproic acid concentrations in most patients receiving the drug. The frequency of adverse effects (particularly hepatic effects) may be dose related. The benefit of improved seizure control which may accompany higher dosages should therefore be weighed carefully against the risk of adverse effects.

When converting a patient whose seizure disorder is controlled with delayed-release divalproex sodium tablets to the extended-release tablets, the drug should be administered once daily using a total daily dose that is 8–20% higher than the corresponding delayed-release dosage that the patient was receiving. For patients whose delayed-release daily dosage cannot be directly converted to a corresponding commercially available extended-release dosage, clinicians may consider increasing the delayed-release total daily dosage to the next higher dosage before converting to the appropriate extended-release dosage.

For the management of status epilepticus refractory to IV diazepam†, 400–600 mg of valproic acid was administered rectally† by enema or in wax base suppositories at 6-hour intervals.

Bipolar Disorder The initial dosage of valproic acid in the treatment of manic episodes is 750 mg daily in divided doses. The dose of valproic acid should be increased as quickly as possible to achieve the lowest therapeutic dose producing the desired clinical effect or desired serum concentration; however, the manufacturer recommends that the dose not exceed 60 mg/kg daily. In placebo-controlled studies of valproic acid for the treatment of manic episodes, the trough serum valproic acid concentration that produced the desired clinical effect ranged from 50–125 mcg/mL. Maximum serum concentrations generally were achieved within 14 days after initiating therapy.

Dosing guidelines for maintenance therapy† with valproic acid are less evidence-based than those for acute therapy, and dosages lower than those employed for acute therapy occasionally have been used. A 1-year study with divalproex sodium found an association between higher serum concentrations and increased appetite and decreased platelet and leukocyte counts.

Migraine **Prophylaxis of Chronic Attacks.** In the prophylaxis of migraine, with or without associated aura, the recommended initial dosage of valproic acid is 250 mg twice daily. Some patients may benefit from doses of up to 1 g daily; however, in clinical trials, there was no evidence that doses of valproic acid exceeding this resulted in greater efficacy.

For the prophylaxis of migraine headache in adults, the recommended initial dosage of divalproex sodium as extended-release tablets is 500 mg once daily for 1 week; dosage may then be increased to 1 g once daily. Although maintenance dosages other than 1 g once daily have not been evaluated in patients with migraine headache, the effective dosage range for these patients is 500 mg to 1 g daily. It should be considered that divalproex sodium extended-release tablets and divalproex sodium delayed-release tablets are *not* bioequivalent. If a patient requires smaller dosage adjustment than that available using the extended-release tablets, the delayed-release tablets should be used instead. If a patient misses a dose of divalproex sodium extended-release tablets, the dose should be taken as soon as possible, unless it is almost time for the next dose. However, if the patient skips a dose, a double dose of divalproex sodium extended-release tablets should *not* be taken to make up for the missed dose.

Acute Attacks. For the acute management of migraine headache† in adults and adolescents, the optimum IV dosage, frequency, and rate of administration have not been established. In most reports, IV valproate sodium was given in doses of 300 mg to 1 g diluted in a compatible IV infusion (e.g., 5% dextrose injection, 0.9% sodium chloride injection) solution (usually about 100–250 mL) and infused IV at rates ranging from 17–100 mg/minute. In some patients, the dose was administered more rapidly (e.g., 500 mg over 2 minutes, 100 mg by direct ["bolus"] IV injection). A repeat dose (equal to the initial dose or less) was given to some patients within a few hours, if reduction of pain was not sufficient. In one study, 500-mg doses of valproate sodium were administered every 8 hours for 2 days. Some patients have received direct IV injections of 100-mg doses repeated at 5-minute intervals or infusions of a single 500-mg dose (diluted in 5 mL of 0.9% sodium chloride injection) into a free-flowing IV line of 0.9% sodium chloride injection.

When IV valproate sodium has been used in the management of chronic daily headache, an initial dose of 15 mg/kg was administered over 30 minutes followed by a dose of 5 mg/kg (infused over 15 minutes) given every 8 hours.

Dosage in Geriatric Patients Because of a decrease in unbound clearance of valproic acid, the starting dosage should be reduced. Subsequent dosage should be increased more slowly in geriatric patients. In addition, the manufacturer recommends regular monitoring of fluid and nutritional intake, dehydration, somnolence, and other adverse effects in these individuals. Dosage reduction or discontinuance of valproic acid should be considered in geriatric patients with decreased food or fluid intake and in those with excessive somnolence. The ultimate therapeutic dosage in these patients should be determined on the basis of tolerability and clinical response.

Cautions

The adverse effect profile of parenteral valproate sodium can be expected to include all of the effects associated with oral administration of the drug. In addition, IV infusion of valproate sodium may cause local effects at the injection site and effects associated with the rate of infusion. (See Cautions: Local and Infusion-related Effects.)

■ **GI Effects** Nausea, vomiting, abdominal pain, anorexia, diarrhea, and dyspepsia may occur in patients receiving valproic acid. The most frequent adverse effects of valproic acid following initiation of therapy with the drug are nausea, vomiting, and indigestion. These adverse effects usually are transient, rarely require discontinuance of therapy, and can be minimized by administering the drug with meals or by beginning therapy with low doses and increasing the dose very gradually. While divalproex sodium shares the toxic GI potential of valproic acid, the frequency of adverse GI effects appears to be lower and the effects possibly less severe with divalproex sodium than with valproic acid; patients who are unable to tolerate the GI effects of valproic acid or valproate sodium may tolerate divalproex sodium, but GI intolerance to divalproex sodium can also occur. Both anorexia with some weight loss and increased appetite with weight gain have been reported in patients receiving valproic acid. Eructation, fecal incontinence, gastroenteritis, glossitis, flatulence, hematemesis, periodontal abscess, tooth disorder, dry mouth, stomatitis, and constipation were reported in 1–5% of patients receiving valproic acid in clinical trials. Dysphagia, gum hemorrhage, and mouth ulceration also have occurred in greater than 1% of patients receiving the drug.

■ **Pancreatitis** Cases of life-threatening pancreatitis have been reported in children and adults shortly after initial use or after several years of therapy with valproic acid. Pancreatitis may be hemorrhagic with a rapid progression from initial symptoms to death. Development of manifestations suggestive of pancreatitis (e.g., abdominal pain, nausea, vomiting, and/or anorexia) requires prompt medical evaluation. (See Cautions: Precautions and Contraindications.) It should be considered that patients receiving valproic acid are at greater risk of developing pancreatitis than that expected in the general population and, in addition, pancreatitis recurred on rechallenge with the drug in several patients. In clinical trials involving 2416 patients, 2 cases of pancreatitis without alternative etiology were reported, representing 1044 patient-years experience.

■ **Nervous System Effects** Sedation and drowsiness may occur with valproic acid therapy, especially in patients receiving other anticonvulsants. (See Drug Interactions: CNS Depressants, Antidepressants, and Anticonvulsants.) Somnolence, asthenia, dizziness, and tremor generally are the most frequently reported adverse nervous system effects in patients receiving valproic acid in clinical trials. Ataxia, emotional lability, abnormal thinking, amnesia, and depression have been reported in up to 5–8% of patients receiving the drug. Some patients have reported increased alertness, insomnia, and nervousness during valproic acid therapy. Coma has been reported rarely in patients receiving valproic acid as monotherapy or in combination with phenobarbital. Rarely, patients have developed encephalopathy with or without fever, without evidence of hepatic dysfunction or abnormal valproic acid plasma concentrations, shortly after the introduction of valproic acid therapy. Although this condition can be reversible upon discontinuance of the drug, there have been fatalities in patients with hyperammonemic encephalopathy, often in patients with underlying urea cycle disorder. (See Cautions: Precautions and Contraindications.) Hearing loss, either reversible or irreversible, has been reported in patients receiving valproic acid therapy; however, a causal relationship to the drug has not been established.

Between 1–5% of patients receiving valproic acid in clinical trials experienced anxiety, confusion, headache, myasthenia, abnormal gait, paresthesia, hypertonia, incoordination, abnormal dreams, personality disorder, hallucinations, euphoria, agitation, catatonia, dysarthria, speech disorder, hypokinesia, increased reflexes, tardive dyskinesia, or vertigo. Asterixis, hypesthesia, parkinsonism, hostility, emotional upset, and psychosis/acute psychosis also have occurred rarely. Hyperactivity, aggressiveness, and other behavioral disturbances have been reported in a few children receiving valproic acid. Several reports have noted reversible cerebral atrophy and dementia in association with valproic acid therapy.

The US Food and Drug Administration (FDA) has analyzed suicidality reports from placebo-controlled studies involving 11 anticonvulsants, including valproic acid, and found that patients receiving anticonvulsants had approximately twice the risk of suicidal behavior or ideation (0.43%) compared with patients receiving placebo (0.24%). FDA's analysis included 199 randomized, placebo-controlled studies of 11 anticonvulsants (carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, and zonisamide) involving over 43,000 patients 5 years of age or older; the studies evaluated the effectiveness of the anticonvulsants in epilepsy, psychiatric disorders (e.g., bipolar disorder, depression, anxiety), and other conditions (e.g., migraine, neuropathic pain). This increased suicidality risk was observed as early as one week after beginning therapy and continued through 24 weeks. The results were generally consistent among the 11 drugs studied. In addition, patients who were treated for epilepsy, psychiatric disorders, and other conditions were all found to be at increased risk for suicidality when compared with placebo; there did not appear to be a specific demographic subgroup of patients to which the increased risk could be attributed. However, the relative risk for suicidality was found to be higher in patients with epilepsy compared with patients who were given one of the drugs for psychiatric or other conditions. (See Cautions: Precautions and Contraindications.)

■ **Hepatic Effects** Minor elevations in serum concentrations of aminotransferases (transaminases) and lactate dehydrogenase occur frequently in patients receiving valproic acid and appear to be dose related. Occasionally, increases in serum bilirubin concentration and abnormal changes in other hepatic function test results occur; these results may reflect potentially serious hepatotoxicity. (See Cautions: Precautions and Contraindications.) Hepatic failure resulting in death has occurred in patients receiving valproic acid, usually during the first 6 months of therapy. Clinical experience indicates that children younger than 2 years of age, especially those receiving multiple anticonvulsants or those with congenital metabolic disorders, severe seizure disorders accompanied by mental retardation, or organic brain disease, have a considerably increased risk of developing fatal hepatotoxicity compared with older patient groups. (See Cautions: Precautions and Contraindications.) Above 2 years of age, the frequency of fatal hepatotoxicity decreases considerably in progressively older patient groups. Severe or fatal hepatotoxicity induced by valproic acid may be preceded by nonspecific symptoms such as loss of seizure control, malaise, weakness, lethargy, anorexia, and vomiting.

Between 1–5% of patients receiving valproic acid in clinical trials experienced increased ALT (SGPT) and increased AST (SGOT) concentrations.

■ **Endocrine and Metabolic Effects** Hyperammonemic encephalopathy, including some fatalities, has been reported in patients with urea cycle disorders, particularly ornithine carbamoyltransferase deficiency, following initiation of valproic acid therapy. Hyperammonemia may occur in patients receiving valproic acid and may occur in the absence of abnormal hepatic function test results. Development of symptoms of unexplained hyperammonemic encephalopathy (e.g., lethargy, vomiting, changes in mental status) requires prompt medical evaluation. (See Cautions: Precautions and Contraindications.)

Hyponatremia and inappropriate antidiuretic hormone (ADH) secretion also have been reported. Hyperglycinemia has been reported in patients receiving valproic acid and was associated with a fatal outcome in one patient with preexisting nonketotic hyperglycinemia. Between 1–5% of patients receiving valproic acid in clinical trials experienced dysmenorrhea, amenorrhea, vaginitis, metrorrhagia, or vaginal hemorrhage. Breast enlargement, galactorrhea, irregular menses, polycystic ovaries, hyperandrogenism, weight gain, Fanconi's syndrome (principally reported in children), and parotid gland swelling have occurred in some patients receiving valproic acid. Abnormal thyroid function test results and decreased carnitine concentrations also have been reported; however, the clinical importance of these abnormalities has not been elucidated.

■ **Hematologic Effects** Valproic acid inhibits the secondary phase of platelet aggregation and may prolong bleeding time. In one study of valproic acid monotherapy for seizures, 27% of patients receiving approximately 50 mg/kg per day had at least one platelet count of 75,000/mm^3. Approximately half of the patients discontinued therapy, with their platelet counts returning to normal; the remaining patients experienced normalization of their platelet counts with continued valproic acid therapy. In this study, the probability of thrombocytopenia appeared to increase significantly at total valproate serum concentrations of 110 mcg/mL or greater (females) or 135 mcg/mL or greater (males). Ecchymosis, petechiae, bruising, hematoma formation, epistaxis, frank hemorrhage, lymphocytosis, leukopenia, eosinophilia, macrocytosis, acute intermittent porphyria, decreased fibrinogen concentrations, anemia (including macrocytic anemia, with or without folate deficiency), bone marrow suppression, pancytopenia, and aplastic anemia also have been reported.

■ **Dermatologic and Sensitivity Reactions** Between 1–5% of patients receiving valproic acid in clinical trials experienced seborrhea, dry skin, pruritus, furunculosis, rash (including maculopapular), or discoid lupus erythematosus. Transient alopecia, cutaneous vasculitis, generalized pruritus, anaphylaxis, photosensitivity, Stevens-Johnson syndrome, erythema nodosum, and erythema multiforme have been reported in patients receiving valproic acid therapy. Rare cases of toxic epidermal necrolysis have been reported, including a fatal case in a 6-month-old infant receiving valproic acid therapy; however, the infant was receiving other drugs concomitantly. An additional case of fatal toxic epidermal necrosis was reported in a 35-year-old patient with acquired immunodeficiency syndrome (AIDS) who was taking several concomitant drugs and who had a history of multiple cutaneous drug reactions.

■ **Local and Infusion-related Effects** In addition to the usual adverse effects associated with oral therapy, IV infusion of valproate sodium can produce local effects at the site of injection as well as adverse effects associated with the rate of IV infusion. In clinical trials involving healthy adults as well as patients with seizure disorders at total IV dosages of 120–6000 mg daily, adverse local effects at the site of infusion were reported in up to 2.6% of patients and included pain (2.6%), injection site reaction (2.4%), and inflammation (0.6%). In these trials, about 2% of patients discontinued parenteral therapy with the drug because of adverse effects, principally because of nausea and vomiting and elevated amylase. Other reasons for discontinuing parenteral valproate sodium therapy included hallucinations, pneumonia, headache, injection site reaction, and abnormal gait.

Dizziness and injection site pain were reported more frequently when valproate sodium was infused IV at a rate of 100 mg/minute relative to slower rates that ranged up to 33 mg/minute. At an IV infusion rate of 200 mg/minute, dizziness and taste perversion occurred more frequently than at an IV infusion rate of 100 mg/minute. In clinical trials, the maximum IV infusion rate studied was 200 mg/minute.

■ **Ocular and Otic Effects** Diplopia, amblyopia, nystagmus, and tinnitus have been reported in up to 7–16% of patients receiving valproic acid in clinical trials. Other adverse ocular and otic effects reported in patients receiv-

ing valproic acid include abnormal vision, otitis media, conjunctivitis, dry eyes, ocular pain, ocular disorder, photophobia, otic pain, and otic disorder. Reversible and irreversible hearing loss (including deafness) has been reported; however, a casual relationship has not been established.

■ **Other Adverse Effects** Infection has been reported in up to 20% of patients receiving valproic acid in clinical trials. Back pain, fever, flu syndrome, bronchitis, rhinitis, pharyngitis, dyspnea, and peripheral edema have been reported in up to 5–12% of patients receiving the drug in clinical trials. Increased cough, chest pain, tachycardia, hypertension, palpitation, arrhythmia, bradycardia, hypotension, postural hypotension, taste perversion, hiccups, facial edema, pneumonia, sinusitis, dysuria, urinary incontinence, cystitis, urinary frequency, arthralgia, myalgia, arthrosis, leg cramps, twitching, malaise, chills, fever with chills, sweating, vasodilation, cyst, neck pain, neck rigidity, and accidental injury also may occur. Adverse effects reported rarely in patients receiving valproic acid include muscular weakness, interstitial nephritis, enuresis, urinary tract infection, bone pain, lupus erythematosus, and fatigue. A case of reversible skeletal muscle weakness and ventilatory failure also has been reported in a geriatric patient receiving valproic acid therapy.

■ **Precautions and Contraindications** Since divalproex sodium is a prodrug of valproate, it shares the toxic potentials of valproic acid, and the usual cautions, precautions, and contraindications of valproic acid therapy should be observed with divalproex sodium therapy.

Patients should be warned that valproic acid may impair ability to perform hazardous activities requiring mental alertness or physical coordination (e.g., operating machinery or driving a motor vehicle).

FDA has informed healthcare professionals about an increased risk of suicidality (suicidal behavior or ideation) observed in an analysis of studies using various anticonvulsants compared with placebo. (See Cautions: Nervous System Effects.) FDA recommends that all patients who are currently receiving or beginning therapy with any anticonvulsant for any indication be closely monitored for the emergence or worsening of depression, suicidal thoughts or behavior (suicidality), and/or unusual changes in mood or behavior. Symptoms such as anxiety, agitation, hostility, mania, and hypomania may be precursors to emerging suicidality. Clinicians should inform patients, their families, and caregivers of the potential for an increased risk of suicidality so that they are aware and able to notify their clinician of any unusual behavioral changes. Patients, family members, and caregivers also should be advised not to make any changes to the anticonvulsant regimen without first consulting with the responsible clinician. They should pay close attention to any day-to-day changes in mood, behavior, and actions; since changes can happen very quickly, it is important to be alert to any sudden differences. In addition, patients, family members, and caregivers should be aware of common warning signs that may signal suicide risk (e.g., talking or thinking about wanting to hurt oneself or end one's life, withdrawing from friends and family, becoming depressed or experiencing worsening of existing depression, becoming preoccupied with death and dying, giving away prized possessions). If these or any new and worrisome behaviors occur, the responsible clinician should be contacted immediately. FDA also recommends that clinicians who prescribe valproic acid or any other anticonvulsant balance the risk for suicidality with the risk of untreated illness. Epilepsy and many other illnesses for which anticonvulsants are prescribed are themselves associated with an increased risk of morbidity and mortality and an increased risk of suicidal thoughts and behavior. If suicidal thoughts and behavior emerge during anticonvulsant therapy, the clinician must consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Results of in vitro studies indicate that valproate appears to stimulate replication of some strains of human immunodeficiency virus (HIV) and cytomegalovirus (CMV) under certain experimental conditions. The clinical importance of these in vitro findings, including any relevance to patients receiving maximally suppressive antiretroviral therapy, is not known. (See Pharmacology: Antiviral Effects.) It has been suggested that these in vitro effects should be considered when interpreting test results concerning the clinical condition of HIV-infected patients (e.g., plasma HIV RNA levels) or patients with CMV infection.

Since valproic acid may cause serious and potentially fatal hepatotoxicity, hepatic function tests should be performed before and at frequent intervals during therapy with the drug, especially during the first 6 months. Since results of hepatic function tests may not be abnormal in all instances, clinicians must also consider the results of careful interim medical history and physical examination of the patient. Valproic acid therapy should be discontinued immediately in the presence of suspected or apparent substantial hepatic dysfunction. In some patients, hepatic dysfunction has progressed despite discontinuance of the drug. Since elevations in hepatic enzyme concentrations may be dose related, the benefit of improved seizure control which may accompany higher doses of the drug must be weighed against the potential risks. Valproic acid should be used with caution in patients with a history of hepatic disease. Children and patients receiving multiple anticonvulsants or those with congenital metabolic disorders, severe seizure disorders accompanied by mental retardation, or organic brain disease may be at particular risk of hepatotoxicity. Because children younger than 2 years of age, especially those with the previously listed conditions, have a considerably increased risk of developing fatal hepatotoxicity compared with older patient groups, valproic acid should be used in these patients only with extreme caution and as a single agent; the benefits of seizure control must be weighed against the potential risks. Above 2 years of age, the frequency of fatal hepatotoxicity decreases considerably in progressively older patient groups. Valproic acid should *not* be used in patients with hepatic disease or substantial hepatic dysfunction.

Because the use of valproic acid has been associated with life-threatening pancreatitis in children and adults (see Cautions: Pancreatitis), patients and guardians should be instructed that if symptoms of pancreatitis (e.g., abdominal pain, nausea, vomiting, anorexia) develop, prompt medical evaluation is needed. If pancreatitis is diagnosed, valproic acid usually should be discontinued and alternative therapy for the underlying medical condition should be initiated as clinically indicated.

Because the use of valproic acid has been associated with hyperammonemic encephalopathy, patients should be advised that if symptoms of this disorder (e.g., lethargy, vomiting, changes in mental status) develop, they should notify their clinician promptly. (See Cautions: Endocrine and Metabolic Effects.) If such symptoms are present, plasma ammonia concentrations should be determined, and, if these concentrations are increased, valproic acid therapy should be discontinued. Appropriate treatment of hyperammonemia should be initiated and the patient should be evaluated for urea cycle disorders. Asymptomatic elevation of ammonia concentrations is more common than hyperammonemic encephalopathy. In patients with asymptomatic elevations, plasma ammonia concentrations should be closely monitored and, if elevations persist, discontinuance of valproic acid therapy should be considered. Prior to the initiation of valproic acid therapy, an evaluation for urea cycle disorders should be considered in patients with a history of unexplained encephalopathy or coma, encephalopathy associated with a protein load, pregnancy-related or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine concentrations; patients with cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low BUN concentration, or protein avoidance; patients with a family history of urea cycle disorders or unexplained infant deaths (particularly males); and patients with other signs or symptoms of urea cycle disorders.

Anticonvulsant drugs (including valproic acid) should not be discontinued abruptly in patients receiving the drugs to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life.

Since valproic acid may cause thrombocytopenia and inhibit platelet aggregation, platelet counts, bleeding time, and coagulation studies should be determined before and periodically during therapy with the drug and before surgery is performed in patients receiving the drug. In one study of the drug as monotherapy for seizures, 27% of patients receiving approximately 50 mg/kg per day of valproic acid had at least one platelet count of 75,000/mm^3 or less; the probability of thrombocytopenia appeared to increase significantly at total serum valproate concentrations of 110 mcg/mL or greater (females) or 135 mcg/mL or greater (males). Some clinicians have recommended thromboelastography as a more reliable method to assess the effects of valproic acid on coagulation. If clinical evidence of hemorrhage, bruising, or a disorder of hemostasis coagulation occurs during valproic acid therapy, dosage should be reduced or the drug withdrawn pending further evaluation.

Valproic acid is contraindicated in patients with known hypersensitivity to the drug. Valproic acid also is contraindicated in patients with known urea cycle disorders. (See Cautions: Endocrine and Metabolic Effects.)

■ **Pediatric Precautions** Experience with valproic acid therapy in the management of seizures indicates that children younger than 2 years of age are at an increased risk of developing fatal hepatotoxicity. (See Cautions: Precautions and Contraindications.) The drug should be used with extreme caution and as single-agent therapy in such children, and the benefits of valproic acid therapy weighed against the risks. The incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups (i.e., older than 2 years of age).

Younger children, especially those receiving enzyme-inducing drugs, will require larger maintenance doses to attain targeted total and unbound valproic acid concentrations for the management of seizures. The variability in free fraction limits the clinical usefulness of monitoring total serum valproic acid concentrations alone. Interpretation of valproic acid concentration in children should include consideration of factors that affect hepatic metabolism and protein binding.

The safety and efficacy of valproic acid for acute manic episodes in patients younger than 18 years of age and for migraine prophylaxis in patients younger than 16 years of age have not been established. In addition, safety and efficacy of divalproex sodium extended-release tablets in pediatric patients have not been established and use of this preparation in this age group is not recommended.

The safety of valproate sodium injection has not been studied in pediatric patients younger than 2 years of age. If a decision is made to use the injection in this age group, the manufacturer states that it should be used with extreme caution and only as monotherapy, and the potential benefits should be weighed against the possible risks. No unusual adverse effects were observed in clinical trials employing IV valproate sodium for the management of seizure disorders in 24 pediatric patients 2–17 years of age.

■ **Geriatric Precautions** The safety and efficacy of valproic acid in geriatric patients (older than 65 years of age) for the treatment of manic episodes associated with bipolar disorder or prevention of migraine headaches have not been established.

In a case review of almost 600 patients treated with valproic acid for manic episodes, approximately 12% of patients were older than 65 years of age. A higher percentage of these patients reported accidental injury, infection, pain, somnolence, or tremor during valproic acid therapy compared with younger patients. Discontinuance of valproic acid therapy occasionally was associated with somnolence or tremor. The manufacturer states that it is unclear whether these events indicate additional risks of drug therapy or whether they result

from preexisting medical conditions or concomitant medication use in these geriatric patients.

Results of a double-blind, multicenter study of geriatric patients (mean age: 83 years) with dementia who were receiving valproic acid (125 mg daily, titrated to a target daily dosage of 20 mg/kg) indicate that the incidence of somnolence was higher in patients receiving valproic acid than in those receiving placebo and discontinuance of therapy because of somnolence was higher in those receiving valproic acid than in those receiving placebo. In about 50% of patients with somnolence, a reduced nutritional intake and weight loss also were observed. The incidence of dehydration also appeared to be higher in geriatric patients receiving valproic acid than in those receiving placebo. In the patients who experienced the mentioned adverse effects, a trend for lower baseline albumin concentration, lower valproic acid clearance, and higher BUN was observed. Therefore, it is recommended that initial dosage of valproic acid be reduced and subsequent dosages be increased more slowly in geriatric patients. In addition, the manufacturer recommends regular monitoring of fluid and nutritional intake, dehydration, somnolence, and other adverse effects in these individuals. Dosage reduction or discontinuance of valproic acid should be considered in geriatric patients with decreased food or fluid intake and in those with excessive somnolence.

■ **Mutagenicity and Carcinogenicity** Studies of valproic acid that used bacterial and mammalian test systems have shown no evidence to date of a mutagenic potential for the drug.

In rats and mice receiving valproic acid dosages of 80 and 170 mg/kg daily for 2 years, an increased incidence of subcutaneous fibrosarcomas occurred in male rats at the higher dosage level and a dose-related trend for an increased incidence of benign pulmonary adenomas was observed in male mice. The importance of these findings to humans is not known.

■ **Pregnancy, Fertility, and Lactation** Safe use of valproic acid during pregnancy has not been established. Adverse fetal effects have been observed in reproduction studies in rats and mice. Valproic acid can cause teratogenic effects in humans, such as neural tube defects (e.g., spina bifida). Several reports suggest an association between use of valproic acid in pregnant, epileptic women and an increased incidence of birth defects (particularly neural tube defects) in children born to these women; such malformations may be associated with high plasma concentrations during the first trimester. Some experts state that prophylactic use of folic acid may prevent or decrease the incidence of neural tube defects. Valproic acid should be used in pregnant women with seizure disorders or women with seizure disorders who might become pregnant only if the drug is clearly shown to be essential in the management of their seizures. Women should be apprised of the potential hazard to the fetus; this is especially important when valproic acid therapy is being contemplated or used for the management of a spontaneously reversible condition not ordinarily associated with permanent injury or risk of death (e.g., prophylaxis of migraine headache). Tests to detect neural tube and other defects using current accepted procedures should be considered a part of routine prenatal care in childbearing women receiving valproic acid for the management of seizure disorders.

Other congenital anomalies (e.g., craniofacial defects, cardiovascular malformations, anomalies involving various body systems) compatible and incompatible with life also have been reported in children of women treated with valproic acid during pregnancy; sufficient data to determine the incidence of these anomalies are not available. The higher incidence of congenital anomalies in the children of women with seizure disorders treated with anticonvulsant drugs during pregnancy cannot be regarded as a direct effect of such therapy. There are intrinsic methodologic problems in obtaining adequate drug teratogenicity data in humans. Genetic factors and/or the epileptic disorder also may contribute to the development of congenital anomalies.

Patients receiving valproic acid may develop clotting abnormalities. A pregnant patient taking multiple anticonvulsant agents, including valproic acid, developed hypofibrinogenemia; the patient then gave birth to an infant with afibrogenemia, who subsequently died of hemorrhage. If valproic acid is to be used during pregnancy, clotting parameters should be monitored closely. Hepatic failure, resulting in the death of a neonate and an infant, also has been reported following the use of valproic acid during pregnancy.

Anticonvulsant drugs should *not* be discontinued in pregnant women in whom the drugs are administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases when the severity and frequency of the seizure disorder are such that discontinuance of therapy does not pose a serious threat to the patient, discontinuance of the drugs may be considered prior to and during pregnancy; however, it cannot be stated with any certainty that even minor seizures do not pose some hazard to the fetus. The clinician should carefully weigh these considerations in treating or counseling epileptic women of childbearing potential.

The effect of valproic acid on the development of the testes and on sperm production and fertility in humans is not known. Chronic toxicity studies in rats and dogs demonstrated reduced spermatogenesis and testicular atrophy. Further animal studies are ongoing.

Since valproic acid is distributed into milk, the drug should be used with caution in nursing women; the potential effects on a nursing infant are not known.

Drug Interactions

■ **CNS Depressants, Antidepressants, and Anticonvulsants** Additive CNS depression may occur when valproic acid is administered concomitantly with other CNS depressants including other anticonvulsants (particularly phenobarbital and primidone) and alcohol. If valproic acid is used in conjunction with other CNS depressant drugs including alcohol, caution should be used to avoid overdosage.

Valproic acid displaces diazepam from its albumin binding sites and also inhibits its metabolism. In a study in a limited number of healthy individuals, coadministration of valproic acid (1.5 g daily) increased the free fraction of diazepam (10 mg) by 90%; plasma clearance and volume of distribution of free diazepam were decreased by 25% and 20%, respectively. The elimination half-life of diazepam was unaffected by concomitant valproic acid administration.

Concomitant use of amitriptyline (a single 50-mg oral dose) and valproic acid (500 mg twice daily) resulted in a 21% decrease in the plasma clearance of amitriptyline and a 34% decrease in the net clearance of nortriptyline (the pharmacologically active metabolite of amitriptyline). In addition, increased amitriptyline concentrations have been reported rarely in patients receiving amitriptyline concomitantly with valproic acid; concomitant use has rarely been associated with toxicity. The manufacturer states that monitoring of amitriptyline concentrations should be considered for patients receiving valproic acid concomitantly with amitriptyline.

Because valproic acid may potentiate the effects of monoamine oxidase inhibitors and other antidepressants, dosage reduction of these drugs may be necessary if valproic acid is administered to patients receiving antidepressants.

Valproic acid inhibits the metabolism of ethosuximide. Administration of a single 500-mg dose of ethosuximide to a limited number of healthy individuals receiving valproic acid (800–1600 mg daily) resulted in a 25% increase in ethosuximide elimination half-life and a 15% decrease in total ethosuximide clearance when compared with ethosuximide administration alone. Patients receiving concomitant valproic acid and ethosuximide therapy, especially if receiving other concomitant anticonvulsant therapy, should have their serum drug concentrations monitored carefully.

Concomitant administration of valproic acid with felbamate (1.2 g daily) in a limited number of patients with epilepsy resulted in a 35% increase in mean peak serum valproic acid concentration, from 86 to 115 mcg/mL when compared with administration of valproic acid alone. Increasing the felbamate dose to 2.4 g daily resulted in another 16% increase in mean peak valproic acid concentration to 133 mcg/mL. A decrease in valproic acid dosage may be required when initiating concomitant felbamate therapy.

Valproic acid inhibits lamotrigine metabolism. In a steady-state study in healthy individuals, the elimination half-life of lamotrigine increased from 26 to 70 hours when concomitant valproic acid was administered. Lamotrigine dosage should be decreased when valproic acid therapy is initiated.

Concomitant administration of valproic acid and phenobarbital (or primidone which is metabolized to phenobarbital) can result in increased phenobarbital plasma concentrations and excessive somnolence. This combination can produce CNS depression (possibly severe) even without substantial increases in serum concentrations of either drug. A few patients have become comatose during therapy with valproic acid and phenobarbital. In a study of concomitant valproic acid (250 mg twice daily for 14 days) and single-dose phenobarbital (60 mg) administration in a limited number of healthy individuals, a 50% increase in phenobarbital half-life, a 30% decrease in phenobarbital clearance, and a 50% increase in unchanged phenobarbital excreted in the urine were observed. If valproic acid is used with a barbiturate, the patient should be closely observed for possible neurologic toxicity, plasma concentrations of the barbiturate should be monitored if possible, and the dosage of the barbiturate decreased if necessary.

Serum concentrations of carbamazepine have been reported to decrease by 17% and concentrations of the metabolite carbamazepine-10,11-epoxide have been reported to increase by 45% during concomitant therapy with valproic acid; such interaction may result in carbamazepine CNS toxicity (e.g., acute psychotic reaction). In addition, carbamazepine has been reported to decrease plasma valproic acid concentrations by altering its clearance during concomitant therapy, which may be clinically important. Discontinuance of carbamazepine following concomitant carbamazepine/valproic acid therapy has been reported to result in increased valproic acid concentrations. If concomitant therapy is being undertaken, or if a patient currently is receiving concomitant carbamazepine/valproic acid therapy and one agent is to be discontinued, careful therapeutic drug monitoring should be considered.

Concomitant administration of valproic acid and clonazepam has produced absence status; therefore, some clinicians recommend that concomitant use of these drugs be avoided.

Valproic acid has been associated both with decreased plasma phenytoin concentrations and increased seizure frequency and with increased plasma concentrations of free phenytoin and phenytoin intoxication. Therefore, it is important to monitor plasma phenytoin concentrations whenever valproic acid is added to or withdrawn from the patient's therapy and adjust the dosage of phenytoin as required. Since valproic acid also may interact with other anticonvulsants, it is advisable to monitor plasma concentrations of concomitantly administered anticonvulsants during initial valproic acid therapy.

■ **Anti-infective Agents** *Acyclovir* In a child receiving both phenytoin and valproic acid, short-term oral therapy with acyclovir apparently reduced the plasma concentrations of both anticonvulsant agents to subtherapeutic levels; an increase in seizure frequency and a worsening in the EEG were observed. Although further study is needed to confirm the effects of acyclovir on the pharmacokinetics of anticonvulsant agents, such concomitant therapy should be undertaken with caution.

Antiretroviral Agents Concomitant use of valproic acid (250 or 500 mg every 8 hours) and oral zidovudine (100 mg every 8 hours) for 4 days in a limited number of adults with human immunodeficiency virus (HIV) infection resulted in an 80% increase in the area under the concentration-time curve (AUC) of zidovudine. The effect of concomitant zidovudine on the pharmacokinetics of valproic acid was not evaluated. Although the clinical importance of this interaction between zidovudine and valproic acid is not known, patients receiving both drugs should be monitored more closely for zidovudine-related adverse effects. Severe anemia has been reported following initiation of valproic acid therapy (500 mg twice daily) in an HIV-infected adult who was receiving an antiretroviral regimen that contained zidovudine, lamivudine, and abacavir; the patient had stable hematologic status at the time valproic acid was started. The manufacturer of zidovudine states that a reduction in zidovudine dosage may be considered if a patient experiences substantial anemia or other severe adverse effect while receiving zidovudine concomitantly with valproic acid.

Hepatotoxicity was reported in an HIV-infected adult receiving valproic acid concomitantly with an antiretroviral regimen containing ritonavir, saquinavir, stavudine, and nevirapine. It has been suggested that this may have occurred as the result of a pharmacokinetic interaction between valproic acid and ritonavir and/or nevirapine.

Concomitant use of efavirenz and valproic acid in HIV-infected adults does not appear to affect the pharmacokinetics of either drug.

Concomitant use of the fixed combination of lopinavir and ritonavir with valproic acid may result in slightly increased lopinavir concentrations, but does not affect valproic acid concentrations. It has been suggested that this pharmacokinetic interaction is not clinically important.

Rifampin A study of administration of a single dose of valproic acid (7 mg/kg) given 36 hours after short-term rifampin administration (600 mg daily for 5 days) revealed a 40% increase in the clearance of valproic acid. Valproic acid dosage adjustment may be required when rifampin therapy is initiated.

■ **Other Drugs** Since valproic acid may affect bleeding time (see Cautions: Hematologic Effects), it should be administered with caution in patients receiving drugs which affect coagulation such as aspirin or warfarin. In addition, valproic acid potentially may displace warfarin from its plasma albumin binding sites. Although the clinical relevance of this interaction is unknown, coagulation tests should be monitored if concomitant valproic acid and anticoagulant therapy is undertaken.

In a study of a limited number of pediatric patients receiving valproic acid and antipyretic aspirin therapy (11–16 mg/kg), a decrease in valproic acid protein binding and metabolism was observed. Free valproic acid concentration increased fourfold, compared with valproic acid therapy alone. The oxidative metabolic pathway of valproic acid was inhibited, resulting in a decrease in excretion of valproic acid metabolites, from 25% to 8.3% of total metabolites excreted. Concomitant aspirin and valproic acid therapy should be instituted with caution.

In vitro studies demonstrated that addition of tolbutamide to plasma samples of patients receiving valproic acid therapy resulted in an increase in the unbound tolbutamide fraction from 20% to 50%. The clinical importance of this displacement is unknown.

Limited pharmacokinetic studies reveal little to no interaction following concomitant administration of valproic acid with the following drugs: antacids, chlorpromazine, haloperidol, H_2-receptor antagonists (i.e., ranitidine, cimetidine), acetaminophen, clozapine, lithium, lorazepam, or oral contraceptives.

Laboratory Test Interferences

■ **Tests for Urinary Ketones** A ketone metabolite in the urine of patients receiving valproic acid may produce false-positive results for urine ketones.

■ **Tests for Thyroid Function** Valproic acid reportedly alters thyroid function test results, but the clinical importance of this effect is not known.

Acute Toxicity

■ **Manifestations** Overdosage of valproic acid may produce somnolence, heart block, or deep coma. One adult who ingested 36 g of valproic acid (as valproate sodium) in addition to 1 g of phenobarbital and 300 mg of phenytoin experienced deep coma 4 hours after ingestion of the drugs. The patient recovered following supportive therapy. Fatalities have been reported following valproic acid overdosage; however, patients have recovered from serum valproic acid concentrations as high as 2.12 mg/mL.

■ **Treatment** Treatment of valproic acid intoxication consists of general supportive therapy, particularly maintenance of adequate urinary output. Because the drug is rapidly absorbed, gastric lavage may be of limited value; since absorption of divalproex sodium delayed-release tablets is delayed, the value of gastric lavage or emesis will vary with time since ingestion if this form of the drug has been ingested. In overdose situations, the free or unbound serum valproic acid concentration is high. Hemodialysis or tandem hemodialysis with hemoperfusion may result in significant removal of drug. Naloxone has been reported to reverse the CNS depressant effects of valproic acid overdosage; however, naloxone should be used with caution since it could also theoretically reverse the anticonvulsant effects of valproic acid.

Pharmacology

■ **Anticonvulsant Effects** The mechanism of the anticonvulsant effects of valproic acid is not known. Effects of the drug may be related, at least in part, to increased brain concentrations of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA). Animal studies have shown that valproic acid inhibits GABA transferase and succinic aldehyde dehydrogenase, enzymes which are important for GABA catabolism. Results of one study indicate the drug inhibits neuronal activity by increasing potassium conductance. In animals, valproic acid protects against seizures induced by electrical stimulation as well as those induced by pentylenetetrazol.

■ **Antiviral Effects** Valproic acid inhibits histone deacetylase 1 (HDAC1) (an enzyme that maintains latency of human immunodeficiency virus [HIV] in resting $CD4^+$ T-cells) and induces HIV expression from resting $CD4^+$ T-cells ex vivo. It has been suggested that this effect may be useful in depleting latent infection in resting $CD4^+$ T-cells in HIV-infected patients. Although highly active antiretroviral therapy (HAART) suppresses plasma HIV-1 RNA levels and restores immune function, the presence of replication-competent provirus in resting $CD4^+$ T-cells and persistent HIV replication prevent HAART from eradicating HIV infection. Efficacy of valproic acid in depleting HIV from resting $CD4^+$ T-cells has been evaluated in a small proof-of-concept pilot study in 4 HIV-infected adults (plasma HIV-1 RNA levels less than 50 copies/mL for at least 2 years) receiving HAART. Enfuvirtide was added to the HAART regimens (to prevent the spread of virus in the presence of valproic acid) and, after 4–6 weeks of this intensified regimen, valproic acid (500–750 mg twice daily) was added. After 16–18 weeks of combined valproic acid and enfuvirtide-intensified HAART, there was a substantial decline in the frequency of replication-competent HIV in circulating resting $CD4^+$ T-cells. These preliminary findings suggest that use of valproic acid with HAART and enfuvirtide may represent a new therapeutic approach that possibly represents a step toward the elimination of HIV infection in resting $CD4^+$ T-cells and eventual cure of HIV infection. However, it is unclear whether latently infected $CD4^+$ T-cells are the only reservoir for HIV, and larger, controlled studies are needed to investigate the possible benefits of valproic acid in HIV-infected patients.

Pharmacokinetics

■ **Absorption** *Oral Administration* Following oral administration, valproate sodium is rapidly converted to valproic acid in the stomach. Valproic acid is rapidly and almost completely absorbed from the GI tract. Absorption of the drug is delayed but not decreased by administration with meals; administration of the drug with milk products does not affect the rate or degree of absorption. Following oral administration of divalproex sodium extended-release tablets, divalproex sodium dissociates into valproic acid in the GI tract. Following oral administration of divalproex sodium delayed-release tablets and passage of the tablets into the upper small intestine, divalproex sodium dissociates into valproic acid, which is then absorbed; because of the enteric coating, absorption is delayed compared with that following oral administration of valproic acid capsules or valproate sodium solution. The bioavailability of valproate from divalproex sodium delayed-release tablets and capsules containing coated particles has been shown to be equivalent to that of valproic acid capsules. The absolute bioavailability of divalproex sodium extended-release tablets following oral administration of a single dose after a meal is about 90%. The manufacturer states that divalproex sodium extended-release tablets and delayed-release tablets are not bioequivalent. Results of 2 multiple-dose studies indicate that divalproex sodium extended-release tablets (administered either in the fasting state or immediately before small meals) have an average bioavailability of 81–89% relative to divalproex sodium delayed-release tablets given twice daily. Administration of divalproex sodium with food would be expected to slow absorption but not affect the extent of absorption.

Peak plasma concentrations of valproic acid are usually attained 1–4 hours following a single oral dose of the acid or the sodium salt, 3–5 hours following a single oral dose of divalproex sodium, and 7–14 hours following oral administration of multiple doses of divalproex sodium extended-release tablets. There is wide interindividual variation in plasma concentrations of the drug with a specific dose. Results of a multiple-dose study indicate that following oral administration of divalproex sodium extended-release tablets once daily average plasma concentrations of the drug are 10–20% lower than those achieved with twice-daily administration of divalproex sodium delayed-release tablets. Plasma concentrations of valproic acid required for therapeutic or toxic effects have not been definitely established. Some reports indicate that therapeutic plasma concentrations may be 50–100 mcg/mL of total (bound and unbound) valproic acid and that concentrations in this range are maintained in most adults receiving 1.2–1.5 g of valproic acid daily. However, the possibility that some patients may be controlled with lower or higher plasma concentrations and that the free fraction of valproic acid increases with increasing dosage should be considered. (See Pharmacokinetics: Distribution.) The onset of therapeutic effects is several days to more than one week following initiation of valproic acid therapy.

The relationship between dose and total valproic acid concentration is nonlinear; concentration does not increase proportionally with dose, because of saturable protein binding. The pharmacokinetics of unbound drug are linear.

Parenteral Administration Equivalent valproic acid dosages as the IV injection (available as valproate sodium), administered over 1 hour, or various conventional or delayed-release oral formulations (available as valproate sodium or divalproate sodium) are expected to result in equivalent peak and trough plasma concentrations and total systemic exposure to the valproic acid. Although the rate of valproic acid absorption may vary with

the specific formulation, any such differences should be of minor clinical importance under steady-state conditions achieved with chronic therapy for seizure disorders.

When oral divalproate sodium delayed-release tablets or IV valproate sodium (as a 1-hour infusion) was administered at a dosage of 250 mg of valproic acid every 6 hours for 4 days in healthy males, the resulting area under the plasma concentration-time curves (AUCs) and peak and trough plasma concentrations of the drug were equivalent at steady state as well as after the initial dose. However, the time to reach peak plasma concentrations was delayed with the tablets, occurring at approximately 4 hours after an oral dose versus at the end of the 1-hour infusion with the IV dose. Because the pharmacokinetics of unbound valproic acid are linear, bioequivalence between IV valproate sodium and oral delayed-release divalproate sodium can be expected up to maximum dosages of 60 mg/kg daily. The AUCs and peak plasma concentrations also were equivalent in healthy males receiving single 500-mg doses as the IV injection (infused over 1 hour) or valproate sodium oral solution. In addition, patients maintained on valproic acid dosages of 750–4250 mg daily (given in divided doses every 6 hours) as oral delayed-release divalproate sodium tablets alone or while stabilized on another anticonvulsant (e.g., carbamazepine, phenytoin, or phenobarbital) exhibited comparable plasma concentrations when switched from oral divalproate sodium to IV valproate sodium (as 1-hour infusions).

When valproate sodium (at a dosage of 1 g of valproic acid) was administered IV over 5, 10, 30, and 60 minutes in healthy individuals, peak plasma concentrations of the drug averaged 145 mcg/mL after the 5-minute infusion compared with 115 mcg/mL after the 60-minute infusion. However, plasma concentrations measured at 90–120 minutes after initiation of the valproate sodium infusions were similar for the 4 rates of infusion.

■ **Distribution** Valproic acid is rapidly distributed; distribution appears to be restricted to plasma and rapidly exchangeable extracellular water. Volume of distribution of total or free valproic acid is 11 or 92 L/1.73 m^2, respectively. Valproic acid has been detected in CSF (approximately 10% of serum concentrations), saliva (about 1% of plasma concentrations), and milk (about 1–10% of plasma concentrations). The drug crosses the placenta.

Plasma protein binding of valproic acid is concentration dependent; the free fraction of drug increases from 10% at a concentration of 40 mcg/mL to 18.5% at a concentration of 130 mcg/mL. Protein binding of valproic acid is decreased in geriatric patients, in patients with renal impairment or hepatic disease, or in the presence of other protein-bound drugs. Conversely, valproic acid may displace other drugs from protein binding sites. Because of decreased protein binding of the drug in special patient populations (i.e., patients with renal or hepatic disease), monitoring of total drug concentrations may be misleading, owing to the increased free fraction of valproic acid.

■ **Elimination** Valproic acid is eliminated by first-order kinetics and reportedly has an elimination half-life of 5–20 hours (average 10.6 hours). Elimination half-lives in the lower portion of the range are usually observed in patients receiving other anticonvulsants concomitantly. Half-lives of up to 30 hours have been reported following overdosage of valproate sodium.

Mean plasma clearance of total or free valproic acid is 0.56 or 4.6 L/hour per 1.73 m^2, respectively. Drug clearance may be decreased in special patient populations (e.g., patients with renal failure, geriatric patients). Because hemodialysis typically reduces plasma valproic acid concentration by about 20%, generally there is no dosage adjustment required in patients with renal failure (i.e., creatinine clearance less than 10 mL/min). Geriatric patients should receive lower initial doses of the drug. (See Dosage and Administration: Dosage.)

Pediatric patients (i.e., age range 3 months to 10 years) have 50% higher clearance of the drug expressed by weight (i.e., mL/minute per kg); over the age of 10 years, pharmacokinetic parameters of valproic acid approximate those in adults. Neonates (i.e., younger than 2 months) have a markedly decreased clearance of valproic acid compared with older children and adults, possibly because of delayed development of metabolic enzyme systems and an increased volume of distribution. In one study, the elimination half-life in children younger than 10 days old ranged from 10–67 hours, compared with 7–13 hours in children older than 2 months.

Valproic acid is metabolized principally in the liver by *beta* (over 40%) and *omega* oxidation (up to 15–20%). Valproic acid metabolites are excreted in urine; 30–50% of an administered dose is excreted as glucuronide conjugates. Less than 3% of an administered dose is excreted in urine unchanged. The major metabolite in urine is 2-propyl-3-ketopentanoic acid; minor urinary metabolites are 2-propylglutaric acid, 2-propyl-5-hydroxypentanoic acid, 2-propyl-3-hydroxypentanoic acid, and 2-propyl-4-hydroxypentanoic acid. Small amounts of the drug are also excreted in feces and in expired air. Results of studies in rats suggest the drug may undergo enterohepatic circulation.

Liver disease impairs the ability to eliminate valproic acid. In one study, the clearance of free valproic acid was decreased by 50% in a limited number of patients with cirrhosis and by 16% in a limited number of patients with acute hepatitis, compared with healthy individuals. Half-life of valproic acid was increased from 12 to 18 hours.

Chemistry and Stability

■ **Chemistry** Valproic acid, valproate sodium, and divalproex sodium are carboxylic acid-derivative anticonvulsants. Valproic acid is structurally unrelated to other commercially available anticonvulsants; it lacks nitrogen and/or an aromatic moiety found in most anticonvulsants. Divalproex sodium is a stable coordination compound consisting of valproic acid and valproate sodium in a 1:1 molar ratio and is formed during partial neutralization of valproic acid with sodium hydroxide. Divalproex sodium is a prodrug of valproate, dissociating into valproate in the GI tract.

Valproic Acid Valproic acid occurs as a colorless to pale yellow, slightly viscous, clear liquid with a characteristic odor and is slightly soluble in water and freely soluble in alcohol. Valproic acid has a pK_a of 4.8.

Valproate Sodium Valproate sodium occurs as a white, crystalline, very hygroscopic powder with a saline taste and is very soluble in water and in alcohol.

Valproate sodium injection is a sterile solution of the drug in water for injection. The injection occurs as a clear, colorless solution; sodium hydroxide and/or hydrochloric acid may be added to adjust the pH to 7.6.

Divalproex Sodium Divalproex sodium occurs as a white powder with a characteristic odor and is insoluble in water and very soluble in alcohol.

■ **Stability** ***Valproic Acid*** USP recommends that valproic acid capsules be stored in tight containers at 15–30°C; however, the manufacturer of Depakene® recommends that the capsules be stored in tight containers at 15–25°C.

Valproate Sodium Valproate sodium oral solution has a pH of 7–8. Valproate sodium oral solution should be stored in tight containers at a temperature less than 30°C; freezing should be avoided.

Valproate sodium injection should be stored at a controlled room temperature of 15–30°C. Because the injection does not contain a preservative, unused portions of the solution should be discarded. When stored in glass or PVC containers at 15–30°C, valproate sodium injection that has been further diluted with at least 50 mL of 5% dextrose injection, 0.9% sodium chloride injection, or lactated Ringer's injection is stable for at least 24 hours.

Divalproex Sodium Divalproex sodium delayed-release tablets should be stored in tight, light-resistant containers at a temperature less than 30°C; divalproex sodium capsules containing coated particles should be stored at a temperature less than 25°C. Divalproex sodium extended-release tablets should be stored at 25°C, but may be exposed to temperatures ranging from 15–30°C.

For further information on uses and dosage and administration of valproic acid, see the Anticonvulsants General Statement 28:12.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Valproate Sodium

Oral		
Solution	250 mg (of valproic acid) per 5 mL*	**Depakene® Syrup**, Abbott **Valproate Sodium Oral Solution**
Parenteral		
Injection, for IV use	100 mg (of valproic acid) per mL*	**Depacon®**, Abbott **Valproate Sodium Injection**

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Valproic Acid

Oral		
Capsules, liquid-filled	250 mg*	**Depakene®**, Abbott

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Divalproex Sodium

Oral		
Capsules (containing coated particles)	equivalent to valproic acid 125 mg	**Depakote® Sprinkle**, Abbott
Tablets, delayed-release	equivalent to valproic acid 125 mg	**Depakote®**, Abbott
	equivalent to valproic acid 250 mg	**Depakote®**, Abbott
	equivalent to valproic acid 500 mg	**Depakote®**, Abbott
Tablets, extended-release	equivalent to valproic acid 250 mg	**Depakote® ER**, Abbott
	equivalent to valproic acid 500 mg	**Depakote® ER**, Abbott

†Use is not currently included in the labeling approved by the US Food and Drug Administration

other indications, both psychiatric and nonpsychiatric, should be advised to monitor patients on a daily basis for the emergence of agitation, irritability, or unusual changes in behavior as well as the emergence of suicidality, and to report such symptoms immediately to a health-care provider.

Although a causal relationship between the emergence of symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and/or mania and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consequently, consideration should be given to changing the therapeutic regimen or discontinuing therapy in patients whose depression is persistently worse or in patients experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, particularly if such manifestations are severe, abrupt in onset, or were not part of the patient's presenting symptoms. FDA also recommends that the drugs be prescribed in the smallest quantity consistent with good patient management, in order to reduce the risk of overdosage.

Bipolar Disorder Precautions It is generally believed (though not established in controlled trials) that treating a major depressive episode with an antidepressant alone may increase the likelihood of precipitating a mixed or manic episode in patients at risk for bipolar disorder. Therefore, patients should be adequately screened for bipolar disorder prior to initiating treatment with an antidepressant; such screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, and depression).

Pediatric Precautions Safety and efficacy of nefazodone in children have not been established.

FDA has determined that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. However, FDA also states that depression and certain other psychiatric disorders are themselves associated with an increased risk of suicide. (See Cautions: Pediatric Precautions, in Fluoxetine Hydrochloride 28:16.04.20.) Anyone considering the use of nefazodone in a child or adolescent for any clinical use must therefore balance the potential risks with the clinical need. (See Suicidality Precautions under Dosage and Administration: Administration.)

■ **Dosage** Patients should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Suicidality Precautions under Dosage and Administration: Administration.)

Major Depressive Disorder For the treatment of major depressive disorder in adults, the recommended initial dosage of nefazodone hydrochloride is 100 mg twice daily. Based on the tolerance and clinical response of the patient, dosage may be increased by increments of 100–200 mg daily at intervals of not less than 1 week up to a maximum of 600 mg daily. While a relationship between dosage and antidepressant effect has not been established, the effective dosage of nefazodone hydrochloride in controlled clinical studies generally ranged from 300–600 mg daily.

Because geriatric or debilitated patients may have reduced nefazodone clearance and/or increased sensitivity to the adverse effects of CNS-active drugs, therapy with nefazodone hydrochloride should be initiated at a dosage of 50 mg twice daily in such patients and subsequent dosage adjustments generally made in smaller increments and at longer intervals than in younger patients. A nefazodone hydrochloride dosage of 200–400 mg daily generally provided optimum therapeutic effect in patients 65 years of age or older in controlled studies.

Although the optimum duration of nefazodone therapy has not been established, acute depressive episodes may require 6 months or longer of sustained antidepressant medication. Whether the dosage of nefazodone required to induce remission of depression would be comparable to that required to maintain euthymia currently is not known.

■ **Dosage in Renal and Hepatic Impairment** While the manufacturer makes no specific recommendations for modification of dosage in patients with hepatic impairment, AUC values for nefazodone and its active metabolite hydroxynefazodone are increased by approximately 25% in patients with cirrhosis; therefore, nefazodone should be used with caution in patients with clinically important hepatic dysfunction. The manufacturer makes no specific recommendations for modification of dosage in patients with renal impairment. Limited data indicate that steady-state plasma concentrations of nefazodone in patients with renal impairment (creatinine clearance: 7–60 mL/minute per 1.73 m^2 body surface area) do not differ from those in healthy individuals.

Description

Nefazodone is a phenylpiperazine-derivative antidepressant agent. While the drug is structurally related to trazodone, nefazodone differs chemically and pharmacologically from selective serotonin-reuptake inhibitors, monoamine oxidase inhibitors, and tricyclic and tetracyclic antidepressant agents. The exact mechanism of antidepressant action of nefazodone has not been fully elucidated but appears more complex than other antidepressant agents and may involve inhibition of reuptake of serotonin (5-hydroxytryptamine [5-HT]) at the presynaptic membrane, antagonism at serotonin type 2 (5-HT_2) receptors, and down-regulation of 5-HT_2 receptor binding sites. Nefazodone also inhibits presynaptic reuptake of norepinephrine and exhibits α_1-adrenergic blocking activity. In vitro studies have demonstrated that the drug possesses little or no affinity for α_2-adrenergic, β-adrenergic, muscarinic, dopaminergic, histamine H_1, 5-HT_{1A}, or GABA-benzodiazepine receptors.

SumMon® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the labeling be consulted for detailed information on the usual cautions, precautions, and contraindications.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Nefazodone Hydrochloride

Oral		
Tablets	50 mg*	Nefazodone Hydrochloride Tablets
	100 mg*	Nefazodone Hydrochloride Tablets
	150 mg*	Nefazodone Hydrochloride Tablets
	200 mg*	Nefazodone Hydrochloride Tablets
	250 mg*	Nefazodone Hydrochloride Tablets

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Trazodone Hydrochloride

■ Trazodone hydrochloride is a triazolopyridine-derivative antidepressant that is chemically and structurally unrelated to tricyclic or tetracyclic antidepressants or to selective serotonin-reuptake inhibitors.

Uses

■ **Major Depressive Disorder** Trazodone is used in the treatment of major depressive disorder. The drug is used in patients who exhibit a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning and is manifested as a change in appetite, psychomotor agitation or retardation, a loss of interest in usual activities, a decrease in sexual drive, increased fatigability, a change in sleep, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and/or suicidal ideation or attempts. Trazodone has been used effectively in the treatment of patients who have major depression with or without prominent anxiety. In addition, trazodone has been used effectively in patients with major depression in hospital, institutional, and outpatient settings. Unlike tricyclic antidepressants, trazodone generally has not been reported to precipitate hypomanic or manic attacks in patients with bipolar disorder; however, further study is needed to determine the safety and efficacy of trazodone when used alone as an antidepressant in these patients.

Trazodone is particularly effective in reducing affective and ideational manifestations of depression, especially anxiety, apathy, irritability, and suicidal thoughts. Somatic signs and symptoms associated with depression, including sleep disturbances and fatigue, are also reduced during trazodone therapy. Most clinical studies have shown that the antidepressant effect of usual dosages of trazodone in patients with moderate to severe depression is about equal to that of usual dosages of amitriptyline, imipramine, or doxepin. However, trazodone has reportedly caused fewer adverse effects (e.g., anticholinergic effects) than these tricyclic antidepressants. (See Cautions: Anticholinergic Effects.) Although trazodone has been reported to have a slightly more rapid onset of action than amitriptyline, desipramine, or imipramine, this has not been established.

Trazodone has been used in patients with major depression who have associated anxiety. Based on limited data, the antidepressant effect of usual dosages of trazodone appears to be greater than that of amitriptyline or imipramine in these patients. Trazodone is particularly effective in reducing anxiety, tension, somatic symptoms, insomnia, and psychomotor retardation in these patients.

For further information on treatment of major depressive disorder and considerations in choosing the most appropriate antidepressant for a particular patient, including considerations related to patient tolerance, patient age, and cardiovascular, sedative, and suicidal risk, see Considerations in Choosing Antidepressants under Uses: Major Depressive Disorder, in Fluoxetine Hydrochloride 28:16.04.20.

■ **Schizophrenic Disorder** Although trazodone has been used in the treatment of schizophrenic disorder†, the drug is less effective than chlorpromazine. Depressive symptomatology may improve during trazodone therapy, but the drug does not appear to relieve psychotic symptoms in most schizophrenic patients. Based on limited data, trazodone has little value when used alone in patients with chronic schizophrenic disorder without depression; however, it

may be a useful adjunct to antipsychotic agents (e.g., phenothiazines) in patients with chronic schizophrenic disorder and associated depression. Unlike tricyclic antidepressants, trazodone does *not* appear to worsen psychotic symptoms in these patients.

■ **Alcohol Dependence** Trazodone has been used in the adjunctive treatment of alcohol dependence†. In a limited number of patients with alcohol dependence, oral (50–75 mg daily) or IV (50 mg twice daily) trazodone has reduced tremor, depression, and anxiety. In one study, trazodone was more effective in patients who had pronounced affective symptomatology during periods of intoxication and abstention than in those who only had affective symptomatology during intoxication. Further study is needed to determine the efficacy of trazodone in the treatment of alcohol dependence.

■ **Erectile Dysfunction** Trazodone has been used in a limited number of patients for the treatment of erectile dysfunction† (ED, impotence); however, the American Urological Association (AUA) states that such therapy currently is not recommended. Although some studies indicated that trazodone was more effective than placebo for the treatment of erectile dysfunction, other comparative studies did not. In addition, pooled analysis of these studies failed to show a statistically beneficial effect of the drug on sexual function, although subgroup analysis suggested possible benefit in those with psychogenic erectile dysfunction.

■ **Other Uses** Trazodone may be useful in the treatment of some patients with anxiety states† (anxiety neuroses). In one study, the drug reduced anxiety, tension, somatic symptoms, and insomnia in most of these patients. Based on limited data, trazodone appears to have a greater anxiolytic effect than some other antidepressant agents (e.g., tricyclic antidepressants); however, further study is needed to confirm this finding.

Trazodone has been used in the symptomatic treatment of a limited number of patients with drug-induced dyskinesias†. In one placebo-controlled study in patients with levodopa-induced dyskinesias, oral trazodone (60–120 mg daily) reduced signs and symptoms of dyskinesia by up to 50%. In this study, most patients showed some improvement, with greatest improvement in facial, oro-buccal-facial, and neck dyskinesias. In another study, IV trazodone (50 mg twice daily) eliminated chronic chlorpromazine- and haloperidol-induced tardive dyskinesias in some patients. The decrease in tremor was accompanied by a reduction in anxiety, which may be partly responsible for the favorable effect of trazodone on tremor in these patients. Additional studies are required to determine the efficacy of trazodone in the treatment of drug-induced dyskinesias.

Dosage and Administration

■ **Administration** Trazodone hydrochloride is administered orally. The drug should be taken shortly after a meal or light snack. If drowsiness occurs, a major portion of the daily dose may be given at bedtime or dosage may be reduced.

■ **Dosage** There is a wide range of individual trazodone hydrochloride dosage requirements, and dosage must be carefully adjusted according to individual tolerance and response, using the lowest possible effective dosage.

Patients receiving trazodone should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Cautions: Precautions and Contraindications.)

Major Depressive Disorder For the treatment of major depressive disorder, the usual initial adult dosage of trazodone hydrochloride is 150 mg daily given in divided doses. Dosage may be increased by 50 mg/day every 3 or 4 days, depending on the patient's therapeutic response and tolerance. The maximum dosage for outpatients usually should not exceed 400 mg daily. Dosages up to 600 mg daily may be required in hospitalized, institutionalized, or severely depressed patients. Dosages up to 800 mg daily have been used in the treatment of some patients with severe depression; however, the manufacturers do not recommend exceeding a dosage of 600 mg daily.

Although symptomatic relief may be seen in some patients during the first week of therapy, optimum antidepressant effect usually occurs within 2 weeks. About 25% of patients who respond to trazodone require up to 4 weeks of therapy to reach optimum response.

To avoid recurrence of depressive symptoms, trazodone therapy may be required for several months following optimum therapeutic response. Dosage during prolonged maintenance therapy should be kept at the lowest effective level; once an adequate response has been achieved, dosage should be gradually reduced and subsequently adjusted according to the patient's therapeutic response and tolerance.

Cautions

Trazodone hydrochloride apparently causes fewer adverse anticholinergic effects than currently available tricyclic antidepressant agents. Other adverse effects, including cardiovascular effects, also appear to occur less frequently with trazodone than with currently available tricyclic antidepressants.

The incidence and severity of adverse reactions to trazodone in relation to dosage and duration of therapy have not been fully characterized; however, adverse effects appear to occur more frequently at dosages greater than 300 mg/day. Total trazodone hydrochloride dosages up to 800 mg daily have been well tolerated by some patients. Adverse effects appear to be mild to moderate in severity and may decrease after the first few weeks of trazodone therapy. Adverse effects may be obviated by a reduction in dosage or alteration in dosage schedule. Serious reactions requiring discontinuance of therapy are relatively rare.

■ **Nervous System Effects** Adverse nervous system effects occur frequently during the first few weeks of therapy with trazodone. The most frequent adverse effect associated with trazodone therapy is drowsiness, which occurs in 20–50% of patients receiving the drug. Other less frequent adverse nervous system effects of trazodone include dizziness and lightheadedness, nervousness, fatigue, malaise, weakness, heaviness or fullness of the head, headache, and insomnia. Confusion, incoordination, anger or hostility, agitation, decreased concentrating ability, impaired memory, impaired speech, disorientation, hallucinations or delusions, and excitement have also occurred. Hypomania, nightmares or vivid dreams, tonic-clonic seizures, tremors, and paresthesias and akathisia occur rarely.

■ **Anticholinergic Effects** Although bothersome anticholinergic effects commonly occur with tricyclic antidepressants, these effects appear to occur less frequently with trazodone. Dry mouth has been reported in about 15–30% of patients during trazodone therapy; it has been suggested that this effect may result from an α-adrenergic blocking effect rather than an anticholinergic effect of trazodone. In several placebo-controlled studies, the incidence of dry mouth was similar in trazodone- and placebo-treated patients. Other anticholinergic effects such as blurred vision, constipation, and urinary retention have been reported less frequently.

■ **Genitourinary Effects** Trazodone therapy has been associated with priapism, with surgical intervention required in approximately one-third of reported cases; in some cases, permanent impairment of erectile function or impotence has resulted. Male patients receiving trazodone who experience prolonged or inappropriate penile erections should immediately discontinue the drug and consult their physician. Decreased or increased libido, retrograde ejaculation, impotence, inhibited female orgasm (anorgasmia), increased urinary frequency, delayed urine flow, and hematuria have also been associated with trazodone therapy.

■ **GI Effects** Adverse GI effects of trazodone include nausea and vomiting, dysgeusia, and abdominal and gastric disorders. Flatulence and diarrhea have also been reported.

■ **Cardiovascular Effects** Trazodone is thought to be less cardiotoxic than currently available tricyclic antidepressant agents. (See Pharmacology: Cardiovascular Effects.) Hypotension (including orthostatic hypotension) is the most frequent adverse cardiovascular effect of trazodone, occurring in about 5% of patients receiving the drug. In most patients, hypotension is mild and not dose related. Syncope, shortness of breath, chest pain, tachycardia, palpitations, and hypertension have also occurred. Bradycardia has occurred in a few patients during long-term therapy.

Various ECG changes have occurred in patients receiving trazodone. In patients with preexisting cardiac disease, trazodone may be arrhythmogenic. PVCs, ventricular couplets, and short episodes (3 or 4 beats) of ventricular tachycardia have occurred in these patients. Arrhythmias have also been reported in patients without preexisting cardiac disease. Cardiac arrest has also been reported. Myocardial infarction has been reported, but this effect has not been attributed directly to trazodone.

■ **Hematologic Effects** Occasional decreases in leukocyte and neutrophil counts have occurred in some patients receiving trazodone. These changes were not considered clinically important and did not require discontinuance of the drug. Anemia has also been associated with trazodone therapy in a few patients.

■ **Other Adverse Effects** Musculoskeletal aches and pains have occurred in about 5% of patients receiving trazodone. A few patients have developed muscle twitches. Pruritus, rash, urticaria, acne, photosensitivity, edema, nasal or sinus congestion, eye irritation, sweating or clamminess, early or absent menses, and tinnitus have been reported in some patients receiving trazodone. Allergic reactions and hypersalivation have rarely occurred. Minimal increases in serum concentrations of alkaline phosphatase, AST (SGOT), and ALT (SGPT) have occurred in some patients receiving trazodone.

■ **Precautions and Contraindications** Worsening of depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior may occur in both adult and pediatric (see Cautions: Pediatric Precautions) patients with major depressive disorder or other psychiatric disorders, whether or not they are taking antidepressants. This risk may persist until clinically important remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. However, there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term, placebo-controlled studies of antidepressants (i.e., selective serotonin-reuptake inhibitors and other antidepressants) have shown an increased risk of suicidality in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. An increased suicidality risk was not demonstrated with antidepressants compared with placebo in adults older than 24 years of age, and a reduced risk was observed in adults 65 years of age or older. It currently is unknown whether the suicidality risk extends to longer-term use (i.e., beyond

several months); however, there is substantial evidence from placebo-controlled maintenance trials in adults with major depressive disorder that antidepressants can delay the recurrence of depression.

The US Food and Drug Administration (FDA) recommends that all patients being treated with antidepressants for any indication be appropriately monitored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during initiation of therapy (i.e., the first few months) and during periods of dosage adjustments. Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, also should be advised to monitor patients on a daily basis for the emergence of agitation, irritability, or unusual changes in behavior as well as the emergence of suicidality, and to report such symptoms immediately to a health-care provider.

Although a causal relationship between the emergence of symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and/or mania and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consequently, consideration should be given to changing the therapeutic regimen or discontinuing therapy in patients whose depression is persistently worse or in patients experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, particularly if such manifestations are severe, abrupt in onset, or were not part of the patient's presenting symptoms. FDA also recommends that the drugs be prescribed in the smallest quantity consistent with good patient management, in order to reduce the risk of overdosage. Because of the possibility of comorbidity between major depressive disorder and other psychiatric and nonpsychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and nonpsychiatric disorders.

It is generally believed (though not established in controlled trials) that treating a major depressive episode with an antidepressant alone may increase the likelihood of precipitating a mixed or manic episode in patients at risk for bipolar disorder. Therefore, patients should be adequately screened for bipolar disorder prior to initiating treatment with an antidepressant; such screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, and depression).

Patients should be warned that trazodone may impair their ability to perform activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle). Patients also should be warned that trazodone may enhance their response to alcohol, barbiturates, or other CNS depressants. Since the risk of dizziness or lightheadedness may be increased during fasting conditions, patients should be advised to take trazodone shortly after a meal or light snack. In addition, total drug absorption may be up to 20% greater when the drug is taken with food rather than on an empty stomach. Because priapism has been associated with trazodone therapy, patients should be instructed to discontinue the drug and consult a physician if prolonged or inappropriate penile erection occurs.

Until additional clinical experience on the safety of trazodone in patients with cardiovascular disease is obtained, it is recommended that these patients be closely monitored, particularly for arrhythmias, while receiving the drug. (See Cautions: Cardiovascular Effects.) It is also recommended that trazodone *not* be used during the initial recovery phase of myocardial infarction.

Leukocyte and differential counts should be performed in patients who develop fever and sore throat or other signs of infection while receiving trazodone. The drug should be discontinued in patients whose leukocyte or absolute neutrophil count decreases to less than normal levels. (See Cautions: Hematologic Effects.)

Trazodone is contraindicated in patients who are hypersensitive to the drug.

■ **Pediatric Precautions** Safety and efficacy of trazodone in children younger than 18 years of age have not been established.

FDA warns that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. The risk of suicidality for these drugs was identified in a pooled analysis of data from a total of 24 short-term (4–16 weeks), placebo-controlled studies of 9 antidepressants (i.e., bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine) in over 4400 children and adolescents with major depressive disorder, obsessive-compulsive disorder (OCD), or other psychiatric disorders. The analysis revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in pediatric patients receiving antidepressants than in those receiving placebo. The average risk of such events was 4% among children and adolescents receiving these drugs, twice the risk (2%) that was observed among those receiving placebo. However, a more recent meta-analysis of 27 placebo-controlled trials of 9 antidepressants (SSRIs and others) in patients younger than 19 years of age with major depressive disorder, OCD, or non-OCD anxiety disorders suggests that the benefits of antidepressant therapy in treating these conditions may outweigh the risks of suicidal behavior or suicidal ideation. No suicides occurred in these pediatric trials.

The risk of suicidality in FDA's pooled analysis differed across the different psychiatric indications, with the highest incidence observed in the major depressive disorder studies. In addition, although there was considerable variation in risk among the antidepressants, a tendency toward an increase in suicidality risk in younger patients was found for almost all drugs studied. It is currently unknown whether the suicidality risk in pediatric patients extends to longer-term use (i.e., beyond several months).

As a result of this analysis and public discussion of the issue, FDA has directed manufacturers of all antidepressants to add a boxed warning to the labeling of their products to alert clinicians of this suicidality risk in children and adolescents and to recommend appropriate monitoring and close observation of patients receiving these agents. (See Cautions: Precautions and Contraindications.) The drugs that are the focus of the revised labeling are all drugs included in the general class of antidepressants, including those that have not been studied in controlled clinical trials in pediatric patients, since the available data are not adequate to exclude any single antidepressant from an increased risk of suicidality. In addition to the boxed warning and other information in professional labeling on antidepressants, FDA currently recommends that a patient medication guide explaining the risks associated with the drugs be provided to the patient each time the drugs are dispensed.

Anyone considering the use of trazodone in a child or adolescent for any clinical use must balance the potential risk of therapy with the clinical need.

■ **Mutagenicity and Carcinogenicity** In vitro tests have *not* shown trazodone to be mutagenic. No evidence of carcinogenesis was seen in animals receiving oral trazodone dosages up to 300 mg/kg daily for 18 months.

■ **Pregnancy, Fertility, and Lactation** Trazodone has been shown to be teratogenic in rats and rabbits when given at dosages 15–50 times the maximum human dosage. The drug also caused increased fetal resorption and other adverse fetal effects in rats when given at dosages approximately 30–50 times the suggested maximum human dosage. There are no adequate and controlled studies to date using trazodone in pregnant women, and the drug should be used during pregnancy only when the potential benefits justify the possible risks to the fetus.

The effect of trazodone on fertility in humans is not known. Impotence, retrograde ejaculation, and decreased or increased libido have occurred in some individuals during trazodone therapy. Reproduction studies in male and female rats using trazodone dosages up to 150 times the usual human dosage have not revealed evidence of impaired fertility.

Because trazodone is distributed into milk, the drug should be used with caution in nursing women.

Drug Interactions

■ **Drugs Affecting Hepatic Microsomal Enzymes** Results of in vitro studies indicate that metabolism of trazodone is mediated by the cytochrome P-450 (CYP) 3A4 isoenzyme, and the possibility exists that drugs that inhibit or induce this isoenzyme may affect the pharmacokinetics of trazodone. Other metabolic pathways that may be involved in the metabolism of trazodone have not been well characterized.

Concomitant use of trazodone with inhibitors of CYP3A4 can result in substantially increased plasma concentrations of trazodone and increase the potential for adverse effects. In one study, concomitant use of ritonavir (200 mg twice daily for 2 days) and trazodone (a single 50-mg dose) in healthy individuals increased maximum plasma concentrations and decreased clearance of trazodone by 34 and 52%, respectively, and increased area under the plasma concentration-time curve (AUC) and half-life of trazodone by greater than two-fold. Adverse effects (e.g., nausea, hypotension, syncope) also were observed with concomitant use of trazodone and ritonavir. The manufacturers of trazodone state that a reduction in trazodone dosage should be considered in patients receiving a potent inhibitor of the CYP3A4 isoenzyme (e.g., indinavir, itraconazole, ketoconazole, nefazodone, ritonavir) concomitantly with trazodone.

Concomitant use of trazodone (100–300 mg daily) with carbamazepine (400 mg daily), an inducer of CYP3A4, decreased plasma concentrations of trazodone and an active metabolite, *m*-chlorophenylpiperazine, by 76 and 60%, respectively. Patients receiving trazodone and carbamazepine concomitantly should be closely monitored and dosage of trazodone increased if necessary.

■ **Serotonergic Agents** ***Fluoxetine*** Elevated plasma trazodone concentrations and adverse effects possibly associated with trazodone toxicity have been reported occasionally during concomitant trazodone and fluoxetine therapy. Although the exact mechanism has not been established, it has been suggested that fluoxetine may inhibit the hepatic metabolism of many antidepressant agents, including trazodone. In addition, both trazodone and fluoxetine possess serotonergic activity; therefore, the possibility of serotonin syndrome also should be considered in patients receiving trazodone and fluoxetine or other selective serotonin-reuptake inhibitor therapy concurrently. For detailed information on serotonin syndrome, see Drug Interactions: Drugs Associated with Serotonin Syndrome in Fluoxetine Hydrochloride 28:16.04.20 and the Monoamine Oxidase Inhibitors General Statement 28:16.04.12. Further study is needed, but current evidence suggests that patients receiving trazodone and fluoxetine concomitantly should be observed closely for adverse effects; monitoring of plasma trazodone concentrations also should be considered and trazodone dosage reduced as necessary.

Monoamine Oxidase Inhibitors It is not known whether interactions between trazodone and monoamine oxidase (MAO) inhibitors can occur. Unlike tricyclic antidepressants, trazodone does not interfere with catecholamine uptake by the adrenergic neuron or the pressor response to tyramine. Therefore, an interaction between trazodone and MAO inhibitors is unlikely. However, both trazodone and MAO inhibitors possess serotonergic activity; therefore, the possibility that serotonin syndrome may occur during concurrent

therapy should be considered. For detailed information on serotonin syndrome, see Drug Interactions: Drugs Associated with Serotonin Syndrome in Fluoxetine Hydrochloride 28:16.04.20 and the Monoamine Oxidase Inhibitors General Statement 28:16.04.12. Because of the absence of clinical experience, if MAO inhibitors are discontinued shortly before or are to be given concomitantly with trazodone, it is recommended that trazodone therapy be initiated cautiously and dosage increased gradually until optimum response is achieved.

Other Serotonergic Agents Trazodone possesses serotonergic activity and rarely has been associated with serotonin syndrome when combined with other serotonergic agents, including buspirone, phenelzine, and dextropropoxyphene. Because severe complications and even fatalities have accompanied the serotonin syndrome, trazodone probably should be used with caution in patients receiving or who recently have received other serotonergic agents. For additional information on potentially serious drug interactions that may occur between trazodone and other serotonergic agents, see Drug Interactions: Drugs Associated with Serotonin Syndrome, in Fluoxetine Hydrochloride 28:16.04.20 and the Monoamine Oxidase Inhibitors General Statement 28:16.04.12.

■ **General Anesthetics** Since little is known about the interaction between trazodone and general anesthetics, it is recommended that trazodone be discontinued for as long as clinically feasible prior to elective surgery.

■ **Electroconvulsive Therapy** Pending further accumulation of clinical data on the concurrent use of trazodone and electroconvulsive therapy (ECT), concurrent use of these therapies should be avoided.

■ **CNS Depressants** Trazodone may be additive with, or may potentiate the action of, other CNS depressants such as opiates or other analgesics, barbiturates or other sedatives, anesthetics, or alcohol. When trazodone is used concomitantly with other CNS depressants, caution should be used to avoid excessive sedation.

■ **Hypotensive Agents** Because trazodone can cause hypotension, including orthostatic hypotension and syncope, concomitant administration of antihypertensive therapy may require a reduction in dosage of the antihypertensive agent(s). Trazodone has been shown to inhibit the hypotensive effect of various antihypertensive agents (e.g., clonidine, methyldopa) in animals; however, this inhibition has not always been reproducible. It is not known whether trazodone can inhibit the hypotensive effect of these agents in humans, and the clinical importance of this potential interaction has not been determined.

■ **Other Drugs** Increased serum digoxin or phenytoin concentrations have reportedly occurred in patients receiving trazodone concurrently with either drug.

■ **Food** The rate and extent of absorption of trazodone are affected by the presence of food. When trazodone is taken shortly after the ingestion of food, there may be a slight increase in the amount of drug absorbed, a decrease in peak plasma concentration of the drug, and a lengthening of the time to reach the peak plasma concentration. Total drug absorption may be up to 20% greater when the drug is taken with food rather than on an empty stomach. In animals, the rate of absorption has been delayed when trazodone was administered concomitantly with food because of a decrease in the rate of transfer of the drug from the stomach to the small intestine.

The effect of food on absorption of trazodone during long-term administration of the drug is not considered clinically important. Concomitant administration of trazodone with food is generally recommended since it appears to decrease the incidence of dizziness or lightheadedness.

Acute Toxicity

Limited information is available on the acute toxicity of trazodone.

■ **Pathogenesis** The acute lethal dose of trazodone in humans is not known. In addition, there is no clearly defined relationship between plasma trazodone concentration and severity of intoxication. The oral LD_{50} of trazodone is 610 mg/kg in mice, 486 mg/kg in rats, 560 mg/kg in rabbits, and 500 mg/kg in dogs. In animals, lethal doses produced dyspnea, salivation, prostration, and clonic seizures.

■ **Manifestations** One patient who intentionally ingested 7.5 g of trazodone experienced only drowsiness and weakness; the patient was aroused at the time of hospitalization and emesis was induced. Another patient had an uneventful recovery after ingesting 9.2 g of trazodone. There have been several reports of accidental ingestion in children; however, the exact amounts ingested are unknown. Each of these children exhibited only lethargy and drowsiness, and recoveries were uneventful. Fatalities have occurred in adults who intentionally ingested trazodone and other drugs (e.g., alcohol, chloral hydrate, amobarbital, chlordiazepoxide, meprobamate) concurrently.

In general, overdosage of trazodone may be expected to produce effects that are extensions of common adverse reactions; vomiting, drowsiness, and lethargy have been the principal effects reported. Other reported effects associated with acute trazodone overdosage have included orthostatic hypotension, tachycardia, coma, headache, tinnitus, dizziness, dyspnea, shivering, aching muscles, incontinence, and dry mouth. Unlike tricyclic antidepressant overdosage, seizures and arrhythmias do not appear to be associated with trazodone overdosage.

■ **Treatment** Treatment of trazodone overdosage generally involves symptomatic and supportive care; there is no specific antidote for trazodone intoxication. In acute overdosage, the stomach should be emptied immediately by inducing emesis or by gastric lavage. If the patient is comatose, having seizures, or lacks the gag reflex, gastric lavage may be performed if an endotracheal tube with cuff inflated is in place to prevent aspiration of vomitus. Although administration of activated charcoal after gastric lavage and/or emesis has been useful in the treatment of acute overdosage with tricyclic antidepressants, the effect of activated charcoal on the absorption of trazodone is not currently known. Appropriate therapy should be instituted if hypotension or excessive sedation occurs. Forced diuresis may be useful in facilitating elimination of the drug. It is not known if trazodone is dialyzable; however, because of extensive protein binding of the drug, hemodialysis is probably *not* effective in enhancing elimination of trazodone.

Pharmacology

The pharmacology of trazodone is complex and in some ways resembles that of tricyclic antidepressants, benzodiazepines, and phenothiazines; however, the overall pharmacologic profile of trazodone differs from each of these classes of drugs.

■ **Nervous System Effects** The precise mechanism of antidepressant action of trazodone is unclear, but the drug has been shown to selectively block the reuptake of serotonin (5-HT) at the presynaptic neuronal membrane. The effects of serotonin may thus be potentiated. Unlike other antidepressant agents (e.g., tricyclic antidepressants), trazodone may have a dual effect on the central serotonergic system. Animal studies indicate that trazodone acts as a serotonin agonist at high doses (6–8 mg/kg), while at low doses (0.05–1 mg/kg), it antagonizes the actions of serotonin. Trazodone does not appear to influence the reuptake of dopamine or norepinephrine within the CNS; however, animal studies indicate that trazodone may enhance release of norepinephrine from neuronal tissue. Trazodone does not cause serotonin release in vitro.

Although the mechanism of action of antidepressant agents may involve inhibition of the reuptake of various neurotransmitters at the presynaptic neuronal membrane, long-term therapy with antidepressant agents also affects postsynaptic neuronal receptor binding sites, resulting in some adaptive changes in neurotransmission. Long-term administration of trazodone reportedly decreases the number of postsynaptic serotonergic (i.e., serotonin$_2$) and β-adrenergic binding sites in the brain of animals. Although the clinical importance of these effects is not known, the decrease in binding sites is associated with a functional increase in serotonergic activity and a reduction in the sensitivity of adenylate cyclase to stimulation by β-adrenergic agonists. It has been suggested that postsynaptic receptor modification is mainly responsible for the antidepressant action observed during long-term administration of trazodone. Further study is needed to determine the role of binding site alteration in the antidepressant action of trazodone and other antidepressants.

In animals, trazodone's effect on various avoidance behaviors is similar to that of phenothiazines. Unlike phenothiazines, however, trazodone potentiates the effects of serotonin. Trazodone does not potentiate the actions of levodopa or alter neuronal concentrations of acetylcholine. Trazodone does not inhibit monoamine oxidase, and unlike amphetamine-like drugs, does not stimulate the CNS.

Unlike many currently available antidepressants, trazodone exhibits little, if any, anticholinergic activity in vitro. Clinical studies show a lower incidence of anticholinergic effects (e.g., dry mouth, blurred vision, urinary retention, constipation) associated with trazodone use than with tricyclic antidepressant use. (See Cautions: Anticholinergic Effects.)

Trazodone produces varying degrees of sedation in normal and mentally depressed patients. The sedative effect is thought to result principally from central α_1-adrenergic blocking activity and possibly from a histamine blocking action of the drug. Trazodone may cause EEG changes, including increased slow-wave and alpha-wave activity. Some increase in fast-wave activity also occurs. Trazodone increases total sleep time, decreases the number and duration of awakenings in depressed patients, and decreases rapid eye movement (REM) sleep. Unlike tricyclic antidepressants, trazodone does not increase stage 4 sleep.

Although the exact mechanism of action has not been determined, trazodone has an anxiolytic effect. This finding is supported by animal studies in which trazodone is active in certain antianxiety test systems. In addition, the drug has demonstrated anxiolytic activity in patients with major depression who also have associated anxiety. (See Uses: Major Depressive Disorder.)

Therapeutic dosages of trazodone do not appear to affect respiration; however, the effect of higher dosages of trazodone in patients with ventilatory insufficiency is not known.

Like many other centrally acting agents, trazodone exhibits analgesic activity in a variety of analgesic test systems. Trazodone also has weak skeletal muscle relaxant activity but lacks anticonvulsant effects.

Trazodone possesses potent peripheral α-adrenergic blocking activity in animals following IV administration of 3–10 mg/kg. In addition, in animals, the drug blocks the peripheral effects of serotonin, epinephrine, norepinephrine, and histamine. The peripheral antihistaminic effects of trazodone are weaker than those of tricyclic antidepressants.

■ **Cardiovascular Effects** The cardiovascular effects of trazodone have been studied in animals and to a limited extent in humans. Unlike other antidepressant agents (e.g., tricyclic antidepressants, monoamine oxidase inhibitors), trazodone has been associated with only minimal cardiovascular effects. (See Cautions: Cardiovascular Effects.) The absence of substantial anti-

cholinergic activity and catecholamine-potentiating effects appears to be the principal reason for the general lack of cardiovascular effects of trazodone.

Trazodone exhibits α-adrenergic blocking activity and does not inhibit catecholamine reuptake. Unlike tricyclic antidepressants, trazodone blocks the pressor response to norepinephrine and lowers arterial blood pressure. However, in one study in normotensive patients with endogenous depression, the effect of trazodone on systemic blood pressure was equivocal. Trazodone does not block the neuronal uptake of tyramine; thus, unlike tricyclic antidepressants, the drug has no effect on the pressor response to this sympathomimetic amine.

Although trazodone does *not* appear to have substantial arrhythmogenic activity, arrhythmias have occurred in some patients with preexisting cardiac disease during trazodone therapy. (See Cautions: Cardiovascular Effects.) In animals, trazodone does *not* affect intra-atrial, ventricular septal, ventricular free-wall, His-Purkinje, or AV nodal conduction. At doses up to 30 mg/kg in animals, trazodone produces only minimal ECG changes, including prolongation of the QT interval and a decrease in heart rate. Unlike tricyclic antidepressants, trazodone does not exert direct quinidine-like cardiotoxic properties. In addition, trazodone does *not* exert a negative inotropic effect at therapeutic dosages; the drug may decrease aortic blood flow as a result of a decrease in heart rate.

To date, there have been no published studies comparing the cardiovascular effects of therapeutic dosages of trazodone with those of antidepressants such as mianserin, nomifensine, or zimelidine. Although available data suggest that trazodone is less cardiotoxic than tricyclic antidepressant agents at therapeutic dosages, the cardiovascular effects of trazodone overdosage have not been well described.

■ **Other Effects** Trazodone may affect the endocrine system. Following oral administration of a single 50-mg dose in one study in healthy adults, trazodone caused a decrease in mean serum prolactin concentration. However, in another study in depressed patients, trazodone did not alter mean serum prolactin concentration following oral administration of 200 mg daily for 2 weeks.

Trazodone-induced antagonism of α_2-adrenergic receptors may relax the tissues and enhance arterial inflow in penile vascular and corporal smooth muscle resulting in an erection.

Pharmacokinetics

In all studies described in the Pharmacokinetics section, trazodone was administered as the hydrochloride salt.

■ **Absorption** Trazodone is rapidly and almost completely absorbed from the GI tract following oral administration. The rate and extent of absorption are affected by the presence of food. When trazodone is taken shortly after the ingestion of food, there may be a slight increase (up to 20%) in the amount of drug absorbed, a decrease in peak plasma concentration of the drug, and a lengthening of the time to reach the peak plasma concentration.

Peak plasma concentrations of trazodone occur approximately 1 hour after oral administration when the drug is taken on an empty stomach or 2 hours after oral administration when taken with food. Following oral administration of multiple doses of trazodone (25 mg 2 or 3 times daily), steady-state plasma concentrations of the drug are usually attained within 4 days and exhibit wide interpatient variation. Following oral administration of a single 25-mg dose of radiolabeled trazodone to healthy adults in one study, mean peak plasma drug concentrations of 650 and 480 ng/mL occurred at 1.5 and 2.5 hours after ingestion, in the fasted and nonfasted state, respectively. Following oral administration of single doses of 25, 50, or 100 mg of trazodone to healthy, fasted adults in another study, mean peak plasma trazodone concentrations were 490, 860, and 1620 ng/mL, respectively. The areas under the plasma concentration-time curves (AUCs) were 3.44, 5.95, and 11.19 mcg-h/mL, for the 25-, 50-, and 100-mg doses, respectively. Limited crossover data are available comparing AUCs in fasted and nonfasted patients; however, it appears that the presence of food slightly increases the AUC for trazodone.

The therapeutic range for plasma trazodone concentrations and the relationship of plasma concentrations to clinical response and toxicity have not been established.

■ **Distribution** Distribution of trazodone into human body tissues and fluids has not been determined. Following oral administration of trazodone in animals, the drug and its metabolites are distributed mainly into the liver, kidneys, small intestine, lungs, adrenal glands, and pancreas, with lower concentrations being distributed into adipose tissue, heart, and skeletal muscle. Trazodone crosses the blood-brain barrier in animals, and concentrations of the drug in the brain are higher than those in plasma during the first 8 hours after oral ingestion.

In vitro, trazodone is 89–95% bound to plasma proteins at plasma trazodone concentrations of 100–1500 ng/mL.

Although it is not known if trazodone crosses the placenta in humans, the drug crosses the placenta in animals. Following a single oral dose of 50 mg, trazodone is distributed into milk in concentrations approximately 10% of maternal plasma concentrations, with a milk-to-plasma ratio (based on areas under the plasma and milk concentration-time curves) of about 0.1–0.2. Based on these data, it is estimated that a nursing infant would ingest less than 0.1% of the dose. It is not known whether trazodone metabolites are distributed into milk.

■ **Elimination** Plasma concentrations of trazodone decline in a biphasic manner. The half-life of trazodone in the initial phase ($t_{1/2\alpha}$) is about 3–6 hours and the half-life in the terminal phase ($t_{1/2\beta}$) is about 5–9 hours. The clearance of trazodone from the body shows wide interindividual variation. The manufacturers state that the drug may accumulate in plasma in some individuals.

Trazodone is extensively metabolized in the liver via hydroxylation, oxidation, *N*-oxidation, and splitting of the pyridine ring. A hydroxylated metabolite and oxotriazolopyridinpropionic acid (an inactive metabolite excreted in urine) are conjugated with glucuronic acid. Results of in vitro studies indicate that metabolism of trazodone to an active metabolite, *m*-chlorophenylpiperazine, is mediated by the cytochrome P-450 (CYP) 3A4 isoenzyme. The manufacturers state that other metabolic pathways involved in metabolism of trazodone have not been well characterized. Results from animal studies indicate that trazodone does not induce its own metabolism.

Approximately 70–75% of an oral dose of trazodone is excreted in urine within 72 hours of administration, principally as metabolites. About 20% of an oral dose of trazodone is excreted in urine as oxotriazolopyridinpropionic acid and its conjugates, and about 10% as a dihydrodiol metabolite; less than 1% of a dose is excreted unchanged. The remainder of an oral dose of the drug is excreted in feces via biliary elimination, principally as metabolites.

Chemistry and Stability

■ **Chemistry** Trazodone hydrochloride is a triazolopyridine-derivative antidepressant. The drug is chemically and structurally unrelated to tricyclic or tetracyclic antidepressants or to selective serotonin-reuptake inhibitors. Trazodone hydrochloride occurs as a white, odorless, crystalline powder with a bitter taste and is freely soluble in water and sparingly soluble in alcohol. The drug has a pK_a of 6.7.

■ **Stability** Commercially available trazodone hydrochloride tablets should be stored at room temperature in tight, light-resistant containers and protected from temperatures greater than 40°C.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Trazodone Hydrochloride

Oral		
Tablets	50 mg*	Trazodone Hydrochloride Tablets
	100 mg*	Trazodone Hydrochloride Tablets
	150 mg*	Trazodone Hydrochloride Dividose* (scored), Sandoz
		Trazodone Hydrochloride Tablets
	300 mg*	Trazodone Hydrochloride Tablets

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name
†Use is not currently included in the labeling approved by the US Food and Drug Administration

TRICYCLICS AND OTHER NOREPINEPHRINE-REUPTAKE INHIBITORS 28:16.04.28

Tricyclic Antidepressants General Statement

■ Tricyclic antidepressants contain a 3-ring structure and differ structurally and pharmacologically from other currently available antidepressants (e.g., selective serotonin-reuptake inhibitors, monoamine oxidase inhibitors).

Uses

■ **Major Depressive Disorder** Tricyclic antidepressants are used in the treatment of major depressive disorder. A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks). According to DSM-IV criteria, a major depressive episode includes at least 5 of the following 9 symptoms (with at least one of the symptoms being depressed mood or loss of interest or pleasure): depressed mood most of the day as indicated by subjective report (e.g., feels sad or empty) or observation made by others; markedly diminished interest or pleasure in all, or almost all, activities most of the day; significant weight loss (when not dieting) or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite; insomnia or hypersomnia; psychomotor agitation or retardation (observable by others, not merely subjective feelings of restlessness or being slowed down); fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt (not merely self-reproach or guilt about being