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concentrations early in the course of treatment because hyponatremia may be clinically silent. In severe cases, confusion and seizure may occur. Dosing and Administration Oxcarbazepine dosing for bipolar disorder has not been established. It is available in 150-, 300-, and 600-mg tablets. The dose range may vary from 150 to 2,400 mg per day given in divided doses twice a day. In clinical trials for mania, the doses typically used were from 900 to 1,200 mg per day with a starting dose of 150 or 300 mg at night. Drug Interactions Drugs such as phenobarbital and alcohol, which induce CYP34A, increase the clearance and reduce oxcarbazepine concentrations. Oxcarbazepine induces CYP3A4/5 and inhibits CYP2C19, which may affect the metabolism of drugs that use that pathway. Women taking oral contraceptives should be told to consult with their gynecologists because oxcarbazepine may reduce concentrations of their contraceptive and thus decrease its efficacy. REFERENCES Alvarez G, Marsh W, Camacho IA, Gracia SL. Effectiveness and tolerability of carbamazepine vs. oxcarbazepine as mood stabilizers. Clin Res Reg Affairs. 2003;20:365. Benedetti A, Lattanzi L, Pini S, Musetti L, Dell'Osso L. Oxcarbazepine as add-on treatment in patients with bipolar manic, mixed, or depressive episode. J Affect Disord. 2004;79:273. Ghaemi NS, Ko JY, Katzow JJ. Oxcarbazepine treatment of refractory bipolar disorder: A retrospective chart review. Bipolar Disord. 2002;4(1):70. Hartong EG, Moleman P, Hoogduin CA, Broekman TG, Nolen WA. Prophylactic efficacy of lithium versus carbamazepine in treatment-naive bipolar patients. J Clin Psychiatry. 2003;64:144. Isojarvi JI, Huuskonen UE, Pakarinen AJ, Vuolteenaho O, Myllyla VV. The regulation of serum sodium after replacing carbamazepine with oxcarbazepine. Epilepsia. 2001;42(6):741. Ketter TA, Wang PW, Becker OV, Nowakowska C, Yang YS. The diverse roles of anticonvulsants in bipolar disorders. Ann Clin Psychiatry. 2003;15:95. Post RM, Frye MA. Carbamazepine. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Vol. 2. Philadelphia: Lippincott Williams & Wilkins; 2009:3073. Wagner KD, Kowatch RA, Emslie GJ, Findling RL, Wilens TE, McCague K. A double-blind, randomized, placebo-controlled trial of oxcarbazepine in the treatment of bipolar disorder in children and adolescents. Am J Psychiatry. 2006;163(7):1179. Weisler RH, Kalai AK, Ketter TA. A multicenter, randomized, placebo-controlled trial of extended-release carbamazepine capsules as monotherapy for bipolar disorder patients with manic or mixed episodes. J Clin Psychiatry. 2004;65(4):478. Zhang ZJ, Kang

WH, Tan QR, Li Q, Gao CG, Zhang FG. Adjunctive herbal medicine with carbamazepine for bipolar disorders: A double-blind, randomized, placebo-controlled study. J Psychiatr Res. 2007;41(3–4):360. 29.14 Cholinesterase Inhibitors and Memantine

Donepezil (Aricept), rivastigmine (Exelon), and galantamine (Reminyl) are cholinesterase inhibitors used to treat mild to moderate cognitive impairment in dementia of the Alzheimer's type. They reduce the inactivation of the neurotransmitter acetylcholine and, thus, potentiate cholinergic neurotransmission, which in turn produces a modest improvement in memory and goal-directed thought. Memantine (Namenda) is not a cholinesterase inhibitor, producing its effects through blockade of Nmethyl-d-aspartate (NMDA) receptors. Unlike the cholinesterase inhibitors, which are indicated for the mild to moderate stages of Alzheimer's disease, memantine is indicated for the moderate to severe stages of the disease. Tacrine (Cognex), the first cholinesterase inhibitor to be introduced, is no longer used because of its multiple daily dosing regimens, its potential for hepatotoxicity, and the consequent need for frequent laboratory monitoring. Routine clinical practice often combines a cholinesterase inhibitor with memantine, and recent studies have shown that this combination may provide beneficial response compared with only cholinesterase inhibitor pharmacotherapy. PHARMACOLOGICAL ACTIONS Donepezil is absorbed completely from the gastrointestinal (GI) tract. Peak plasma concentrations are reached about 3 to 4 hours after oral dosing. The half-life of donepezil is 70 hours in elderly persons, and it is taken only once daily. Steady-state levels are achieved within about 2 weeks. The presence of stable alcoholic cirrhosis reduces clearance of donepezil by 20 percent. Rivastigmine (Exelon) is rapidly and completely absorbed from the GI tract and reaches peak plasma concentrations in 1 hour, but this is delayed by up to 90 minutes if rivastigmine is taken with food. The halflife of rivastigmine is 1 hour, but because it remains bound to cholinesterases, a single dose is therapeutically active for 10 hours, and it is taken twice daily. Galantamine (Reminyl) is an alkaloid similar to codeine and is extracted from daffodils of the plant Galanthus nivalis. It is readily absorbed, with maximum concentrations reached after 30 minutes to 2 hours. Food decreases the maximum concentration by 25 percent. The elimination half-life of galantamine is approximately 6 hours. Tacrine (Cognex) is absorbed rapidly from the GI tract. Peak plasma concentrations are reached about 90 minutes after oral dosing. The half-life of tacrine is about 2 to 4 hours, thereby necessitating four-times-daily dosing. The primary mechanism of action of cholinesterase inhibitors is reversible, nonacylating inhibition of acetylcholinesterase and butyrylcholinesterase, the enzymes that catabolize acetylcholine in the central nervous system (CNS). The enzyme inhibition increases synaptic concentrations of acetylcholine, especially in the hippocampus and cerebral cortex. Unlike tacrine, which is nonselective for all forms of acetylcholinesterase, donepezil appears to be selectively active within the CNS and has little activity in the periphery. Donepezil's favorable side effect profile appears to correlate with its lack of inhibition of cholinesterases in the GI tract. Rivastigmine appears to have somewhat more peripheral activity than donepezil and is thus more

likely to cause GI adverse effects than is donepezil. THERAPEUTIC INDICATIONS Cholinesterase inhibitors are effective for the treatment of mild to moderate cognitive impairment in dementia of the Alzheimer's type. In long-term use, they slow the progression of memory loss and diminish apathy, depression, hallucinations, anxiety, euphoria, and purposeless motor behaviors. Functional autonomy is less well preserved. Some persons note immediate improvement in memory, mood, psychotic symptoms, and interpersonal skills. Others note little initial benefit but are able to retain their cognitive and adaptive faculties at a relatively stable level for many months. A practical

benefit of cholinesterase inhibitor use is a delay or reduction of the need for nursing home placement. Donepezil and rivastigmine may be beneficial for patients with Parkinson’s disease and Lewy body disease and for treatment of cognitive deficits caused by traumatic brain injury. Donepezil is under study for treatment of mild cognitive impairment that is less severe than that caused by Alzheimer’s disease. People with vascular dementia may respond to acetylcholinesterase inhibitors. Occasionally, cholinesterase inhibitors elicit an idiosyncratic catastrophic reaction, with signs of grief and agitation, which is selflimited after the drug is discontinued. Use of cholinesterase inhibitors to improve cognition by nondemented individuals should be discouraged. PRECAUTIONS AND ADVERSE REACTIONS Donepezil Donepezil is generally well tolerated at recommended dosages. Fewer than 3 percent of those taking donepezil experience nausea, diarrhea, and vomiting. These mild symptoms are more common with a 10-mg dose than with a 5-mg dose, and when present, they tend to resolve after 3 weeks of continued use. Donepezil may cause weight loss. Donepezil treatment has been infrequently associated with bradyarrhythmias, especially in those with underlying cardiac disease. A small number of persons experience syncope. Rivastigmine Rivastigmine is generally well tolerated, but recommended dosages may need to be scaled back in the initial period of treatment to limit GI and CNS adverse effects. These mild symptoms are more common at dosages above 6 mg a day, and when present, they tend to resolve after the dosage is lowered. The most common adverse effects associated with rivastigmine are nausea, vomiting, dizziness, headache, diarrhea, abdominal pain, anorexia, fatigue, and somnolence. Rivastigmine may cause weight loss, but it does not appear to cause hepatic, renal, hematologic, or electrolyte abnormalities. Galantamine

The most common side effects of galantamine are dizziness, headache, nausea, vomiting, diarrhea, and anorexia. These side effects tend to be mild and transient. Tacrine Tacrine is the least used of the cholinesterase inhibitors but requires more discussion than the others because it is cumbersome to titrate and use, and it poses the risk of potentially significant elevations in hepatic transaminase levels. These increases occur in 25 to 30 percent of persons. Aside from elevated transaminase levels, the most common specific adverse effects associated with tacrine treatment are nausea, vomiting, myalgia, anorexia, and rash, but only nausea, vomiting, and anorexia have been found to have a clear relation to the dosage. Transaminase elevations characteristically develop during the first 6 to 12 weeks of treatment, and cholinergically mediated events are dosage related. Hepatotoxicity. Tacrine is associated with increases in the plasma activities of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The ALT measurement is the more sensitive indicator of the hepatic effects of tacrine. About 95 percent of patients who develop elevated ALT serum levels do so in the first 18 weeks of treatment. The average length of time for elevated ALT concentrations to return to normal after stopping tacrine treatment is 4 weeks. For routine monitoring of hepatic enzymes, AST and ALT activities should be measured weekly for the first 18 weeks, every month for the second 4 months, and every 3 months thereafter. Weekly assessments of AST and ALT should be performed for at least 6 weeks after any increase in dosage. Patients with mildly elevated ALT activity should be monitored weekly and not be rechallenged with tacrine until the ALT activity returns to the normal range. For any patient with elevated ALT activity and jaundice, tacrine treatment should be stopped, and the patient should not be given the drug again. Table 29.14-1 summarizes the incidence of major adverse side effects associated with each of the cholinesterase inhibitors. Table 29.14-1 Incidence of Major Adverse Side Effects with Cholinesterase Inhibitors (%) Drug Interactions

All cholinesterase inhibitors should be used cautiously with drugs that also possess cholinomimetic activity, such as succinylcholine (Anectine) and bethanechol (Urecholine). The coadministration of cholinesterase inhibitors and drugs that have cholinergic antagonist activity (e.g., tricyclic drugs) is probably counterproductive. Paroxetine (Paxil) has the most marked anticholinergic effects of any of the newer antidepressant and anxiolytic drugs and should be avoided for that reason, as well as its inhibiting effect on the metabolism of some of the cholinesterase inhibitors. Donepezil undergoes extensive metabolism via both CYP2D6 and 3A4 isozymes. The metabolism of donepezil may be increased by phenytoin (Dilantin), carbamazepine (Tegretol), dexamethasone (Decadron), rifampin (Rifadin), and phenobarbital (Solfoton). Commonly used agents such as paroxetine, ketoconazole (Nizoral), and erythromycin can significantly increase donepezil concentrations. Donepezil is highly protein bound, but it does not displace other protein-bound drugs, such as furosemide (Lasix), digoxin (Lanoxin), or warfarin (Coumadin). Rivastigmine circulates mostly unbound to serum proteins and has no significant drug interactions. Similar to donepezil, galantamine is metabolized by both CYP2D6 and 3A4 isozymes and thus may interact with drugs that inhibit these pathways. Paroxetine and ketoconazole should be used with great caution. Laboratory Interferences No laboratory interferences have been associated with the use of cholinesterase inhibitors. Dosage and Clinical Guidelines Before initiation of cholinesterase inhibitor therapy, potentially treatable causes of dementia should be ruled out and the diagnosis of dementia of the Alzheimer’s type established. Donepezil is available in 5- and 10-mg tablets. Treatment should be initiated at 5 mg each night. If well tolerated and of some discernible benefit after 4 weeks, the dosage should be increased to a maintenance dosage of 10-mg each night. Donepezil absorption is unaffected by meals. Rivastigmine is available in 1.5-, 3-, 4.5-, and 6-mg capsules. The recommended initial dosage is 1.5 mg twice daily for a minimum of 2 weeks, after which increases of 1.5 mg a day can be made at intervals of at least 2 weeks to a target dosage of 6 mg a day, taken in two equal dosages. If tolerated, the dosage may be further titrated upward to a maximum of 6 mg twice daily. The risk of adverse GI events can be reduced by administration of rivastigmine with food. Galantamine is available in 4-, 8-, and 16-mg tablets. The suggested dose range is 16 to 32 mg per day given twice a day. The higher dose is actually better tolerated than the lower dose. The initial dosage is 8 mg per day, and after a minimum of 4 weeks, the dose can be raised. All subsequent dosage increases should occur at 4-week intervals and should be based on tolerability.

Tacrine is available in 10-, 20-, 30-, and 40-mg capsules. Before the initiation of tacrine treatment, a complete physical and laboratory examination should be conducted, with special attention to liver function tests and baseline hematologic indexes. Treatment should be initiated at 10 mg four times a day and then raised by increments of 10 mg a dose every 6 weeks up to 160 mg a day; the person’s tolerance of each dosage is indicated by the absence of unacceptable side effects and lack of elevation of ALT activity. Tacrine should be given four times daily—ideally 1 hour before meals because the absorption of tacrine is reduced by about 25 percent when it is taken during the first 2 hours after meals. If tacrine is used, the specific guidelines for tacrine-induced ALT listed above should be followed. MEMANTINE Pharmacological Actions Memantine is well absorbed after oral administration, with peak concentrations reached in about 3 to 7 hours. Food has no effect on the absorption of memantine. Memantine has linear pharmacokinetics over the therapeutic dosage range and has a terminal elimination half-life of about 60 to 80 hours. Plasma protein binding is 45 percent. Memantine undergoes little metabolism, with the majority (57 to 82 percent) of an administered dose excreted unchanged in urine; the remainder is converted primarily to three

polar metabolites: the N-gludantan conjugate, 6-hydroxy memantine, and 1nitroso-deaminated memantine. These metabolites possess minimal NMDA receptor antagonist activity. Memantine is a low- to moderate-affinity NMDA receptor antagonist. It is thought that overexcitation of NMDA receptors by the neurotransmitter glutamate may play a role in Alzheimer's disease because glutamate plays an integral role in the neural pathways associated with learning and memory. Excess glutamate overstimulates NMDA receptors to allow too much calcium into nerve cells, leading to the eventual cell death observed in Alzheimer's disease. Memantine may protect cells against excess glutamate by partially blocking NMDA receptors associated with abnormal transmission of glutamate while allowing for physiologic transmission associated with normal cell functioning. Therapeutic Indications Memantine is the only approved therapy in the United States for moderate to severe Alzheimer's disease. Precautions and Adverse Reactions Memantine is safe and well tolerated. The most common adverse effects are dizziness, headache, constipation, and confusion. The use of memantine in patients with severe renal impairment is not recommended. In a documented case of an overdose with up to 400 mg of memantine, the patient experienced restlessness, psychosis, visual

hallucinations, somnolence, stupor, and loss of consciousness. The patient recovered without permanent sequelae. Drug Interactions In vitro studies conducted with marker substrates of CYP450 enzymes (CYP1A2, 2A6, 2C9, 2D6, 2E1, and 3A4) showed minimal inhibition of these enzymes by memantine. No pharmacokinetic interactions with drugs metabolized by these enzymes are expected. Because memantine is eliminated in part by tubular secretion, coadministration of drugs that use the same renal cationic system, including hydrochlorothiazide triamterene (Dyrenium), cimetidine (Tagamet), ranitidine (Zantac), quinidine, and nicotine, could potentially result in altered plasma levels of both agents. Coadministration of memantine and a combination of hydrochlorothiazide and triamterene did not affect the bioavailability of either memantine or triamterene, and the bioavailability of hydrochlorothiazide decreased by 20 percent. Urine pH is altered by diet, drugs (e.g., carbonic anhydrase inhibitors, topiramate [Topamax], sodium bicarbonate), and the clinical state of the patient (e.g., renal tubular acidosis or severe infections of the urinary tract). The clearance of memantine is reduced by about 80 percent under alkaline urine conditions at pH 8. Therefore, alterations of urine pH toward the alkaline condition may lead to an accumulation of the drug with a possible increase in adverse effects. Hence, memantine should be used with caution under these conditions. Laboratory Interferences No laboratory interferences have been associated with the use of memantine. Dosage and Clinical Guidelines Memantine is available in 5- and 10-mg tablets, with a recommended starting dose of 5 mg daily. The recommended target dose is 20 mg per day. The drug is administered twice daily in separate doses with 5-mg increment increases weekly depending on tolerability. Patients with mild to moderate disease receiving memantine in combination with a cholinesterase inhibitor have not been found to experience significantly greater benefit in cognition or overall function than those who receive a cholinesterase inhibitor alone. REFERENCES Auchus AP, Brasher HR, Salloway S, Korczyn AD, DeDeyn PP. Galantamine treatment of vascular dementia: A randomized trial. Neurology. 2007;69:448. Black SE, Doody R, Li H, McRae T, Jambor KM. Donepezil preserves cognition and global function in patients with severe Alzheimer's disease. Neurology. 2007;69:459. Cummings J, Lefevre G, Small G, Appel-Dingemanse S. Pharmacokinetic rationale for rivastigmine patch. Neurology. 2007;69(4 Suppl 1):S10.

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