30 - 29.30 Stimulant Drugs and Atomoxetine

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Suzuki H, Gen K, Inoue Y. Comparison of the anti-dopamine D(2) and anti-serotonin 5-HT(2A) activities of chlorpromazine, bromperidol, haloperidol and second-generation antipsychotics parent compounds and metabolites thereof. J Psychopharmacol. 2013;27(4):396–400. Tandon R, Belmaker RH, Gattaz WF, Lopez-Ibor JJ, Jr., Okasha A, Singh B, Stein DJ, Olie JP, Fleischhacker WW, Moeller HJ. World Psychiatric Association Pharmacopsychiatry Section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia. Schizophr Res. 2008;100(1–3):20. 29.30 Stimulant Drugs and Atomoxetine Stimulant drugs increase motivation, mood, energy, and wakefulness. They are also called sympathomimetics, because they mimic the physiological effects of the neurotransmitter epinephrine. Several chemical classes are included in this group. Currently these drugs are most commonly used to treat symptoms of poor concentration and hyperactivity in children and adults with attentiondeficit/hyperactivity disorder (ADHD). Paradoxically, many patients with ADHD find that these drugs can have a calming effect. Sympathomimetics are also approved for use in increasing alertness in narcolepsy. Amphetamines were the first stimulants to be synthesized. They were created in the late 19th century and were used by Bavarian soldiers in the mid-1880s to maintain wakefulness, alertness, energy, and confidence in combat. They have been used in a similar fashion in most wars since then. They were not widely used clinically until the 1930s, when they were marketed as Benzedrine inhalers for relief of nasal congestion. When their psychostimulant effects were noted, these drugs were used to treat sleepiness associated with narcolepsy. They have been classified as controlled drugs because of their rapid onset, immediate behavioral effects, and propensity to develop tolerance, which leads to the risk of abuse and dependence in vulnerable individuals. Their manufacture, distribution, and use are regulated by state and federal agencies. In 2005, pemoline was withdrawn from the market because of significant risks of treatmentemergent hepatotoxicity. Sympathomimetics have been widely used in persons with ADHD and narcolepsy because no equally effective agents have been available. They have also been found effective in treating certain cognitive disorders that result in secondary depression or profound apathy (e.g., acquired immunodeficiency syndrome [AIDS], multiple sclerosis, poststroke depression and dementia, closed head injury) as well as in the augmentation of antidepressant medications in specific treatment-resistant depressions. Atomoxetine is included

in this section because it is used to treat ADHD, even though it is not a psychostimulant. PHARMACOLOGICAL ACTIONS All of these drugs are well absorbed from the gastrointestinal tract. Amphetamine (Adderall) and dextroamphetamine (Dexedrine, Dextrostat) reach peak plasma concentrations in 2 to 3 hours and have a half-life of about 6 hours, thereby

necessitating once- or twice-daily dosing. Methylphenidate is available in immediaterelease (Ritalin), sustained-release (Ritalin SR), and extended-release (Concerta, Quillivant XR) formulations. Immediate-release methylphenidate reaches peak plasma concentrations in 1 to 2 hours and has a short half-life of 2 to 3 hours, thereby necessitating multiple-daily dosing. The sustained-release formulation reaches peak plasma concentrations in 4 to 5 hours and doubles the effective half-life of methylphenidate. The extended-release formulation reaches peak plasma concentrations in 6 to 8 hours and is designed to be effective for 12 hours in once-daily dosing. Dexmethylphenidate (Focalin) reaches peak plasma concentration in about 3 hours and is prescribed twice daily. Lisdexamfetamine dimesylate, also known as l-lysine-d-amphetamine (Vyvanse), is an amphetamine prodrug. In this formulation, dextroamphetamine is coupled with the amino acid l-lysine. Lisdexamfetamine becomes active upon cleavage of the lysine portion of the molecule by enzymes in the red blood cells. This results in the gradual release of dextroamphetamine into the bloodstream. Apart from having an extended duration of action, this type of formulation reduces its abuse potential. It is the only prodrug of its kind. Lisdexamfetamine is indicated for the treatment of ADHD in children 6 to 12 years and in adults as an integral part of a total treatment program that may include other measures (i.e., psychological, educational, social). The safety and efficacy of lisdexamfetamine dimesylate in patients 3 to 5 years old has not been established. In contrast to Adderall, which contains approximately 75 percent dextroamphetamine and 25 percent levoamphetamine, lisdexamfetamine is a single, dextro-enantiomer amphetamine molecule. In most cases this makes the drug better tolerated, but there are some patients who experience greater benefit from the mixed isomer preparation. Methylphenidate, dextroamphetamine, and amphetamine are indirectly acting sympathomimetics, with the primary effect causing the release of catecholamines from presynaptic neurons. Their clinical effectiveness is associated with increased release of both dopamine and norepinephrine. Dextroamphetamine and methylphenidate are also weak inhibitors of catecholamine reuptake and inhibitors of monoamine oxidase. For modafinil, the specific mechanism of action is unknown. Narcolepsy–cataplexy results from deficiency of hypocretin, a hypothalamic neuropeptide. Hypocretinproducing neurons are activated after modafinil administration. Modafinil does not appear to work through a dopaminergic mechanism. It does have α1-adrenergic agonist properties, which may account for its alerting effects, because the wakefulness induced by modafinil can be attenuated by prazosin, an α1-adrenergic antagonist. Some evidence suggests that modafinil has some norepinephrine reuptake blocking effects. Armodafinil (Nuvigil) is the R-enantiomer of modafinil. Both drugs have similar clinical effects and side effects. THERAPEUTIC INDICATIONS

Attention-Deficit/Hyperactivity Disorder (ADHD) Sympathomimetics are the first-line drugs for treatment of ADHD in children and are effective about 75 percent of the time. Methylphenidate and dextroamphetamine are equally effective and work within 15 to 30 minutes. Pemoline (Cylert) requires 3 to 4 weeks to reach its full efficacy; however, because of toxicity, it is rarely used. Sympathomimetic drugs decrease hyperactivity, increase attentiveness, and reduce impulsivity. They may also reduce comorbid oppositional behaviors associated with ADHD. Many persons take these drugs throughout their schooling and beyond. In responsive persons, use of a

sympathomimetic may be a critical determinant of scholastic success. Sympathomimetics improve the core ADHD symptoms of hyperactivity, impulsivity, and inattentiveness and permit improved social interactions with teachers, family, other adults, and peers. The success of long-term treatment of ADHD with sympathomimetics, which are efficacious for most of the various constellations of ADHD symptoms present from childhood to adulthood, supports a model in which ADHD results from a genetically determined neurochemical imbalance that requires lifelong pharmacologic management. Methylphenidate is the most commonly used initial agent, at a dosage of 5 to 10 mg every 3 to 4 hours. Dosages may be increased to a maximum of 20 mg four times daily or 1 mg/kg a day. Use of the 20 mg sustained-release formulation to achieve 6 hours of benefit and eliminate the need for dosing at school is supported by many experts, although other authorities believe it is less effective than the immediate-release formulation. Dextroamphetamine is about twice as potent as methylphenidate on a per milligram basis and provides 6 to 8 hours of benefit. Some 70 percent of nonresponders to one sympathomimetic may benefit from another. All of the sympathomimetic drugs should be tried before switching to drugs of a different class. The previous dictum that sympathomimetics worsen tics and therefore should be avoided by persons with comorbid ADHD and tic disorders has been questioned. Small dosages of sympathomimetics do not appear to cause an increase in the frequency and severity of tics. Alternatives to sympathomimetics for ADHD include bupropion (Wellbutrin), venlafaxine (Effexor), guanfacine (Tenex), clonidine (Catapres), and tricyclic drugs. Further studies are needed to determine whether modafinil improves the symptoms of ADHD. Short-term use of the sympathomimetics induces a euphoric feeling; however, tolerance develops for both the euphoric feeling and the sympathomimetic activity. Narcolepsy and Hypersomnolence Narcolepsy consists of sudden sleep attacks (narcolepsy), sudden loss of postural tone (cataplexy), loss of voluntary motor control going into (hypnagogic) or coming out of (hypnopompic) sleep (sleep paralysis), and hypnagogic or hypnopompic hallucinations. Sympathomimetics reduce narcoleptic sleep attacks and improve wakefulness in other types of hypersomnolent states. Modafinil is approved as an antisomnolence agent for

treatment of narcolepsy, for people who cannot adjust to night shift work, and for those who do not sleep well because of obstructive sleep apnea. Other sympathomimetics are also used to maintain wakefulness and accuracy of motor performance in persons subject to sleep deprivation, such as pilots and military personnel. Persons with narcolepsy, unlike persons with ADHD, may develop tolerance for the therapeutic effects of the sympathomimetics. In direct comparison with amphetamine-like drugs, modafinil is equally effective at maintaining wakefulness, with a lower risk of excessive activation. Depressive Disorders Sympathomimetics may be used for treatment-resistant depressive disorders, usually as augmentation of standard antidepressant drug therapy. Possible indications for use of sympathomimetics as monotherapy include depression in elderly persons, who are at increased risk for adverse effects from standard antidepressant drugs; depression in medically ill persons, especially persons with AIDS; obtundation caused by chronic use of opioids; and clinical situations in which a rapid response is important but for which electroconvulsive therapy is contraindicated. Depressed patients with abulia and anergia may also benefit. Dextroamphetamine may be useful in differentiating pseudodementia of depression from dementia. A depressed person generally responds to a 5 mg dose with increased alertness and improved cognition. Sympathomimetics are thought to provide only shortterm benefit (2 to 4 weeks) for depression, because most persons rapidly develop tolerance for the antidepressant effects of the drugs. However, some clinicians report that long-term treatment with

sympathomimetics can benefit some persons. Encephalopathy Caused by Brain Injury Sympathomimetics increase alertness, cognition, motivation, and motor performance in persons with neurological deficits caused by strokes, trauma, tumors, or chronic infections. Treatment with sympathomimetics may permit earlier and more robust participation in rehabilitative programs. Poststroke lethargy and apathy may respond to long-term use of sympathomimetics. Obesity Sympathomimetics are used in the treatment of obesity because of their anorexiainducing effects. Because tolerance develops for the anorectic effects and because of the drugs' high abuse potential, their use for this indication is limited. Of the sympathomimetic drugs, phentermine (Adipex-P, Fastin) is the most widely used for appetite suppression. Phentermine was the second half of "fen-phen," an off-label combination of fenfluramine and phentermine, widely used to promote weight loss until fenfluramine and dexfenfluramine were withdrawn from commercial availability because of an association with cardiac valvular insufficiency, primary pulmonary

hypertension, and irreversible loss of cerebral serotoninergic nerve fibers. The toxicity of fenfluramine is attributed to the fact that it stimulates release of massive amounts of serotonin from nerve endings, a mechanism of action not shared by phentermine. Use of phentermine alone has not been reported to cause the same adverse effects as those caused by fenfluramine or dexfenfluramine. Careful limitation of caloric intake and judicious exercise are at the core of any successful weight loss program. Sympathomimetic drugs facilitate loss of, at most, an additional fraction of a pound per week. Sympathomimetic drugs are effective appetite suppressants only for the first few weeks of use; then the anorexigenic effects tend to decrease. Fatigue Between 70 and 90 percent of individuals with multiple sclerosis experience fatigue. Modafinil, armodafinil, amphetamines, methylphenidate, and the dopamine receptor agonist amantadine (Symmetrel) are sometimes effective in combating this symptom. Other causes of fatigue such as chronic fatigue syndrome respond to stimulants in many cases. PRECAUTIONS AND ADVERSE REACTIONS The most common adverse effects associated with amphetamine-like drugs are stomach pain, anxiety, irritability, insomnia, tachycardia, cardiac arrhythmias, and dysphoria. Sympathomimetics cause a decreased appetite, although tolerance usually develops for this effect. The treatment of common adverse effects in children with ADHD is usually straightforward (Table 29.30-1). The drugs can also cause increases in heart rate and blood pressure and may cause palpitations. Less common adverse effects include the possible induction of movement disorders, such as tics, Tourette's disorder–like symptoms, and dyskinesias, all of which are often self-limited over 7 to 10 days. If a person taking a sympathomimetic develops one of these movement disorders, a correlation between the dose of the medication and the severity of the disorder must be firmly established before adjustments are made in the medication dosage. In severe cases, augmentation with risperidone (Risperdal), clonidine (Catapres), or guanfacine (Tenex) is necessary. Methylphenidate may worsen tics in one-third of persons; these persons fall into two groups: those whose methylphenidate-induced tics resolve immediately upon metabolism of the dosage and a smaller group in whom methylphenidate appears to trigger tics that persist for several months but eventually resolve spontaneously. Table 29.30-1 Management of Common Stimulant-induced Adverse Effects in Attentiondeficit/Hyperactivity Disorder

Longitudinal studies do not indicate that sympathomimetics cause growth suppression. Sympathomimetics may exacerbate glaucoma, hypertension, cardiovascular disorders, hyperthyroidism, anxiety disorders, psychotic disorders, and seizure disorders. High dosages of sympathomimetics can cause dry mouth, pupillary dilation, bruxism, formication, excessive

ebullience, restlessness, emotional lability, and occasionally seizures. Long-term use of high dosages can cause a delusional disorder that resembles paranoid schizophrenia. Seizures can be treated with benzodiazepines, cardiac effects with β-adrenergic receptor antagonists, fever with cooling blankets, and delirium with dopamine receptor antagonists (DRAs). Overdosages of sympathomimetics result in hypertension, tachycardia, hyperthermia, toxic psychosis, delirium, hyperpyrexia, convulsions, coma, chest pain, arrhythmia, heart block, hypertension or hypotension, shock, and nausea. Toxic effects of amphetamines can be seen at 30 mg, but idiosyncratic toxicity can occur at doses as low as 2 mg. Conversely, survival has been reported up to 500 mg. The most limiting adverse effect of sympathomimetics is their association with psychological and physical dependence. At the doses used for treatment of ADHD, development of psychological dependence virtually never occurs. A larger concern is the presence of adolescent or adult cohabitants who might confiscate the supply of sympathomimetics for abuse or sale. The use of sympathomimetics should be avoided during pregnancy, especially during

the first trimester. Dextroamphetamine and methylphenidate pass into the breast milk, and it is not known whether modafinil or armodafinil do. DRUG INTERACTIONS The coadministration of sympathomimetics and tricyclic or tetracyclic antidepressants, warfarin (Coumadin), primidone (Mysoline), phenobarbital (Luminal), phenytoin (Dilantin), or phenylbutazone (Butazolidin) decreases the metabolism of these compounds, resulting in increased plasma levels. Sympathomimetics decrease the therapeutic efficacy of many antihypertensive drugs, especially guanethidine (Esimil, Ismelin). The sympathomimetics should be used with extreme caution with monoamine oxidase inhibitors (MAOIs). LABORATORY INTERFERENCES Dextroamphetamine may elevate plasma corticosteroid levels and interfere with some assay methods for urinary corticosteroids. DOSAGE AND ADMINISTRATION Many psychiatrists believe that amphetamine use has been overly regulated by governmental authorities. Amphetamines are listed as schedule II drugs by the Drug Enforcement Agency. Some states keep a registry of patients who receive amphetamines. Such mandates worry both patients and physicians about breaches in confidentiality, and physicians are concerned that their prescribing practices may be misinterpreted by official agencies. Consequently, some physicians may withhold prescription of sympathomimetics, even from persons who may benefit from the medications. The dosage ranges and the available preparations for sympathomimetics are presented in Table 29.30-2. Vyvanse dosing is a special case, because many patients are switched to this formulation after being treated with other stimulants. A conversion table is shown in Table 29.30-3. It is available in 20, 30, 40, 50, 60, and 70 mg capsules. Dosage should be individualized according to the therapeutic needs and response of the patient. Lisdexamfetamine (Vyvanse) should be administered at the lowest effective dosage. In patients who are either starting treatment for the first time or switching from another medication, 30 mg once daily in the morning is the recommended dose. Dosages may go up or down in 10 mg or 20 mg increments in intervals of approximately 1 week. Afternoon doses should be avoided because of the potential for insomnia. The drug may be taken with or without food. Table 29.30-2 Sympathomimetics Commonly Used in Psychiatry

Table 29.30-3 Lisdexamfetamine (Vyvanse) Dosage Equivalency Conversions Dextroamphetamine, methylphenidate, amphetamine, benzphetamine, and methamphetamine are schedule II drugs and in some states require triplicate prescriptions. Phendimetrazine (Adipost, Bontril) and phenmetrazine (Prelude) are schedule III drugs, and modafinil, armodafinil, phentermine, diethylpropion (Tenuate), and mazindol (Mazanor, Sanorex) are schedule IV drugs. Pretreatment

evaluation should include an evaluation of the patient’s cardiac function, with particular attention to the presence of hypertension or tachyarrhythmias.

The clinician should also examine the patient for the presence of movement disorders, such as tics and dyskinesia, because these conditions can be exacerbated by the administration of sympathomimetics. If tics are present, many experts will not prescribe sympathomimetics but will instead choose clonidine or antidepressants. However, recent data indicate that sympathomimetics may cause only a mild increase in motor tics and may actually suppress vocal tics. Liver function and renal function should be assessed, and dosages of sympathomimetics should be reduced for persons with impaired metabolism. Persons with ADHD can take immediate-release methylphenidate at 8 am, 12 noon, and 4 pm. Dextroamphetamine, Adderall, sustained-release methylphenidate, or 18 mg of extended-release methylphenidate may be taken once at 8 am. The starting dose of methylphenidate ranges from 2.5 mg of regular to 20 mg of the sustained-release formulation. If this is inadequate, it may be increased to a maximum dose of 80 mg in children and 90 mg daily in adults. The dosage of dextroamphetamine is 2.5 to 40 mg a day up to 0.5 mg/kg a day. Quillivant XR (methylphenidate hydrochloride) is a once-daily, extended-release liquid formulation of methylphenidate HCL. Quillivant XR is supplied as a liquid solution designed for oral administration and is taken once a day. The recommended dose for patients 6 years and older is 20 mg orally once daily in the morning with or without food. The dose may be titrated weekly in increments of 10 mg to 20 mg. Daily doses above 60 mg have not been studied and are not recommended. Before administering the dose, vigorously shake the bottle of Quillivant XR for at least 10 seconds, to ensure that the proper dose is administered. The clinical effects of the drug are evident from 45 minutes to 12 hours after dosing. The starting dosage of modafinil is 200 mg in the morning in medically healthy individuals and 100 mg in the morning in persons with hepatic impairment. Some persons take a second 100 mg or 200 mg dose in the afternoon. The maximum recommended daily dosage is 400 mg, although dosages of 600 to 1,200 mg a day have been used safely. Adverse effects become prominent at dosages greater than 400 mg a day. Compared with amphetamine-like drugs, modafinil promotes wakefulness but produces less attentiveness and less irritability. Some persons with excessive daytime sleepiness extend the activity of the morning modafinil dose with an afternoon dose of methylphenidate. Armodafinil is virtually identical to modafinil, but is dosed differently, the dosing range being 50–250 mg daily. ATOMOXETINE (STRATTERA) Atomoxetine is the first nonstimulant drug to be approved by the Food and Drug Administration (FDA) as a treatment of ADHD in children, adolescents, and adults. It is included in this chapter because it shares this indication with the stimulants described earlier. Pharmacological Actions

Atomoxetine is believed to produce a therapeutic effect through selective inhibition of the presynaptic norepinephrine transporter. It is well absorbed after oral administration and is minimally affected by food. High-fat meals may decrease the rate but not the extent of absorption. Maximum plasma concentrations are reached after approximately 1 to 2 hours. At therapeutic concentrations, 98 percent of atomoxetine in plasma is bound to protein, mainly albumin. Atomoxetine has a half-life of approximately 5 hours and is metabolized principally by the cytochrome P450 (CYP)2D6 pathway. Poor metabolizers of this compound reach a fivefold higher area under the curve and fivefold higher peak plasma concentration than normal or extensive metabolizers. This is important to consider in patients receiving medications that inhibit the CYP2D6 enzyme. For example, the antidepressant-like pharmacology of atomoxetine has led to its

use as an add-on to selective serotonin reuptake inhibitors (SSRIs) or other antidepressants. Drugs such as fluoxetine (Prozac), paroxetine (Paxil), and bupropion (Wellbutrin) are CYP2D6 inhibitors and may raise atomoxetine levels. Therapeutic Indications Atomoxetine is used for the treatment of ADHD. It should be considered for use in patients who find stimulants too activating or who experience other intolerable side effects. Because atomoxetine has no abuse potential, it is a reasonable choice in the treatment of patients with both ADHD and substance abuse, patients who complain of ADHD symptoms but are suspected of seeking stimulant drugs, and patients who are in recovery. Atomoxetine may enhance cognition when used to treat patients with schizophrenia. It may also be used as an alternative or add-on to antidepressants in patients who fail to respond to standard therapies. Precautions and Adverse Reactions Common side effects of atomoxetine include abdominal discomfort, decreased appetite with resulting weight loss, sexual dysfunction, dizziness, vertigo, irritability, and mood swings. Minor increases in blood pressure and heart rate have also been observed. There have been cases of severe liver injury in a small number of patients taking atomoxetine. The drug should be discontinued in patients with jaundice (yellowing of the skin or whites of the eyes, itching) or laboratory evidence of liver injury. Atomoxetine should not be taken at the same time as, or within 2 weeks of taking, an MAOI or by patients with narrow-angle glaucoma. The effects of overdose greater than twice the maximum recommended daily dose in humans are unknown. No specific information is available on the treatment of overdose with atomoxetine. Dosage and Clinical Guidelines Atomoxetine is available as 10, 18, 25, 40, and 60 mg capsules. In children and

adolescents who weigh up to 70 kg, atomoxetine should be initiated at a total daily dose of approximately 0.5 mg/kg and increased after a minimum of 3 days to a target total daily dose of approximately 1.2 mg/kg, administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon or early evening. The total daily dose in smaller children and adolescents should not exceed 1.4 mg/kg or 100 mg, whichever is less. Dosing of children and adolescents who weigh more than 70 kg and adults should start at a total daily dose of 40 mg and then be increased after a minimum of 3 days to a target total daily dose of approximately 80 mg. The doses can be administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon or early evening. After 2 to 4 additional weeks, the dose may be increased to a maximum of 100 mg in patients who have not achieved an optimal response. The maximum recommended total daily dose in children and adolescents over 70 kg and adults is 100 mg. REFERENCES Adler LA, Sutton VK, Moore RJ, Dietrich AP, Reimherr FW. Quality of life assessment in adult patients with attentiondeficit/hyperactivity disorder treated with a tomoxetine. J Clin Psychopharmacol. 2006;26(6):648. Aiken CB. Pramipexole in psychiatry: A systematic review of the literature. J Clin Psychiatry. 2007;68(8):1230. Amiri S, Mohammadi MR, Mohammadi M, Nouroozinejad GH, Kahbazi M. Modafinil as a treatment for attentiondeficit/hyperactivity disorder in children and adolescents: A double-blind, randomized clinical trial. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(1):145. Bangs ME, Emsile GJ, Spencer TJ, Ramsey JL, Carlson C. Efficacy and safety of atomoxetine in adolescents with attentiondeficit/hyperactivity disorder and major depression. J Child Adolesc Psychopharmacol. 2007;17(4):407. Barone P, Scazella L, Marconi R, Antonini A, Morgante L. Pramipexole versus sertraline in the treatment of depression in Parkinson’s disease: A national multicenter parallel-group randomized study. J Neuro. 2006;253(5):601. Cheng JY, Chen RY, Ko JS, Ng EM. Efficacy and safety of atomoxetine for attention-deficit/hyperactivity disorder in children and adolescents-meta-analysis and meta-regression analysis. Psychopharmacology (Berl). 2007;194(2):197. Eliyahu U, Berlin S, Hadad E, Heled Y, Moran DS. Psychostimulants and military operations. Mil Med.

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