16 - 29.16 Dopamine Receptor Agonists and Precurso

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Ritvo JI, Park C. The psychiatric management of patients with alcohol dependence. Curr Treat Options Neurol. 2007;9(5):381. Vaglini F, Viaggi C, Piro V, Pardini C, Gerace C, Scarselli M. Acetaldehyde and parkinsonism: Role of CYP450 2E1. Front Behav Neurosci. 2013;7:71. Weiss RD, Kueppenbender KD. Combining psychosocial treatment with pharmacotherapy for alcohol dependence. J Clin Psychopharmacol. 2006;26(Suppl 1):S37. Weiss RD, O'malley SS, Hosking JD, Locastro JS, Swift R, COMBINE Study Research Group. Do patients with alcohol dependence respond to placebo? Results from the COMBINE Study. J Stud Alcohol Drugs. 2008;69(6):878. Zarkin GA, Bray JW, Aldridge A, Mitra D, Mills MJ, Couper DJ, Cisler RA, COMBINE Cost-Effectiveness Research Group. Cost and cost-effectiveness of the COMBINE study in alcohol-dependent patients. Arch Gen Psychiatry. 2008;65(10):1214. 29.16 Dopamine Receptor Agonists and Precursors Dopamine agonists activate dopamine receptors in the absence of endogenous dopamine and have been widely used to treat idiopathic Parkinson's disease, hyperprolactinemia, and certain pituitary tumors (prolactinoma). Because dopamine stimulates the heart and increases blood flow to the liver, kidneys, and other organs, low levels of dopamine are associated with low blood pressure and low cardiac input. Dopamine agonist drugs are also administered to treat shock and congestive heart failure. Their use in psychiatry has been limited to treat such adverse effects of antipsychotic drugs as parkinsonism, extrapyramidal symptoms, akinesia, focal perioral tremors, hyperprolactinemia, galactorrhea, and neuroleptic malignant syndrome. The drugs in this class most commonly prescribed are bromocriptine (Parlodel), levodopa (also called l-Dopa; Larodopa), carbidopa-levodopa (Sinemet), and amantadine (Symmetrel). Amantadine is used primarily for the treatment of medication-induced movement disorders, such as neuroleptic-induced parkinsonism. It is also used as an antiviral agent for the prophylaxis and treatment of influenza A infection and Cotard's syndrome, a rare neuropsychiatric disorder in which a person holds a delusional belief that he or she is dead. There are also a few reports of amantadine's role in augmenting antidepressant

medications in patients with treatment-resistant depression. New dopamine receptor agonists include ropinirole (Requip), pramipexole (Mirapex), apomorphine (Apokyn), and pergolide (Permax). Of these drugs, pramipexole is the most widely prescribed in psychiatry as an augmenter of antidepressants. In 2007, pergolide was removed from the market because of the risk of serious damage to patients' heart valves. In 2012, the U.S. Food and Drug Administration (FDA) notified health care professionals about a possible increased risk of heart failure with pramipexole. This warning was based on studies that suggested a potential risk of heart failure; however, further review is required because of study limitations. PHARMACOLOGICAL ACTIONS

l-Dopa is rapidly absorbed after oral administration, and peak plasma levels are reached after 30 to 120 minutes. The half-life of l-Dopa is 90 minutes. Absorption of l-Dopa can be significantly reduced by changes in gastric pH and by ingestion with meals. Bromocriptine and ropinirole are rapidly absorbed but undergo first-pass metabolism such that only about 30 to 55 percent of the dose is bioavailable. Peak concentrations are achieved 1.5 to 3 hours after oral administration. The half-life of ropinirole is 6 hours. Pramipexole is rapidly absorbed with little first-pass metabolism and reaches peak concentrations in 2 hours. Its half-life is 8 hours. Oral forms of apomorphine have been studied, but this form is not available in the United States. Subcutaneous apomorphine injection results in rapid and controlled systemic delivery, with linear pharmacokinetics over a dose ranging from 2 to 8 mg. After l-Dopa enters the dopaminergic neurons of the central nervous system (CNS), it is converted into the neurotransmitter dopamine. Apomorphine, bromocriptine, ropinirole, and pramipexole act directly on dopamine receptors. l-Dopa, pramipexole, and ropinirole bind about 20 times more selectively to dopamine D3 than D2 receptors; the corresponding ratio for bromocriptine is less than 2 to 1. Apomorphine binds selectively to D1 and D2 receptors, with little affinity for D3 and D4 receptors. l-Dopa, pramipexole, and ropinirole have no significant activity at nondopaminergic receptors, but bromocriptine binds to serotonin 5-HT1 and 5-HT2 and α1-, α2-, and β-adrenergic receptors. THERAPEUTIC INDICATIONS Medication-induced Movement Disorders In present-day clinical psychiatry, dopamine receptor agonists are used for the treatment of medication-induced parkinsonism, extrapyramidal symptoms, akinesia, and focal perioral tremors. Their use has diminished sharply, however, because the incidence of medication-induced movement disorders is much lower with the use of the newer, atypical antipsychotics (serotonin-dopamine antagonists). Dopamine receptor agonists are effective in treating idiopathic restless legs syndrome and may also be helpful when this is a medication side effect. Ropinirole has an indication for restless legs syndrome. For the treatment of medication-induced movement disorders, most clinicians rely on anticholinergics, amantadine, and antihistamines because they are equally effective and have few adverse effects. Bromocriptine remains in use in the treatment of neuroleptic malignant syndrome; however, the incidence of this disorder is diminishing with the decreased use of dopamine receptor antagonists (DRAs). Dopamine receptor agonists are also used to counteract the hyperprolactinemic effects of DRAs, which result in the side effects of amenorrhea and galactorrhea. Mood Disorders

Bromocriptine has long been used to enhance response to antidepressant drugs in refractory patients. Ropinirole has been reported to be useful as augmentation to antidepressant therapy and as a treatment for medication-resistant bipolar II depression. Ropinirole may also be helpful in the treatment of antidepressant-induced sexual dysfunction. Pramipexole is often used in the augmentation of antidepressants in treatment-resistant depression. Some studies have found pramipexole to be superior to sertraline (Zoloft) in the treatment of depression in Parkinson's

disease, as well as reducing anhedonia in Parkinson’s patients. Sexual Dysfunction Dopamine receptor agonists improve erectile dysfunction in some patients. However, they are rarely used because they frequently cause adverse effects at therapeutic dosages. Phosphodiesterase-5 inhibitor agents are better tolerated and more effective (see Section 29.26). PRECAUTIONS AND ADVERSE REACTIONS Adverse effects are common with dopamine receptor agonists, thus limiting the usefulness of these drugs. Adverse effects are dosage dependent and include nausea, vomiting, orthostatic hypotension, headache, dizziness, and cardiac arrhythmias. To reduce the risk of orthostatic hypotension, the initial dosage of all dopamine receptor agonists should be quite low, with incremental increases at intervals of at least 1 week. These drugs should be used with caution in persons with hypertension, cardiovascular disease, and hepatic disease. After long-term use, persons, particularly elderly persons, may experience choreiform and dystonic movements and psychiatric disturbances— including hallucinations, delusions, confusion, depression, and mania—and other behavioral changes. Long-term use of bromocriptine can produce retroperitoneal and pulmonary fibrosis, pleural effusions, and pleural thickening. In general, ropinirole and pramipexole have a similar but milder adverse effect profile than l-Dopa and bromocriptine. Pramipexole and ropinirole may cause irresistible sleep attacks that occur suddenly without warning and have caused motor vehicle accidents. The most common adverse effects of apomorphine are yawning, dizziness, nausea, vomiting, drowsiness, bradycardia, syncope, and perspiration. Hallucinations have also been reported. Apomorphine’s sedative effects are exacerbated with concurrent use of alcohol or other CNS depressants. Dopamine receptor agonists are contraindicated during pregnancy, especially for nursing mothers, because they inhibit lactation. DRUG INTERACTIONS DRAs are capable of reversing the effects of dopamine receptor agonists, but this is not

usually clinically significant. The concurrent use of tricyclic drugs and dopamine receptor agonists has been reported to cause symptoms of neurotoxicity, such as rigidity, agitation, and tremor. They may also potentiate the hypotensive effects of diuretics and other antihypertensive medications. Dopamine receptor agonists should not be used in conjunction with monoamine oxidase inhibitors (MAOIs), including selegiline (Eldepryl), and MAOIs should be discontinued at least 2 weeks before the initiation of dopamine receptor agonist therapy. Benzodiazepines, phenytoin (Dilantin), and pyridoxine may interfere with the therapeutic effects of dopamine receptor agonists. Ergot alkaloids and bromocriptine should not be used concurrently because they may cause hypertension and myocardial infarction. Progestins, estrogens, and oral contraceptives may interfere with the effects of bromocriptine and may raise plasma concentrations of ropinirole. Ciprofloxacin (Cipro) can raise plasma concentrations of ropinirole, and cimetidine (Tagamet) can raise plasma concentrations of pramipexole. LABORATORY INTERFERENCES l-Dopa administration has been associated with false reports of elevated serum and urinary uric acid concentrations, urinary glucose test results, urinary ketone test results, and urinary catecholamine concentrations. No laboratory interferences have been associated with the administration of the other dopamine receptor agonists. DOSAGE AND CLINICAL GUIDELINES Table 29.16-1 lists the various dopamine receptor agonists and their formulations. For the treatment of antipsychotic-induced parkinsonism, the clinician should start with a 100-mg dose of levodopa three times a day, which may be increased until the person is functionally improved. The maximum dosage of l-Dopa is 2,000 mg a day, but most persons respond to dosages below 1,000 mg per day. The dosage of the carbidopa component of the l-Dopa-carbidopa formulation should total at least 75 mg a day. Table 29.16-1 A vailable Preparations of Dopamine Receptor Agonists and Carbidopa

The dosage of bromocriptine for mental disorders is uncertain, although it seems prudent to begin with low dosages (1.25 mg twice daily) and to increase the dosage gradually. Bromocriptine is usually taken with meals to help reduce the likelihood of nausea. The starting dosage of pramipexole is 0.125 mg three times daily, which is increased to 0.25 mg three times daily in the second week and is increased by 0.25 mg per dose each week until therapeutic benefit or adverse effects emerge. Persons with idiopathic Parkinson's disease usually experience benefit at total daily doses of 1.5 mg, and the maximum daily dose is 4.5 mg. For ropinirole, the starting dosage is 0.25 mg three times daily and is increased by 0.25 mg per dose each week to a total daily dose of 3 mg, then by 0.5 mg per dose each week to a total daily dose of 9 mg, and then by 1 mg per dose each week to a maximum dosage of 24 mg a day until therapeutic benefit or adverse effects emerge. The average daily dose for persons with idiopathic Parkinson's disease is about 16 mg. The recommended subcutaneous dose of apomorphine in Parkinson's disease is 0.2 to 0.6 mL subcutaneously during acute hypomobility episodes delivered via metered injector pen. Apomorphine can be administered three times daily, with a maximum dose of 0.6 mL five times daily. AMANTADINE Amantadine is an antiviral drug used for the prophylaxis and treatment of influenza. It was found to have antiparkinsonian properties and is now used to treat that disorder as well as akinesias and other extrapyramidal signs, including focal perioral tremors (rabbit syndrome). Pharmacologic Actions Amantadine is well absorbed from the GI tract after oral administration, reaches peak plasma concentrations in approximately 2 to 3 hours, has a half-life of about 12 to 18 hours, and attains steady-state concentrations after approximately 4 to 5 days of therapy. Amantadine is excreted unmetabolized in the urine. Amantadine plasma

concentrations can be twice as high in elderly persons as in younger adults. Patients with renal failure accumulate amantadine in their bodies. Amantadine augments dopaminergic neurotransmission in the CNS; however, the precise mechanism for the effect is unknown. The mechanism may involve dopamine release from presynaptic vesicles, blocking reuptake of dopamine into presynaptic nerve terminals, or an agonist effect on postsynaptic dopamine receptors. Therapeutic Indications The primary indication for amantadine use in psychiatry is to treat extrapyramidal signs and symptoms, such as parkinsonism, akinesia, and rabbit syndrome (focal perioral tremor of the choreoathetoid type) caused by the administration of DRA or SDA drugs. Amantadine is as effective as the anticholinergics (e.g., benztropine [Cogentin]) for these indications and results in improvement in approximately half of all persons who take it. Amantadine, however, is not generally considered as effective as the anticholinergics for the treatment of acute dystonic reactions and is not effective in treating tardive dyskinesia and akathisia. Amantadine is a reasonable compromise for persons with extrapyramidal symptoms who would be sensitive to additional anticholinergic effects, particularly those taking a low-potency DRA or the elderly. Elderly persons are susceptible to anticholinergic adverse effects, both in the CNS, such as anticholinergic delirium, and in the peripheral nervous system, such as urinary retention. Amantadine is associated with less memory impairment than are the anticholinergics. Amantadine has been reported to be of benefit in treating some selective serotonin reuptake inhibitor–associated side effects, such as lethargy, fatigue, anorgasmia, and ejaculatory inhibition. Amantadine is used in general medical practice for the treatment of parkinsonism of all causes, including idiopathic parkinsonism. Precautions and Adverse Effects The most common CNS effects of amantadine are mild dizziness, insomnia, and impaired concentration (dosage related), which occur in 5 to 10 percent of all persons. Irritability, depression, anxiety, dysarthria, and ataxia occur in 1 to 5 percent of all persons. More severe CNS adverse effects, including seizures and psychotic

symptoms, have been reported. Nausea is the most common peripheral adverse effect of amantadine. Headache, loss of appetite, and blotchy spots on the skin have also been reported. Livedo reticularis of the legs (a purple discoloration of the skin caused by dilation of blood vessels) has been reported in up to 5 percent of persons who take the drug for longer than 1 month. It usually diminishes with elevation of the legs and resolves in almost all cases when drug use is terminated. Amantadine is relatively contraindicated in persons with renal disease or a seizure disorder. Amantadine should be used with caution in persons with edema or

cardiovascular disease. Some evidence indicates that amantadine is teratogenic and therefore should not be taken by pregnant women. Because amantadine is excreted in breast milk, women who are breast-feeding should not take the drug. Suicide attempts with amantadine overdosages are life-threatening. Symptoms can include toxic psychoses (confusion, hallucinations, aggressiveness) and cardiopulmonary arrest. Emergency treatment beginning with gastric lavage is indicated. Drug Interactions Coadministration of amantadine with phenelzine (Nardil) or other MAOIs can result in a significant increase in resting blood pressure. The coadministration of amantadine with CNS stimulants can result in insomnia, irritability, nervousness, and possibly seizures or irregular heartbeat. Amantadine should not be coadministered with anticholinergics because unwanted side effects—such as confusion, hallucinations, nightmares, dry mouth, and blurred vision—may be exacerbated. Dosage and Clinical Guidelines Amantadine is available in 100-mg capsules and as a 50-mg per 5-mL syrup. The usual starting dosage of amantadine is 100 mg given orally twice a day, although the dosage can be cautiously increased up to 200 mg given orally twice a day if indicated. Amantadine should be used in persons with renal impairment only in consultation with the physician treating the renal condition. If amantadine is successful in the treatment of the drug-induced extrapyramidal symptoms, it should be continued for 4 to 6 weeks and then discontinued to see whether the person has become tolerant to the neurological adverse effects of the antipsychotic medication. Amantadine should be tapered over 1 to 2 weeks after a decision has been made to discontinue the drug. Persons taking amantadine should not drink alcoholic beverages. REFERENCES Finnema SJ, Bang-Andersen B, Jørgensen M, Christoffersen CT, Gulyás B, Wikström HV, Farde L, Halldin C. The dopamine D1 receptor agonist (S)-[11C] N-methyl-NNC 01-0259 is not sensitive to changes in dopamine concentration—A positron emission tomography examination in the monkey brain. Synapse. 2013;67(9):586–595. Javitt DC, Zukin SR, Heresco-Levy U, Umbricht D. Has an angel shown the way? Etiological and therapeutic implications of the PCP/NMDA model of schizophrenia. Schizophr Bull. 2012;38(5):958–966. Melis M, Scheggi S, Carta G, Madeddu C, Lecca S, Luchicchi A, Cadeddu F, Frau R, Fattore L, Fadda P, Ennas MG, Castelli MP, Fratta W, Schilstrom B, Banni S, De Montis MG, Pistis M. PPARα regulates cholinergic-driven activity of midbrain dopamine neurons via a novel mechanism involving α7 nicotinic acetylcholine receptors. J Neurosci. 2013;33(14):6203– 6211. Monn JA, Valli MJ, Massey SM, Hao J, Reinhard MR, Bures MG, Heinz BA, Wang X, Carter JH, Getman BG, Stephenson GA, Herin M, Catlow JT, Swanson S, Johnson BG, McKinzie DL, Henry SS. Synthesis and pharmacological characterization of 4-substituted-2-aminobicyclo [3.1. 0] hexane-2, 6-dicarboxylates: Identification of new potent and selective metabotropic glutamate 2/3 receptor agonists. J Med Chem. 2013;56(11):4442–4555. Papanastasiou E, Stone JM, Shergill S. When the drugs don’t work: the potential of glutamatergic antipsychotics in

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