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old or with a history of cardiac illness) should be routinely monitored. Nifedipine is available in 10- and 20-mg capsules and 30-, 60-, and 90-mg extendedrelease tablets. Administration should be started at 10 mg orally three or four times a day and can be increased up to a maximum dosage of 120 mg a day. Nimodipine is available in 30-mg capsules. It has been used at 60 mg every 4 hours for ultra–rapid-cycling bipolar disorder and sometimes briefly at up to 630 mg per day. Isradipine is available in 2.5- and 5-mg capsules, with a maximum of 20 mg/day. An extended-release formulation of isradipine has been discontinued. Amlodipine is available in 2.5-, 5-, and 10-mg tablets. Administration should start at 5 mg once at night and can be increased to a maximum dosage of 10 to 15 mg a day. Diltiazem is available in 30-, 60-, 90-, and 120-mg tablets; 60-, 90-, 120-, 180-, 240-, 300-, and 360-mg extended-release capsules; and 60-, 90-, 120-, 180-, 240-, 300-, and 360-mg extended-release tablets. Administration should start with 30 mg orally four times a day and can be increased up to a maximum of 360 mg a day. Elderly persons are more sensitive to the calcium channel inhibitors than are younger adults. No specific information is available regarding the use of the agents for children. REFERENCES Bachmann RF, Schloesser RJ, Gould TD, Manji HK. Mood stabilizers target cellular plasticity and resilience cascades. Mol Neurobiol. 2005;32:173. Dubovsky SL. Calcium channel inhibitors. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock’s Comprehensive Textbook of Psychiatry. 9th edition. Vol. 2. Philadelphia: Lippincott Williams & Wilkins: 2009:3065. Dubovsky SL, Buzan RD, Thomas M, Kassner C, Cullum CM. Nicardipine improves the antidepressant action of ECT but does not improve cognition. J ECT. 2001;17:3. Hasan M, Pulman J, Marson AG. Calcium antagonists as an add-on therapy for drug-resistant epilepsy. Cochrane Database Syst Rev. 2013;3:CD002750. Ikeda A, Kato T. Biological predictors of lithium response in bipolar disorder. Psychiatry Clin Neurosci. 2003;57:243. Kato T, Ishiwata M, Mori K, Washizuka S, Tajima O. Mechanisms of altered Ca2+ signaling in transformed lymphoblastoid cells from patients with bipolar disorder. Int J Neuropsychopharmacol. 2003;6:379. Nahorski SR. Pharmacology of intracellular signaling pathways. Br J Pharmacol. 2006;147:S38. Suzuki K, Kusumi I, Sasaki A, Koyama T. Serotonin-induced platelet intracellular calcium mobilization in various psychiatric disorders: Is it specific to bipolar disorder? J Affect Disord. 2001;64:291. Triggle DJ. Calcium channel antagonists: Clinical uses—past, present and future.

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Carbamazepine (Tegretol) possesses some structural similarity to the tricyclic antidepressant imipramine (Tofranil). It was approved for use in the United States for the treatment of trigeminal neuralgia in 1968 and for temporal lobe epilepsy (complex partial seizures) in 1974. Interestingly, carbamazepine was first synthesized as a potential antidepressant, but because of its atypical profile in a number of animal models, it was initially developed for use in pain and seizure disorders. It is now recognized in most guidelines as a second-line mood stabilizer useful in the treatment and prevention of both phases of bipolar affective disorder. A long-acting sustained release formulation (Equetro) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of acute mania in 2002. An analog of carbamazepine, oxcarbazepine (Trileptal), was marketed as an antiseizure medication in the United States in 2000, after being used as a treatment for pediatric epilepsy in Europe since 1990. Because of its similarity to carbamazepine, many clinicians began to use it as a treatment for patients with bipolar disorder. Despite some reports that oxcarbazepine has mood-stabilizing properties, this has not been confirmed in large, placebo-controlled trials. CARBAMAZEPINE Pharmacologic Actions Absorption of carbamazepine is slow and unpredictable. Food enhances absorption. Peak plasma concentrations are reached 2 to 8 hours after a single dose, and steadystate levels are reached after 2 to 4 days on a steady dosage. It is 70 to 80 percent protein bound. The half-life of carbamazepine ranges from 18 to 54 hours, with an average of 26 hours. However, with chronic administration, the half-life of carbamazepine decreases to an average of 12 hours. This results from induction of hepatic CYP450 enzymes by carbamazepine, specifically autoinduction of carbamazepine metabolism. The induction of hepatic enzymes reaches its maximum level after about 3 to 5 weeks of therapy. The pharmacokinetics of carbamazepine are different for two long-acting preparations of carbamazepine, each of which uses slightly different technology. One formulation, Tegretol XR, requires food to ensure normal gastrointestinal (GI) transit time. The other preparation, Carbatrol, relies on a combination of intermediate, extended-release, and very slow release beads, making it suitable for bedtime administration. Carbamazepine is metabolized in the liver, and the 10,11-epoxide metabolite is active as an anticonvulsant. Its activity in the treatment of bipolar disorders is unknown. Long-term use of carbamazepine is associated with an increased ratio of the epoxide to the parent molecule. The anticonvulsant effects of carbamazepine are thought to be mediated mainly by binding to voltage-dependent sodium channels in the inactive state and prolonging their inactivation. This secondarily reduces voltage-dependent calcium channel activation and, thus, synaptic transmission. Additional effects include reduction of currents through

N-methyl-d-aspartate (NMDA) glutamate-receptor channels, competitive antagonism of adenosine α1-receptors, and potentiation of central nervous system (CNS) catecholamine neurotransmission. Whether any or all of these mechanisms also result in mood stabilization is not known. Therapeutic Indications Bipolar Disorder ACUTE MANIA. The acute antimanic effects of carbamazepine are typically evident within the first several days of treatment. About 50 to 70 percent of all persons respond within 2 to 3 weeks of initiation. Studies suggest that carbamazepine may be especially

effective in persons who are not responsive to lithium (Eskalith), such as persons with dysphoric mania, rapid cycling, or a negative family history of mood disorders. The antimanic effects of carbamazepine can be, and often are, augmented by concomitant administration of lithium, valproic acid (Depakene), thyroid hormones, dopamine receptor antagonists (DRAs), or serotonin-dopamine antagonists (SDAs). Some persons may respond to carbamazepine but not lithium or valproic acid and vice versa. PROPHYLAXIS. Carbamazepine is effective in preventing relapses, particularly among patients with bipolar II disorder and schizoaffective disorder, and dysphoric mania. ACUTE DEPRESSION. A subgroup of treatment-refractory patients with acute depression responds well to carbamazepine. Patients with more severe episodic and less chronic depression seem to be better responders to carbamazepine. Nevertheless, carbamazepine remains an alternative drug for depressed persons who have not responded to conventional treatments, including electroconvulsive therapy (ECT). Other Disorders. Carbamazepine helps to control symptoms associated with acute alcohol withdrawal, although benzodiazepines are more effective in this population. Carbamazepine has been suggested as a treatment for the paroxysmal recurrent component of posttraumatic stress disorder (PTSD). Uncontrolled studies suggest that carbamazepine is effective in controlling impulsive, aggressive behavior in nonpsychotic persons of all ages, including children and elderly persons. Carbamazepine is also effective in controlling nonacute agitation and aggressive behavior in patients with schizophrenia and schizoaffective disorder. Persons with prominent positive symptoms (e.g., hallucinations) may be likely to respond, as are persons who display impulsive aggressive outbursts. Precautions and Adverse Reactions Carbamazepine is relatively well tolerated. Mild GI (nausea, vomiting, gastric distress, constipation, diarrhea, and anorexia) and CNS (ataxia, drowsiness) side effects are the most common. The severity of these adverse effects is reduced if the dosage of carbamazepine is increased slowly and kept at the minimal effective plasma

concentration. In contrast to lithium and valproate (other drugs used to manage bipolar disorder), carbamazepine does not appear to cause weight gain. Because of the phenomena of autoinduction, with consequent reductions in carbamazepine concentrations, side effect tolerability may improve over time. Most of the adverse effects of carbamazepine are correlated with plasma concentrations above 9 µg/mL. The rarest but most serious adverse effects of carbamazepine are blood dyscrasias, hepatitis, and serious skin reactions (Table 29.13-1). Table 29.13-1 Adverse Events Associated with Carbamazepine Blood Dyscrasias. The drug’s hematologic effects are not dose related. Severe blood dyscrasias (aplastic anemia, agranulocytosis) occur in about 1 in 125,000 persons treated with carbamazepine. There does not appear to be a correlation between the degree of benign white blood cell (WBC) suppression (leukopenia), which is seen in 1 to 2 percent of persons, and the emergence of life-threatening blood dyscrasias. Persons should be warned that the emergence of such symptoms as fever, sore throat, rash, petechiae, bruising, and easy bleeding can potentially herald a serious dyscrasia, and they should seek medical evaluation immediately. Routine hematologic monitoring in carbamazepine-treated persons is recommended at 3, 6, 9, and 12 months. If there is no significant evidence of bone marrow suppression by that time, many experts would reduce the interval of monitoring. However, even assiduous monitoring may fail to detect severe blood dyscrasias before they cause symptoms. Hepatitis. Within the first few weeks of therapy, carbamazepine can cause both hepatitis associated with increases in liver enzymes, particularly transaminases, and cholestasis associated with elevated bilirubin and alkaline phosphatase. Mild transaminase elevations warrant observation only, but persistent elevations more than three times the upper limit of normal indicate the need to discontinue the

drug. Hepatitis can recur if the drug is reintroduced to the person and can result in death. Dermatologic Effects. About 10 to 15 percent of those treated with carbamazepine develop a benign maculopapular rash within the first 3 weeks of treatment. Stopping the medication usually leads to resolution of the rash. Some patients may experience life-threatening dermatologic syndromes, including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. The possible emergence of these serious dermatologic problems causes most

clinicians to discontinue carbamazepine use in people who develop any type of rash. The risk of drug rash is about equal between valproic acid and carbamazepine in the first 2 months of use but is subsequently much higher for carbamazepine. If carbamazepine seems to be the only effective drug for a person who has a benign rash with carbamazepine treatment, a retrial of the drug can be undertaken. Many patients can be rechallenged without reemergence of the rash. Pretreatment with prednisone (Deltasone; 40 mg a day) may suppress the rash, although other symptoms of an allergic reaction (e.g., fever and pneumonitis) may develop even with steroid pretreatment. Renal Effects. Carbamazepine is occasionally used to treat diabetes insipidus not associated with lithium use. This activity results from direct or indirect effects at the vasopressin receptor. It may also lead to the development of hyponatremia and water intoxication in some patients, particularly elderly persons, or when used in high doses. Other Adverse Effects. Carbamazepine decreases cardiac conduction (although less than the tricyclic drugs do) and can thus exacerbate preexisting cardiac disease. Carbamazepine should be used with caution in persons with glaucoma, prostatic hypertrophy, diabetes, or a history of alcohol abuse. Carbamazepine occasionally activates vasopressin receptor function, which results in a condition resembling the syndrome of secretion of inappropriate antidiuretic hormone, characterized by hyponatremia and, rarely, water intoxication. This is the opposite of the renal effects of lithium (i.e., nephrogenic diabetes insipidus). Augmentation of lithium with carbamazepine does not reverse the lithium effect, however. Emergence of confusion, severe weakness, or headache in a person taking carbamazepine should prompt measurement of serum electrolytes. Carbamazepine use rarely elicits an immune hypersensitivity response consisting of fever, rash, eosinophilia, and possibly fatal myocarditis. Cleft palate, fingernail hypoplasia, microcephaly, and spina bifida in infants may be associated with the maternal use of carbamazepine during pregnancy. Pregnant women should not use carbamazepine unless absolutely necessary. All women with childbearing potential should take 1 to 4 mg of folic acid daily even if they are not trying to conceive. Carbamazepine is secreted in breast milk. Drug Interactions Carbamazepine decreases serum concentrations of numerous drugs as a result of prominent induction of hepatic CYP3A4 (Table 29.13-2). Monitoring for a decrease in clinical effects is frequently indicated. Carbamazepine can decrease the blood concentrations of oral contraceptives, resulting in breakthrough bleeding and uncertain prophylaxis against pregnancy. Carbamazepine should not be administered with monoamine oxidase inhibitors (MAOIs), which should be discontinued at least 2 weeks before initiating treatment with carbamazepine. Grapefruit juice inhibits the hepatic metabolism of carbamazepine. When carbamazepine and valproate are used in

combination, the dosage of carbamazepine should be decreased because valproate displaces carbamazepine binding on proteins, and the dosage of valproate may need to be increased. Table 29.13-2 Carbamazepine: Drug Interactions Laboratory Interferences Circulating levels of thyroxine and triiodothyronine are associated with a decrease in

thyroid-stimulating hormone and may be associated with treatment. Carbamazepine is also associated with an increase in total serum cholesterol, primarily by increasing highdensity lipoproteins. The thyroid and cholesterol effects are not clinically significant. Carbamazepine may interfere with the dexamethasone (Decadron) suppression test and may also cause false-positive pregnancy test results. Dosing and Administration The target dose for antimanic activity is 1,200 mg a day, although this varies considerably. Immediate-release carbamazepine needs to be taken three or four times a day, which leads to lapses in compliance. Extended-release formulations are thus preferred because they can be taken once or twice a day. One form of extended-release carbamazepine, Carbatrol, comes as 100-, 200-, and 300-mg capsules. Another form, Equetro, is identical to Carbatrol and is marketed as a treatment for bipolar disorder. These capsules contain tiny beads with three different types of coatings so they dissolve at different times. Capsules should not be crushed or chewed. The contents can be sprinkled over food, however, without affecting the extended-release qualities. This formulation can be taken either with or without meals. The entire daily dose can be given at bedtime. The rate of absorption is faster when it is given with a high-fat meal. Another extended-release form of carbamazepine, Tegretol XR, uses a different drugdelivery system than Carbatrol. It is available in 100-, 200-, and 300-mg tablets. Preexisting hematologic, hepatic, and cardiac diseases can be relative contraindications for carbamazepine treatment. Persons with hepatic disease require only one third to one half the usual dosage; the clinician should be cautious about raising the dosage in such persons and should do so only slowly and gradually. The laboratory examination should include a complete blood count with platelet count, liver function tests, serum electrolytes, and an electrocardiogram in persons older than 40 years of age or with a preexisting cardiac disease. An electroencephalogram is not necessary before the initiation of treatment, but it may be helpful in some cases for the documentation of objective changes correlated with clinical improvement. Table 29.13-3 presents a brief user’s guide to carbamazepine in bipolar disorder. Table 29.13-3 Carbamazepine in Bipolar Illness: A Brief User’s Guide

Routine Laboratory Monitoring Serum levels for antimanic efficacy have not been established. The anticonvulsant blood concentration range for carbamazepine is 4 to 12 µg/mL, and this range should be reached before determining that carbamazepine is not effective in the treatment of a mood disorder. A clinically insignificant suppression of the WBC count commonly occurs during carbamazepine treatment. This benign decrease can be reversed by adding lithium, which enhances colony-stimulating factor. Potential serious hematologic effects of carbamazepine, such as pancytopenia, agranulocytosis, and aplastic anemia, occur in about 1 in 125,000 patients. Complete laboratory blood assessments may be performed every 2 weeks for the first 2 months of treatment and quarterly thereafter, but the FDA has revised the package insert for carbamazepine to suggest that blood monitoring be performed at the discretion of the physician. Patients should be informed that fever, sore throat, rash, petechiae, bruising, or unusual bleeding may indicate a hematologic problem and should prompt immediate notification of a physician. This approach is probably more effective than is frequent blood monitoring during long-term treatment. It has also been suggested that liver and renal function tests be conducted quarterly, although the benefit of conducting tests this frequently has been questioned. It seems reasonable, however, to assess hematologic status, along with liver and renal functions whenever a routine examination of the person is being conducted. A monitoring protocol is listed in Table 29.13-4.

Table 29.13-4 Laboratory Monitoring of Carbamazepine for Adult Psychiatric Disorders Carbamazepine treatment should be discontinued and a consult with a hematologist should be

obtained if the following laboratory values are found: total WBC count below 3,000/mm3, erythrocytes below 4.0 × 106/mm3, neutrophils below 1,500/mm3, hematocrit less than 32 percent, hemoglobin less than 11 g/100 mL, platelet count below 100,000/mm3, reticulocyte count below 0.3 percent, and a serum iron concentration below 150 mg/100 mL. OXCARBAZEPINE Although structurally related to carbamazepine, the usefulness of oxcarbazepine as a treatment for mania has not been established in controlled trials. Pharmacokinetics Absorption is rapid and unaffected by food. Peak concentrations occur after about 45 minutes. The elimination half-life of the parent compound is 2 hours, which remains stable over long-term treatment. The monohydroxide has a half-life of 9 hours. Most of the drug’s anticonvulsant activity is presumed to result from this monohydroxy derivative. Side Effects The most common side effects are sedation and nausea. Less frequent side effects are cognitive impairment, ataxia, diplopia, nystagmus, dizziness, and tremor. In contrast to carbamazepine, oxcarbazepine does not have an increased risk of serious blood dyscrasias, so hematologic monitoring is not necessary. The frequency of benign rash is lower than observed with carbamazepine, and serious rashes are extremely rare. However, about 25 to 30 percent of patients who develop an allergic rash while taking carbamazepine also develop a rash with oxcarbazepine. Oxcarbazepine is more likely to cause hyponatremia than carbamazepine. Approximately 3 to 5 percent of patients taking oxcarbazepine develop this side effect. It is advisable to obtain serum sodium

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