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29.3 a2-Adrenergic Receptor Agonists, a1-Adrenergic Receptor Antagonists: Clonidine, Guanfacine, Prazosin, and Yohimbine

schizophrenia patients: A randomized, double-blind placebo controlled trial. Psychoneuroendocrinology. 2007;32:96. Zarrouf FA, Bhanot V. Neuroleptic malignant syndrome: Don’t let your guard down yet. Curr Psychiatry. 2007;6(8):89. 29.3 α2-Adrenergic Receptor Agonists, α1-Adrenergic Receptor Antagonists: Clonidine, Guanfacine, Prazosin, and Yohimbine Clonidine (Catapres) was developed initially as an antihypertensive medication because of its noradrenergic effects. It is an α2-adrenergic receptor agonist and reduces plasma norepinephrine. It has been studied in many neurologic and psychiatric conditions, including attention-deficit/hyperactivity disorder (ADHD), tic disorders, opiates and alcohol withdrawal, and posttraumatic stress disorder (PTSD). Its use has been somewhat limited by sedation and hypotension, which are common, and in children, its use is limited by its cardiac effects. Guanfacine (Tenex), another α2-adrenergic receptor agonist, has been preferentially used because of its differential affinity for certain α2adrenergic receptor subtypes, resulting in less sedation and hypotension. However, there have been fewer clinical studies of guanfacine than of clonidine. Prazosin (Minipress) is an α1-postsynaptic antagonist. It reduces blood pressure (BP) through vasodilation. Prazosin has shown benefits in treating sleep disorders associated with PTSD. CLONIDINE AND GUANFACINE Pharmacologic Actions Guanfacine is an agonist on presynaptic α2-receptors. It inhibits sympathetic outflow and causes vasodilation of blood vessels. It is marketed

as a treatment for high BP. It is more selective and less potent than clonidine, the other widely used α2-agonist. Clonidine and guanfacine are well absorbed from the gastrointestinal tract and reach peak plasma levels 1 to 3 hours after oral administration. The half-life of clonidine is 6 to 20 hours and that of guanfacine is 10 to 30 hours. The agonist effects of clonidine and guanfacine on presynaptic α2-adrenergic receptors in the sympathetic nuclei of the brain result in a decrease in the amount of norepinephrine released from the presynaptic nerve terminals. This serves generally to reset the body's sympathetic tone at a lower level and decrease arousal. Therapeutic Indications There is considerably more experience in clinical psychiatry with clonidine than with guanfacine. There is recent interest in the use of guanfacine for the same indications

that respond to clonidine due to guanfacine's longer half-life and relative lack of sedative effects. Withdrawal from Opioids, Alcohol, Benzodiazepines, or Nicotine. Clonidine and guanfacine are effective in reducing the autonomic symptoms of rapid opioid withdrawal (e.g., hypertension, tachycardia, dilated pupils, sweating, lacrimation, and rhinorrhea) but not the associated subjective sensations. Clonidine administration (0.1 to 0.2 mg two to four times a day) is initiated before detoxification and is then tapered off over 1 to 2 weeks (Table 29.3-1). Table 29.3-1 Oral Clonidine Protocols for Opioid Detoxification Clonidine and guanfacine can reduce symptoms of alcohol and benzodiazepine withdrawal, including anxiety, diarrhea, and tachycardia. They can reduce craving, anxiety, and the irritability symptoms of nicotine withdrawal. The transdermal patch formulation of clonidine is associated with better long-term compliance for purposes of detoxification than is the tablet formulation. Tourette's Disorder. Clonidine and guanfacine are effective drugs for the treatment of Tourette's disorder. Most clinicians begin treatment for Tourette's disorder

with the standard dopamine receptor antagonists haloperidol (Haldol) and pimozide (Orap) and the serotonin-dopamine antagonists risperidone (Risperdal) and olanzapine (Zyprexa). However, if concerned about the adverse effects of these drugs, the clinician may begin treatment with clonidine or guanfacine. The starting dose of clonidine for children is 0.05 mg a day; it can be increased to 0.3 mg a day in divided doses. Up to 3 months are needed before the beneficial effects of clonidine can be seen in patients with Tourette's disorder. The response rate has been reported to be up to 70 percent. Other Tic Disorders. Clonidine and guanfacine reduce the frequency and severity of tics in persons with tic disorder with or without comorbid ADHD. Hyperactivity and Aggression in Children. Clonidine and guanfacine can be useful alternatives for the treatment of ADHD. They are used in place of sympathomimetics and antidepressants, which may produce paradoxical worsening of hyperactivity in some children with intellectual disability, aggression, or features on the spectrum of autism. Clonidine and guanfacine can improve mood, reduce activity level, and improve social adaptation. Some impaired children may respond favorably to clonidine, but others may simply become sedated. The starting dose is 0.05 mg a day; it can be raised to 0.3 mg a day in divided doses. The efficacy of clonidine and guanfacine for control of hyperactivity and aggression often diminishes over several months of use. Clonidine and guanfacine can be combined with methylphenidate (Ritalin) or dextroamphetamine (Dexedrine) to treat hyperactivity and inattentiveness, respectively. A small number of cases have been reported of sudden death of children taking clonidine together with methylphenidate; however, it has not been conclusively demonstrated that these medications contributed to these deaths. The clinician should explain to the family that the efficacy and safety of this combination have not been investigated in controlled trials. Periodic cardiovascular assessments, including vital signs and electrocardiograms, are warranted if this combination is used. Posttraumatic Stress Disorder. Acute

exacerbations of PTSD may be associated with hyperadrenergic symptoms such as hyperarousal, exaggerated startle response, insomnia, vivid nightmares, tachycardia, agitation, hypertension, and perspiration. Preliminary reports suggested that these symptoms may respond to the use of clonidine or, especially for overnight benefit, to the use of guanfacine. More recent studies have failed to demonstrate that guanfacine produces an improvement in PTSD symptoms. Other Disorders. Other potential indications for clonidine include other anxiety disorders (panic disorder, phobias, obsessive-compulsive disorder, and generalized anxiety disorder) and mania, in which it may be synergistic with lithium (Eskalith) or carbamazepine (Tegretol). Anecdotal reports have noted the efficacy of clonidine in schizophrenia and tardive dyskinesia. A clonidine patch can reduce the hypersalivation and dysphagia caused by clozapine. Low-dose use has been reported effective in hallucinogen-persisting perceptive disorders.

Precautions and Adverse Reactions The most common adverse effects associated with clonidine are dry mouth and eyes, fatigue, sedation, dizziness, nausea, hypotension, and constipation, which result in discontinuation of therapy by about 10 percent of all persons taking the drug. Some persons also experience sexual dysfunction. Tolerance may develop to these adverse effects. A similar but milder adverse profile is seen with guanfacine, especially in doses of 3 mg or more per day. Clonidine and guanfacine should not be taken by adults with BP below 90/60 mm Hg or with cardiac arrhythmias, especially bradycardia. Development of bradycardia warrants gradual, tapered discontinuation of the drug. Clonidine in particular is associated with sedation, and tolerance does not usually develop to this adverse effect. Uncommon central nervous system (CNS) adverse effects of clonidine include insomnia, anxiety, and depression; rare CNS adverse effects include vivid dreams, nightmares, and hallucinations. Fluid retention associated with clonidine treatment can be treated with diuretics. The transdermal patch formulation of clonidine may cause local skin irritation, which can be minimized by rotating the sites of application. Overdose. Persons who take an overdose of clonidine may present with coma and constricted pupils, symptoms similar to those of an opioid overdose. Other symptoms of overdose are decreased BP, pulse, and respiratory rate. Guanfacine overdose produces a milder version of these symptoms. Clonidine and guanfacine should be avoided during pregnancy and by nursing mothers. Elderly persons are more sensitive to the drug than are younger adults. Children are susceptible to the same adverse effects as are adults. Withdrawal. Abrupt discontinuation of clonidine can cause anxiety, restlessness, perspiration, tremor, abdominal pain, palpitations, headache, and a dramatic increase in BP. These symptoms may appear about 20 hours after the last dose of clonidine, and these may also be seen if one or two doses are skipped. A similar set of symptoms occasionally occurs 2 to 4 days after discontinuation of guanfacine, but the usual course is gradual return to baseline BP over 2 to 4 days. Because of the possibility of discontinuation symptoms, doses of clonidine and guanfacine should be tapered slowly. Drug Interactions Clonidine and guanfacine cause sedation, especially early in therapy, and when administered with other centrally active depressants, such as barbiturates, alcohol, and benzodiazepines, the potential for additive sedative effects should be considered. Dose reduction may be required in patients receiving agents that interfere with atrioventricular (AV) node and sinus node conduction such as β-blockers, calcium channel blockers, and digitalis. This combination increases the risk of AV block and bradycardia. Clonidine should not be given with tricyclic antidepressants, which can inhibit the hypotensive effects of clonidine.

Laboratory Interferences No known laboratory interferences are associated with the use of clonidine or guanfacine. Dosage and Clinical Guidelines Clonidine is available in 0.1-, 0.2-, and 0.3-

mg tablets. The usual starting dosage is 0.1 mg orally twice a day; the dosage can be raised by 0.1 mg a day to an appropriate level (up to 1.2 mg per day). Clonidine must always be tapered when it is discontinued to avoid rebound hypertension, which may occur about 20 hours after the last clonidine dose. A weekly transdermal formulation of clonidine is available at doses of 0.1, 0.2, and 0.3 mg per day. The usual starting dosage is the 0.1-mg-a-day patch, which is changed each week for adults and every 5 days for children; the dose can be increased, as needed, every 1 to 2 weeks. Transition from the oral to the transdermal formulations should be accomplished gradually by overlapping them for 3 to 4 days. Guanfacine is available in 1- and 2-mg tablets. The usual starting dosage is 1 mg before sleep, and this can be increased to 2 mg before sleep after 3 to 4 weeks, if necessary. Regardless of the indication for which clonidine or guanfacine is being used, the drug should be withheld if a person becomes hypotensive (BP below 90/60 mm Hg). An extended-release preparation of guanfacine (Intuniv) is also available. Extendedrelease guanfacine should be dosed once daily. Tablets should not be crushed, chewed, or broken before swallowing because this will increase the rate of guanfacine release. It should not be administered with high fat meals due to increased exposure. The extendedrelease formulation should not be substituted for immediate-release guanfacine tablets on a milligram-per-milligram basis because of differing pharmacokinetic profiles. If switching from immediate-release guanfacine, discontinue that treatment, and titrate with extended-release guanfacine according to the following recommended schedule:

1. Begin at a dose of 1 mg/day, and adjust in increments of no more than 1 mg/week, for both monotherapy and adjunctive therapy to a psychostimulant.
2. Maintain the dose within the range of 1 to 4 mg once daily, depending on clinical response and tolerability, for both monotherapy and adjunctive therapy to a psychostimulant. In clinical trials, patients were randomized or dose optimized to doses of 1 mg, 2 mg, 3 mg, or 4 mg and received extended-release guanfacine once daily in the morning in monotherapy trials and once daily in the morning or the evening in the adjunctive therapy trial.
3. In monotherapy trials, clinically relevant improvements were observed beginning at doses in the range 0.05 to 0.08 mg/kg once daily. Efficacy increased with increasing weight-adjusted dose (mg/kg). If well tolerated, doses up to 0.12 mg/kg once daily may provide additional benefit. Doses above 4 mg/day have not been systematically studied in controlled clinical trials.
4. In the adjunctive trial, the majority of subjects reached optimal doses in the 0.05 to

0.12 mg/kg/day range. In clinical trials, there were dose-related and exposure-related risks for several clinically significant adverse reactions (e.g., hypotension, bradycardia, sedative events). Thus, consideration should be given to dosing an extended-release preparation of guanfacine on a milligram-per-kilogram basis in order to balance the exposure-related potential benefits and risks of treatment. YOHIMBINE Yohimbine (Yocon) is an α2-adrenergic receptor antagonist that is used as a treatment for both idiopathic and medication-induced erectile disorder. Currently, sildenafil (Viagra) and its congeners and alprostadil (Impulse, Edex) are considered more efficacious for this indication than yohimbine. Yohimbine is derived from an alkaloid found in Rubaceae and related trees and in the Rauwolfia serpentina plant. Pharmacologic Actions Yohimbine is erratically absorbed after oral administration, with bioavailability ranging from 7 to 87 percent. There is extensive hepatic first-pass metabolism. Yohimbine affects the sympathomimetic autonomic nervous system by increasing plasma concentrations of norepinephrine. The half-life of yohimbine

is 0.5 to 2 hours. Clinically, yohimbine produces increased parasympathetic (cholinergic) tone. Therapeutic Indications Yohimbine has been used to treat erectile dysfunction. Penile erection has been linked to cholinergic activity and to α2-adrenergic blockade, which theoretically results in increased penile inflow of blood, decreased penile outflow of blood, or both. Yohimbine is reported to help counteract the loss of sexual desire and the orgasmic inhibition caused by some serotonergic antidepressants (e.g., selective serotonin reuptake inhibitors). It has not been found useful in women for these indications. Precautions The side effects of yohimbine include anxiety, elevated BP and heart rate, increased psychomotor activity, irritability, tremor, headache, skin flushing, dizziness, urinary frequency, nausea, vomiting, and sweating. Patients with panic disorder show heightened sensitivity to yohimbine and experience increased anxiety, increased BP, and increased plasma 3-methoxy-4-hydroxyphenylglycol (MHPG). Yohimbine should be used with caution in female patients and should not be used in patients with renal disease, cardiac disease, glaucoma, or a history of gastric or duodenal ulcer. Drug Interactions

Yohimbine blocks the effects of clonidine, guanfacine, and other α2-receptor agonists. Laboratory Interferences No known laboratory interferences are associated with yohimbine use. Dosage and Clinical Guidelines Yohimbine is available in 5.4-mg tablets. The dosage of yohimbine in the treatment of erectile disorder is approximately 16 mg a day given in doses that range from 2.7 to 5.4 mg three times a day. In the event of significant adverse effects, dose should first be reduced and then gradually increased again. Yohimbine should be used judiciously in psychiatric patients because it may have an adverse effect on their mental status. Because yohimbine has no consistent effect on erectile dysfunction, its use remains controversial. Phosphodiesterase-5 (PDE-5) inhibitors are the preferred medication for this disorder. PRAZOSIN Prazosin (Minipress) is a quinazoline derivative and one of a new chemical class of antihypertensives. It is an α1-adrenergic receptor antagonist as opposed to the drugs mentioned above, which are α2-blockers. Pharmacologic Actions The exact mechanism of the hypotensive action or prazosin is unknown, particularly as it effects nightmare suppression. Prazosin causes a decrease in total peripheral resistance that is related to its action as an α1-adrenergic receptor antagonist. BP is lowered in both the supine and standing positions. This effect is most pronounced on the diastolic BP. After oral administration, human plasma concentrations reach a peak at about 3 hours with a plasma half-life of 2 to 3 hours. The drug is highly bound to plasma protein. Tolerance has not been observed to develop with long-term therapy. Therapeutic Action Prazosin is used in psychiatry to suppress nightmares, particularly those associated with PTSD. Precautions and Adverse Reactions During clinical trials and subsequent marketing experience, the most frequent reactions were dizziness (10.3 percent); headache (7.8 percent); drowsiness (7.6 percent); lack of energy (6.9 percent); weakness (6.5 percent); palpitations (5.3 percent); and nausea (4.9 percent). In most instances, side effects disappeared with continued therapy or

have been tolerated with no decrease in dose of drug. Prazosin should not be used in nursing mothers or during pregnancy. Drug Interactions No adverse drug interactions have been reported. Laboratory Interferences No laboratory interferences have been reported. Dosage and Clinical Guidelines The drug is supplied in 1-, 2-, and 5-mg capsules and a nasal spray. The therapeutic dosages most commonly used have ranged from 6 to 15 mg daily given in divided doses. Doses higher than 20 mg do not increase efficacy. When adding a diuretic or other antihypertensive agent, the dose should be reduced to 1 or 2 mg three times a day and retitration then carried out. Concomitant use with a PDE-5 inhibitor can result in additive BP lowering effects and symptomatic hypotension; therefore, PDE-5 inhibitor therapy should be initiated at the lowest dose in patients

taking prazosin. Table 29.3-2 provides a summary of α2-adrenergic receptor agonists used in psychiatry. Table 29.3-2 α2-Adrenergic Receptor Agonists Used in Psychiatrya REFERENCES Arnsten AFT, Li B. Neurobiology of executive functions: Catecholamine influences on prefrontal cortical functions. Biol Psychiatry. 2005;57:1377. Biederman J, Melmed RD, Patel A, McBurnett K, Konow J, Lyne A, Scherer N. A randomized, double blind, placebocontrolled study of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. Pediatrics. 2008;121(1):e73–e84. Boehlein JK, Kinzie JD. Pharmacologic reduction of CNS noradrenergic activity in PTSD: The case for clonidine and prazosin. J Psychiatr Pract. 2007;13:72.

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