BOOK CHAPTER

Drug Therapy for the Management of Attention Deficit-Hyperactivity Disorder

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Abstract

Attention deficit-hyperactivity disorder (ADHD) is a neurobehavioral developmental disorder in children and adults. It affects about 3%–10% of children and 2%–5% of adolescents and adults. ADHD is characterized by a persistent pattern of impulsiveness, inattention, and hyperactivity. It occurs about four times as commonly in boys than girls. The first-line treatment options for ADHD include behavioral therapy, pharmacotherapy with stimulants, or both. Methylphenidate and amphetamine salts are the stimulant drugs of choice for ADHD. Amphetamines act by increasing presynaptic release of dopamine and other biogenic amines in the brain. Methylphenidate inhibits the reuptake of dopamine and norepinephrine, and therefore its pharmacology is identical to that of amphetamines. Atomoxetine, a selective norepinephrine reuptake inhibitor–type atypical antidepressant, is an alternative, nonstimulant drug for ADHD. Stimulants are generally safe but are associated with adverse effects including headache, insomnia, anorexia, and weight loss. There is increased awareness about serious cardiovascular and psychiatric adverse events with ADHD drugs. Stimulants have a high potential for abuse and dependence.

Key Words

amphetamine, atomoxetine, attention deficit-hyperactivity disorder (ADHD), drug abuse, methylphenidate

MAJOR DRUG CLASSES

Stimulants

Amphetamines

Nonamphetamines

Nonstimulants

Norepinephrine reuptake inhibitors

α_2-Adrenergic receptor agonists

ABBREVIATIONS

ADHD	Attention deficit-hyperactivity disorder
CNS	Central nervous system
DA	Dopamine
DAT	Dopamine transporter
GI	Gastrointestinal
5-HT	Serotonin
MAO	Monoamine oxidase
NE	Norepinephrine
NET	Norepinephrine transporter
VMAT2	Vesicular monoamine transporter-2

Therapeutic Overview

Attention deficit-hyperactivity disorder (ADHD) is one of the most common childhood neurobehavioral disorders; it affects 4%–12% of children. ADHD affects males more than females (3–9 : 1) and can persist into adulthood. The most common symptoms of ADHD in children are **impulsiveness** , **inattention** , and **hyperactivity** , with individuals manifesting one or all of these symptoms to varying degrees. As a consequence, three subtypes of ADHD have been defined: (1) predominantly hyperactive-impulsive, (2) predominantly inattentive, and (3) combined hyperactive-impulsive and inattentive.

THERAPEUTIC OVERVIEW

Symptoms of ADHD	Inattentiveness Hyperactivity Impulsivity
Drug treatment of ADHD	Stimulants (amphetamines and nonamphetamines) Non-stimulants (norepinephrine reuptake inhibitors and α_2 -adrenergic receptor agonists)

Pathophysiology

The exact pathophysiology of ADHD is unclear but is believed to involve suboptimal norepinephrine (NE) and dopamine (DA) neurotransmission in the **frontal lobe** . Although studies do not show any definitive pathologic marker for ADHD, the **prefrontal cortex** , which regulates attention, and the **basal ganglia** , which regulate movements and impulsivity, are consistently reported as smaller than normal and/or deformed. There are, however, several factors that may contribute to ADHD, including genetics and environment.

ADHD often shows a familial pattern, and genetics is believed to play a role in about 75% of cases. Polymorphisms in several genes have been reported, including those coding for DA receptor subtypes (D1, D4, and D5), adrenergic α_{2A} receptors, the DA transporter (DAT), and several enzymes including DA β-hydroxylase, monoamine oxidase A (MAO-A), and catechol-O-methyltransferase (COMT). In addition, twin studies have suggested that approximately 9%–20% of the variance in ADHD symptoms can be attributed to environmental or nongenetic factors including **alcohol use** and **tobacco smoke** exposure during pregnancy and **lead exposure** in very early life. Complications during pregnancy and birth, such as hypoxia, might also play a role. Thus multiple factors may contribute to weakened prefrontal cortical circuits regulating cognitive control and attention.

There is currently no cure for ADHD. The most effective treatment, which can dramatically improve the key behavioral symptoms and improve the quality of life for both patients and their families, is the combination of behavioral therapy and drug treatment. Two broad classes of drugs are used for the pharmacotherapy of ADHD, stimulants and nonstimulants (Fig. 18.1 (f0010)). These drugs have been shown to be safe and efficacious for many children when used appropriately. The symptoms of ADHD and drugs used to control these symptoms are presented in the Therapeutic Overview Box (tit0025) .

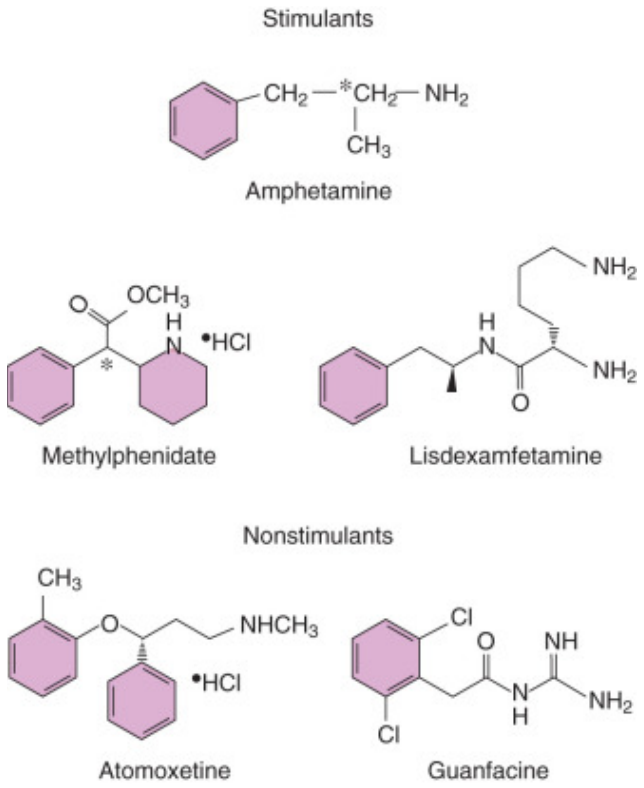

FIG. 18.1

Chemical Structures of Amphetamines and Related Agents Used to Treat ADHD.

The asterisks denote an asymmetric (chiral) carbon.

Mechanisms of Action

Stimulants

The stimulant drugs used to treat ADHD are sympathomimetic amines that act on the central nervous system (CNS) by enhancing DA and NE neurotransmission. The amphetamine drugs include **dextroamphetamine** and the prodrug **lisdexamfetamine** , and the non-amphetamine drugs include **methylphenidate** and **dexmethylphenidate** . The effects of the amphetamines arise primarily from enhanced DA and NE neurotransmission through increased release and possibly decreased reuptake. The amphetamines target both DAT and the vesicular monoamine transporter-2 (VMAT2). Similarly, the nonamphetamine stimulant methylphenidate and its derivatives enhance DA and NE neurotransmission by inhibiting both DAT and NE reuptake (NET) and directly increasing DA release by affecting presynaptic storage of the monoamine.

Nonstimulants: Norepinephrine Reuptake Inhibitors and α_2-Adrenergic Receptor Agonists

Atomoxetine is a selective norepinephrine reuptake inhibitor (SNRI) and the first nonstimulant approved for the treatment of ADHD. Because the prefrontal cortex has a relative lack of DA transporters, DA is taken back into nerve terminals by NET. Thus, atomoxetine increases synaptic levels of both NE and DA in the prefrontal cortex.

Guanfacine is a selective agonist of α_{2A}-adrenergic receptors, similar to clonidine. These postsynaptic receptors are widely distributed in the brain, including the prefrontal cortex, and their activation promotes optimal adrenergic transmission in these regions.

Relationship of Mechanisms of Action to Clinical Response

Stimulants

Amphetamines are very effective for the treatment of ADHD. They increase DA and NE neurotransmission in the prefrontal cortex at doses lower than those required to affect DA transmission in subcortical structures such as the nucleus accumbens (Fig. 18.2 (f0015)). As a consequence, when used at doses appropriate for ADHD, they do not lead to addiction.

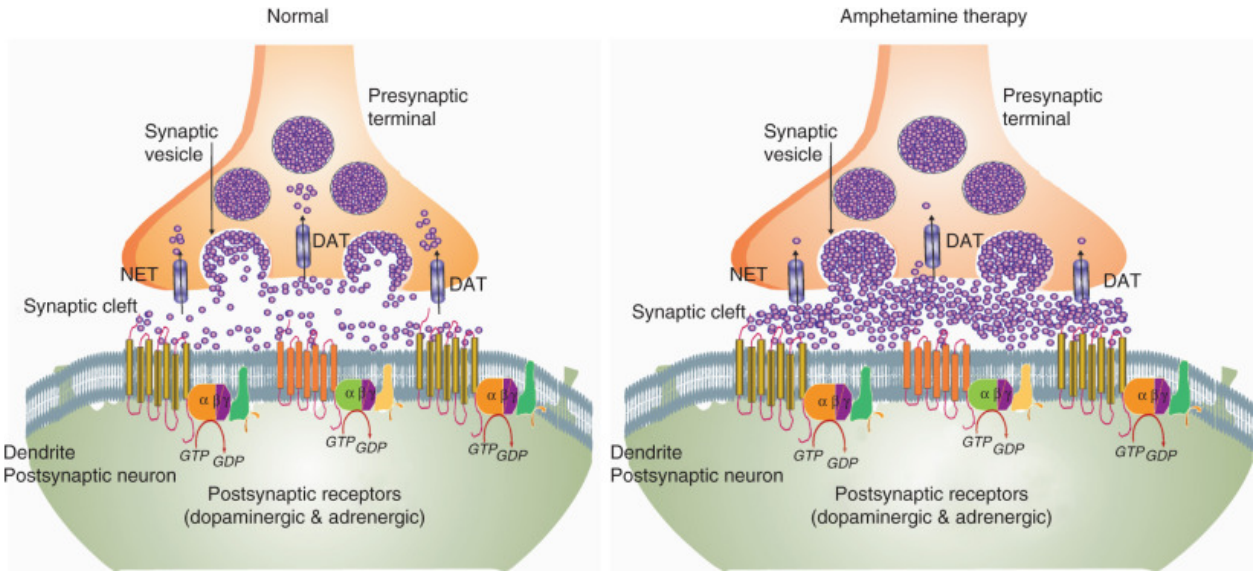

FIG. 18.2

A Simplified Diagram Depicting the Mode of Action of Amphetamines in the Brain.

Amphetamines increase the release of presynaptic dopamine and other biogenic amines such as norepinephrine and serotonin in certain areas within the brain (similar to indirect-acting sympathomimetics). They modify the uptake of these neurotransmitters within the synaptic cleft by inhibiting the reuptake process or reuptake transporters, such as dopamine transporter (DAT) and norepinephrine transporter (NET). GTP, Guanosine triphosphate; GDP, guanosine diphosphate.

Methylphenidate is the most commonly prescribed stimulant for ADHD and is available in several formulations. Clinically used methylphenidate is a racemic mixture (50 : 50) comprised of the *d* - and *l* -enantiomers. The *d* -enantiomer is more pharmacologically active than the *l* -enantiomer. Methylphenidate has been shown to be safe and effective, with no tolerance to its therapeutic effects, for more than 1 year.

The amphetamines are comparable in efficacy with methylphenidate but are twice as potent. Dextroamphetamine is three to four times more potent than the *l* -isomer to produce CNS stimulation. There is no evidence that mixed amphetamine salts (salts of the two isomers) are superior to dextroamphetamine; however, some clinicians prefer the mixed formulations.

Although lisdexamfetamine was initially approved to treat children aged 6–12, it is now approved to treat children older than 12 as well as adults.

Nonstimulants

Several placebo-controlled clinical trials have demonstrated the effectiveness of atomoxetine for ADHD. However, it is less efficacious than either amphetamine or methylphenidate. Atomoxetine is typically prescribed for individuals who do not respond to the stimulants or who cannot tolerate the adverse effects of these agents, including children of low weight or stature.

Guanfacine is also used for individuals who cannot tolerate the adverse effects of the stimulants, particularly for those with tics. It may be used alone or added to an ADHD stimulant medicine as part of a total treatment plan, including behavioral therapy.

Pharmacokinetics

Stimulants

Amphetamine is available as a racemic mixture, the dextro isomer, and a mixture of the two, in both immediate and extended-release formulations. Amphetamine is readily absorbed after oral administration, enters the brain rapidly due to its high lipophilicity, and reaches peak plasma levels within 1–2 hours, with a duration of several hours. Dextroamphetamine is also absorbed orally, with a peak effect at 3 hours and a half-life of 6.8 hours. Mixed amphetamine salts are available in an extended-release capsule that provides 12 hours of symptom control. Amphetamines are eliminated via the kidneys, with approximately 30%–40% of the drug excreted unchanged at normal urinary pH. Because amphetamine is a weak base with a pKa of 9.9, urinary pH has a marked effect on excretion; alkalinization of the urine will lead to more amphetamine as the free base and will decrease excretion, while urinary acidification will increase excretion. Amphetamine is also metabolized by CYP2D6, DA β-hydroxylase, and other enzymes to several metabolites, some of which are active sympathomimetics, including 4-hydroxyamphetamine and norephedrine.

Lisdexamfetamine is a prodrug that is rapidly absorbed from the gastrointestinal (GI) tract and converted to dextroamphetamine and the amino acid L-lysine via enzymatic hydrolysis by red blood cells. It is the dextroamphetamine that is responsible for the drug's activity. Lisdexamfetamine was developed to create a longer lasting and more difficult to abuse version of dextroamphetamine to reduce abuse potential.

Methylphenidate is orally absorbed with a bioavailability of approximately 25%. Methylphenidate is available in short-acting, intermediate-acting, and long-acting once-daily preparations. The racemic mixture has an overall half-life of 4–6 hours, with elimination by metabolism via hepatic ester hydrolysis to ritalinic acid. Single-pulse, sustained-release methylphenidate products use a wax matrix to prolong release. These intermediate-acting agents are used infrequently because of their unpredictable absorption, variable duration of action, and availability of long-acting beaded double-pulse or osmotic-release preparations. The half-life of dexmethylphenidate is 2.2 hours.

Once-daily preparations, including modified-release methylphenidate, once-daily extended-release methylphenidate, and the osmotically released oral system (OROS) formulation, have gained popularity because they avoid frequent dosing and provide all-day symptom coverage. The OROS methylphenidate formulation has an advantage of lower abuse potential because it cannot be crushed and snorted. The tablet uses an osmotic delivery system to extend the duration of action of methylphenidate for up to 12 hours and is coated with immediate-release methylphenidate (22% of the dose) for immediate action within 1 hour. The remainder of the dose is delivered by an osmotic pump that gradually releases the drug over a 10-hour period. Therefore, the total methylphenidate dose is released over 6–10 hours. Beaded methylphenidate products use an extended-release formulation with a bimodal release mechanism containing 50% of the dose in immediate-release beads and 50% in enteric-coated, delayed-release beads. These delivery systems mimic the twice-daily administration release pattern of methylphenidate.

All extended-release once-daily preparations of methylphenidate have the potential for increased insomnia compared with conventional preparations, given that drug levels persist into the late afternoon and evening hours. It is unknown whether the cardiovascular adverse effects are more problematic with extended-release preparations due to persistent blood drug levels over 8–12 hours.

A methylphenidate transdermal patch is available that produces comparable drug levels to those of regular preparations given three times a day. The patch is a useful option for children who are unable to swallow pills; wearing the patch for 9 hours provides a full day of symptom coverage.

Nonstimulants

Atomoxetine is absorbed orally, with a bioavailability of 63%. It is metabolized by CYP2D6 to the 4-hydroxy metabolite, which is equal in potency to the parent compound. Atomoxetine is administered as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening. It binds extensively (98%) to plasma proteins and can be discontinued without being tapered.

Guanfacine is also readily absorbed following oral administration and 70% bound to plasma proteins, irrespective of dose. Guanfacine is metabolized primarily by CYP3A4 followed by glucuronidation. Both parent and metabolites are excreted via the urine.

Pharmacovigilance: Adverse Effects and Drug Interactions

All drug products approved for ADHD should be dispensed with a patient medication guide to alert patients or parents to boxed warnings, possible cardiovascular risks, and adverse psychiatric symptoms associated with the use of these drugs. Drugs for the treatment of ADHD can pose serious risks, particularly when they are misused; precautions must be taken.

Stimulants

Stimulant medications elicit a biphasic action: low doses reduce locomotor activity and distractibility, while high doses cause sleeplessness and other symptoms of excessive stimulation. In the CNS, the potency is methamphetamine > d-amphetamine > l-amphetamine. In the periphery, the potency is l-amphetamine > d-amphetamine; methamphetamine has few or no peripheral effects.

Amphetamines have potent CNS stimulant actions in addition to peripheral sympathomimetic effects common to indirect-acting adrenergic agents. All amphetamines stimulate medullary centers, leading to increased respiration and motor activity. Common adverse effects include headaches, insomnia, anorexia, tic exacerbation, dry mouth, GI upset, weight loss, and reduced growth velocity.

Amphetamines cause a dose-dependent acute and chronic toxicity. Acute toxic CNS effects include restlessness, dizziness, pupillary dilation, delusion, hallucinations, increased sexual activity, tremor, hypertensive reflexes, talkativeness, tenseness, irritability, weakness, fever, and euphoria. Cardiovascular effects include headache, chilliness, flushing, palpitation, cardiac arrhythmias, hypertension, and circulatory collapse. Excessive sweating is also evident following amphetamine administration.

Massive overdoses lead to loss of consciousness following **seizures** and a **hypertensive crisis** . The drug of choice for treating amphetamine toxicity is **haloperidol** , a D2 receptor antagonist and typical antipsychotic agent (Chapter 16). With chronic amphetamine use, a loss of biogenic amine neurons has been reported. Recommended monitoring parameters

while taking these medications include cardiac evaluation in patients with risk factors including monitoring blood pressure and heart rate, height and weight in pediatrics, and complete blood count with differential annually, if prolonged treatment is required.

Drug interactions may occur with amphetamines and other agents that increase NE or DA levels including MAO inhibitors and other antidepressants. Amphetamines are contraindicated in patients with hardening of the arteries, heart disease, hypertension, hyperactive thyroid, and glaucoma. Patients should be monitored for signs of abuse and dependence while on amphetamine therapy.

Methylphenidate leads to many of the same adverse effects as the amphetamines, including nervousness, insomnia, headache, anorexia, GI upset, weight loss, slow growth, and psychiatric effects. Methylphenidate use can cause cardiovascular effects such as sudden death in susceptible patients, strokes and heart attacks, and hypertension. In addition, it can lead to psychiatric effects such as exacerbating psychotic symptoms in bipolar illness, manic symptoms, and aggression. Methylphenidate is contraindicated in patients with symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism or glaucoma, psychiatric conditions of anxiety, tension, and agitation. No methylphenidate product should be used during or within 14 days following MAO inhibitors.

The stimulants are all Schedule II controlled substances and have a high potential for abuse. Drug dependence on and addiction to these compounds are discussed in Chapter 24 .

Nonstimulants

Common side effects of atomoxetine in children include upset stomach, decreased appetite, nausea or vomiting, dizziness, somnolence, and mood swings. In adults, insomnia, constipation, dry mouth (xerostomia), nausea, decreased appetite, dizziness, sexual side effects, urinary hesitancy/retention, problems urinating, and menstrual cramps are not uncommon. Atomoxetine is contraindicated in persons with narrow-angle glaucoma and MAO inhibitor usage within 14 days. Dose adjustment is needed for individuals with hepatic or renal impairment. The major potential risks and side effects of atomoxetine include suicidal thoughts or actions, hepatotoxicity, weight loss/slowed growth, and impaired motor skills. Recommended monitoring parameters while taking this drug include cardiac evaluation in patients with risk factors, height and weight in pediatrics, liver function, and suicidal evaluation in teens, especially during initial treatment or after dose changes. Atomoxetine carries boxed warnings and additional warnings regarding hepatotoxicity and suicidal ideation.

As a consequence of atomoxetine metabolism by CYP2D6, CYP2D6 phenotype will greatly affect circulating levels (Chapter 4).

Guanfacine had little effect in a study in healthy volunteers. Adverse reactions include hypotension, somnolence, bradycardia, and syncope. Guanfacine should be discontinued carefully to avoid abrupt withdrawal effects.

Adverse effects associated with use of drugs for the treatment of ADHD are presented in the Clinical Problems Box (tit0030) .

New Developments

Currently available treatments for ADHD focus on reducing symptoms and improving functioning at home, school, or work through both behavioral and drug therapy. Despite the fact that stimulant medications have been proven safe and effective for the treatment of ADHD, an estimated 30%–50% of children and adults with ADHD either do not respond to or cannot tolerate treatment with stimulants. Although the nonstimulant medications atomoxetine and guanfacine were developed for individuals who could not tolerate the stimulants, many patients fail to respond to these compounds.

Interest in the use of modafinil, which is approved for promoting wakefulness in individuals with narcolepsy, shift work sleep disorder, and sleep apnea, for patients with inattentive and combined ADHD was spurred by off-label clinical findings that it reduced the symptoms of ADHD. Although double-blind randomized trials supported the efficacy and tolerability of modafinil for pediatric patients with ADHD, enthusiasm was tempered because of the development of serious adverse skin reactions and Stevens-Johnson syndrome.

New information on the neurobiology of ADHD, including elucidating the role of genetics and environmental factors, will hopefully give rise to the development of newer and more selective medications.

Clinical Relevance for Healthcare Professionals

Most children are treated with drugs for ADHD for a prolonged period of time. As a consequence, all healthcare professionals should reevaluate the efficacy and safety issues of pharmacotherapy in individual patients periodically. The substantial increase in the number of people prescribed stimulants for longer periods of time may increase reports of adverse psychiatric events and cardiovascular toxicity. All individuals involved in the treatment of children and young adults with ADHD must be vigilant on these issues. Furthermore, all healthcare professionals are urged to educate patients and their families about the potential dangers of misusing stimulants.

Further Reading

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Reddy DS: Current pharmacotherapy of attention deficit hyperactivity disorder. Drugs Today 2013; 49: pp. 647-665.

Dopheide JA: A calming influence: an analysis of ADHD treatments. Pharm Times 2006, August; pp. 1-16.

Websites

https://www.nimh.nih.gov/health/topics/attention-deficit-hyperactivity-disorder-adhd/index.shtml (https://www.nimh.nih.gov/health/topics/attention-deficit-hyperactivity-disorder-adhd/index.shtml)

The National Institute of Mental Health maintains an excellent website with links to resources for healthcare professionals, teachers, and parents on this topic, as well as clinical trial information.

https://www.cdc.gov/ncbddd/adhd/treatment.html (https://www.cdc.gov/ncbddd/adhd/treatment.html)

The Centers for Disease Control and Prevention also has an excellent website with links to numerous resources.

CLINICAL PROBLEMS

Stimulants	Common adverse effects	Increased respiration and motor activity, headaches, insomnia, anorexia, dry mouth, GI upset, weight loss, reduced growth velocity
	Toxic effects	Restlessness, dizziness, pupillary dilation, delusion, hallucinations, increased sexual activity, tremor, hypertensive reflexes, talkativeness, tenseness, irritability, weakness, fever and euphoria, chills, flushing, palpitations, cardiac arrhythmias, hypertension, and circulatory collapse
Nonstimulants	Atomoxetine	Somnolence, nausea, vomiting
	Guanfacine	Somnolence, bradycardia, hypotension, syncope

TRADE NAMES

In addition to generic and fixed-combination preparations, the following trade-named materials are some of the important compounds available in the United States.

Stimulants

Amphetamine (Adderall)

Dextroamphetamine (Dexedrine, Dextrostat)

Lisdexamfetamine (Vyvanse)

Dexmethylphenidate (Focalin)

Methylphenidate (Ritalin, Methylin)

Methylphenidate patch (Daytrana)

Methylphenidate OROS system (Concerta)

Methylphenidate ER oral suspension (Quillivant)

Nonstimulants

Atomoxetine (Strattera)

Guanfacine (Intuniv)

Self-Assessment Questions

1. A 7-year-old boy is having major difficulty in school with inattentiveness and hyperactivity. Which neurotransmitter systems in the brain may be functioning suboptimally?

A. Dopamine and serotonin.

B. Dopamine and norepinephrine.

C. Norepinephrine and serotonin.

D. Dopamine and glutamate.

2. A 10-year-old girl was diagnosed with ADHD and prescribed a stimulant. One of the most common adverse effects associated with the use of the stimulants is:

A. Sedation.

B. Hypotension.

C. Elevated liver function tests.

D. Itching.

E. Anorexia.

3. An 8-year-old boy in the 50th percentile of height and weight for his age was recently diagnosed with ADHD. Which of the following is the best drug to begin treatment with for this boy?

A. Amphetamine.

B. Methylphenidate.

C. Dextroamphetamine.

D. Lisdexamfetamine.

E. Atomoxetine.

4. One of the most common adverse effects of guanfacine experienced by a 14-year-old boy prescribed the drug for ADHD is:

A. Insomnia.

B. Tachycardia.

C. Nervousness.

D. Hypotension.

E. Arrhythmias.

5. Which of the following is a prodrug that must be hydrolyzed to be active for the treatment of ADHD?

A. Methylphenidate.

B. Atomoxetine.

C. Dextroamphetamine.

D. Lisdexamfetamine.

E. Methamphetamine.

6. The primary mechanism of action of amphetamines that is beneficial in the treatment of ADHD in children is:

A. Selective agonism of α_2-adrenergic receptors.

B. Selective inhibition of NE reuptake.

C. Release of DA and NE from presynaptic nerve terminals.

D. Selective inhibition of vesicular DA transport.

E. Selective inhibition of β-adrenergic receptors.

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