Review Article

A Review of the Pathophysiology, Etiology, and Treatment of Attention-Deficit Hyperactivity Disorder (ADHD)

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Abstract

Objective: To review the pathophysiology, etiology, and treatment of attention-deficit hyperactivity disorder (ADHD). **Data Sources and Data Extraction**: A literature search was conducted in PubMed and EMBASE using the terms *attention deficit hyperactive disorder, ADHD, pathophysiology, etiology*, and *neurobiology*. Limits applied were the following: published in the past 10 years (January 2003 to August 2013), humans, review, meta-analysis, and English language. These yielded 63 articles in PubMed and 74 in EMBASE. After removing duplicate/irrelevant articles, 86 articles and their relevant reference citations were reviewed. **Data Synthesis:** ADHD is a neurological disorder that affects children, but symptoms may persist into adulthood. Individuals suffering from this disorder exhibit hyperactivity, inattention, impulsivity, and problems in social interaction and academic performance. Medications used to treat ADHD such as methylphenidate, amphetamine, and atomoxetine indicate a dopamine/norepinephrine deficit as the neurochemical basis of ADHD, but the etiology is more complex. Moreover, these agents have poor adverse effect profiles and a multitude of drug interactions. Because these drugs are also dispensed to adults who may have concomitant conditions or medications, a pharmacist needs to be aware of these adverse events and drug interactions. This review, therefore, focuses on the pathophysiology, etiology, and treatment of ADHD and details the adverse effects and drug interaction profiles of the drugs used to treat it. **Conclusions:** Published research shows the benefit of drug therapy for ADHD in children, but given the poor adverse effect and drug interaction profiles, these must be dispensed with caution.

Keywords

ADHD, attention-deficit hyperactivity disorder, etiology, pathophysiology, treatment, dopamine, norepinephrine, prefrontal cortex, methylphenidate, amphetamine, atomoxetine, guanfacine, clonidine, bupropion, tricyclic antidepressants, treatment guidelines

Pathophysiology of ADHD

Attention-deficit hyperactivity disorder (ADHD) is among the most common neurobehavioral problems afflicting children between 6 and 17 years of age; its prevalence in the United States is believed to range from 2% to 18% in this age group.[1] ADHD is considered to be a heritable, chronic, neurobehavioral disorder that is characterized by hyperactivity, inattention, and impulsivity.[2] Three subtypes of ADHD are now recognized: predominantly hyperactive impulsive, predominantly inattentive, and a combined type, characterized by a combination of the first 2 subtypes.[1,3]

Children and adolescents suffering from ADHD experience challenging key formative years. Because of impulsive behavior and slower rates of processing information,[4] they perform poorly on standardized tests, score lower grades, and are more likely to drop out of school.[2] Impulsiveness also increases the risk of motor vehicle accidents and spontaneous sexual encounters, which may explain higher rates of teen pregnancies and incidence of sexually transmitted diseases in these individuals.[2,5] Lower self-esteem leads to problems in social relationships, tendency for substance abuse, and problems with law enforcement agencies.[2] In addition, ADHD often presents with one or more comorbidities such as oppositional defiant disorder (ODD), major depressive disorder (MDD), and anxiety disorders, thus bestowing additional challenges on these individuals.[1]

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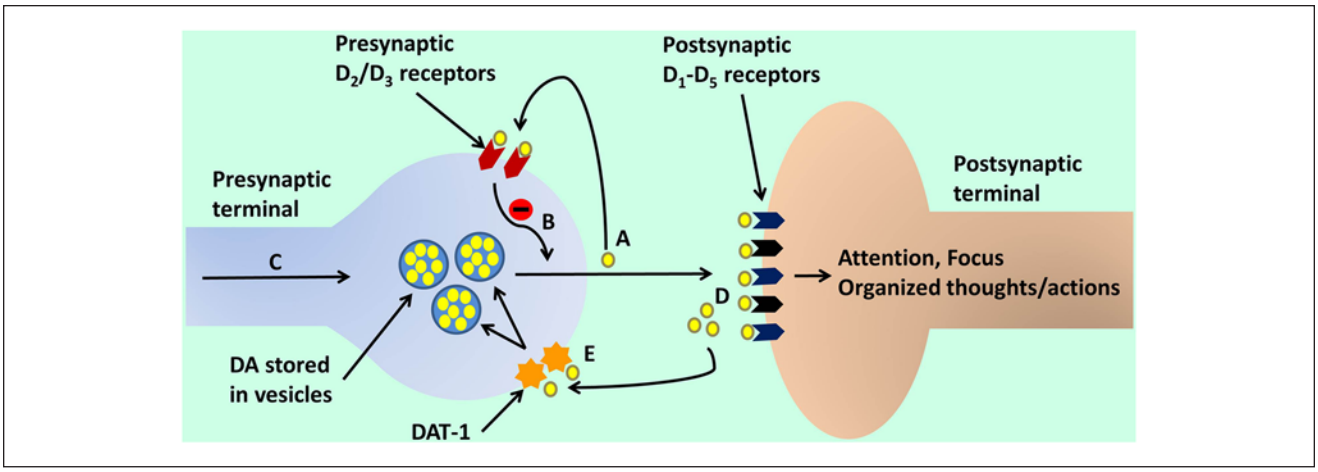

Figure 1. Integration of the hypoactive and hyperactive catecholamine postulates of ADHD: DA (yellow circles) acts on 5 DA receptors (labeled as D_1-D_5) that may be present on postsynaptic neurons (shown in blue). The D_2 and D_3 receptors are also localized on the presynaptic neurons (shown in dark red). In the absence of an action potential, a small amount of vesicular DA is released into the synapse by the presynaptic terminal (A). This constitutes the tonic pool that acts on the D_2/D_3 presynaptic receptors, which provide a feedback inhibition to inhibit the release of DA (B). Following the arrival of an action potential at the presynaptic terminal (C), a large amount of vesicular DA is released into the synapse; this constitutes the phasic pool (D) that acts on the postsynaptic receptors. The amount of DA released in the phasic pool is dependent on the feedback inhibition provided by the D_2/D_3 receptor stimulation by the tonic pool. The action of DA on the postsynaptic receptors is terminated following its reuptake into the presynaptic terminal by the DA transporter-1 (DAT-1) (E). Similarly, NE receptors are classified as α and β receptors, which are further classified as α_1 (α_{1A}, α_{1B}, α_{1D}) and α_2 (α_{2A}, α_{2B}, α_{2C}) and β_1, β_2, and β_3 receptors. Like the D_2/D_3 receptors, the presynaptic α_2 receptors act as autoreceptors but are believed to be present to a greater extent at postsynaptic sites in the brain, with α_{2A} being the most predominant type in the PFC. Like DAT-1, the NE transporter (NET) reuptakes the released NE back into the presynaptic terminal for storage and future release, and thus, the level of postsynaptic receptors for NE is dependent on both the activity of the presynaptic α_{2A} receptors and NET. It is hypothesized that when an individual is bored/fatigued, too little DA/NE is released, thereby resulting in an insufficient activation of postsynaptic D_1 and α_{2A} receptors; this leads to the individual being easily distracted and impulsive. Under stressful conditions, too much of these NTs are released, leading to overstimulation of these receptors, which leads to misguided attention and responses. A modest stimulation of the postsynaptic receptors of DA/NE favors guided attention, focus, and organization of thoughts and actions. In ADHD, the tonic pool is hypothesized to be reduced, which allows for a larger-than-normal phasic release of DA and, hence, disorganized behavior leading to inattention, hyperactivity, and so on. By blocking the DAT-1/NET, stimulants enhance the tonic pool and thus attenuate the larger-than-normal phasic release caused by the action potential, which may be the underlying problem in ADHD.
Abbreviations: ADHD, attention-deficit hyperactivity disorder; DA, dopamine; NE, norepinephrine; PFC, prefrontal cortex.

About 60% to 80% of the symptoms of ADHD persist into adulthood.[2] Thus, ADHD is not just a childhood disorder that resolves spontaneously after adolescence. It is estimated that about 4% to 4.5% of adults in the United States have ADHD.[6,7] Manifestations in adults include inferior job performance, lower socioeconomic status, and marital/relationship problems.[8] Thus, the lower quality of life in individuals afflicted with ADHD necessitates treatment to avoid multiple issues that these individuals face as children, adolescents, and adults.

Etiology of ADHD

Although the exact etiology of ADHD is still unknown, initial hypotheses of reduced brain function were based on several observations of reduced volume or functionality of gray and white matter in the brain, leading to deficits in cognitive processing, attention, motor planning, speed of processing responses, and other behavioral issues observed in ADHD.[4] More recently, the prefrontal cortex (PFC), caudate, and cerebellum have emerged as the primary areas showing deficits in ADHD. These areas are interconnected by a network of neurons and together regulate attention, thoughts, emotions, behavior, and actions.[9,10] Studies in ADHD patients have shown slower maturation of PFC[11] or a smaller volume and reduced activity of the PFC, caudate, or cerebellum.[9] The network activity between these areas is "extremely sensitive to the neurochemical environment,"[9] and is maintained by neurotransmitters (NTs), dopamine (DA), and norepinephrine (NE) acting in conjunction with each other via multiple receptors[12-15] that may be either presynaptic or postsynaptic (Figure 1).[16,17]

Several studies have reported that the DA receptor density in several brain regions of ADHD patients is lower than normal.[4,18,19] Polymorphisms of the genes that encode DA D_4 receptors (DRD4), DA D_5 receptors (DRD5), and DA

transporter (DAT-1) have also been reported to cause reduced functionality of the dopaminergic system.[20] Whereas a decreased receptor density or genetic polymorphisms related to the NE system in ADHD has not been determined,[20] disruption of α_{2A} receptor function leads to impaired attention and impulse control and hyperactivity.[9] Taken together, these studies pointed to a reduced DA and/or NE function hypothesis in ADHD, which was in perfect agreement with the mechanism of action of the medications used to treat ADHD. For example, methylphenidate, amphetamine, and atomoxetine enhance DA and NE transmission in PFC, whereas guanfacine stimulates postsynaptic α_{2A} receptors directly.[9]

However, several studies pointed toward a hyperactive DA and/or NE system in ADHD.[14] More recently, an A559V mutation and a R615C mutation in DAT-1 has been identified in some ADHD patients, which either increase the efflux of DA or decrease the presynaptic uptake of DA, indicating a hyperactive DA response in these individuals.[16,21,22] Moreover, methylphenidate and amphetamine ameliorate ADHD symptoms in the A559V mutation cohort by blocking the increased efflux of DA.[21] It is also argued that if a simple deficit in NT level exists in ADHD, direct stimulation of the postsynaptic receptors should ameliorate ADHD symptoms. However, administering DA agonists such as piribedil, amantadine,[14] or levodopa/carbidopa combination[23,24] does not improve attention in ADHD patients. Taken together, the studies pointing toward underactive or hyperactive DA/NE systems imply a more complex etiology of ADHD.

The hypoactive and hyperactive catecholamine hypotheses of ADHD have been integrated by the facts that DA and NE may exhibit an inverted U-shaped dose-response curve[9] similar to that observed with vitamins, where either extreme is a problem and that 2 separate pools of DA[14] and NE[25] exist in the brain (Figure 1). An appropriate level of DA/NE is required for optimal functioning of the PFC, and disruption leads to ADHD. Medications helpful in ADHD restore the delicate balance of the NTs in the PFC and are discussed later. However, a correct diagnosis of ADHD must precede prescription of these drugs to avoid exposing unaffected individuals to these drugs unnecessarily.

Diagnosis of ADHD

Although several imaging studies have investigated the possibility of finding a diagnostic marker for ADHD,[26-31] this potential has not yet been realized, possibly because of the complexity of the disorder itself. Clinicians in the United States should therefore follow the guidelines set forth in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-V) for diagnosing ADHD.[3] However, given that there are 3 subtypes of ADHD, each with differing symptomatology, the requirement that at least 6 symptoms must be displayed by children (5 for individuals older than 17 years) for at least 6 months to be diagnosed as suffering from a particular subtype of ADHD and that some degree of functional impairment must be obvious in multiple settings,[1,3,32] correct diagnosis of ADHD based on these subjective criteria is difficult. Comorbidities such as ODD, MDD, and anxiety disorders create more difficulties for ADHD diagnosis because of the similarities of these disorders with symptoms and characteristics of ADHD.

Although the criteria listed in DSM-V for ADHD are an improvement over DSM-IV-TR, they still fail to address the issue of sex differences in ADHD.[1,33] For example, whereas males are 3 times more likely to have ADHD than females and exhibit the predominantly hyperactive or combined type,[2] females are more likely to exhibit the predominantly inattentive subtype and tend to suffer from mental impairment and eating disorders.[34] Males tend to have more problems with aggression and are more likely to abuse the law.[34] Clinicians must be aware of these sexual and developmental differences between individuals to ensure that ADHD is not over- or underdiagnosed. Thus, diagnosing ADHD is a complex and challenging process and must be done by trained professionals carefully after repeated observations and reports obtained from parents, teachers, or other caregivers and ensuring that there are no other underlying disorders that may potentially be mislabeled as ADHD.[5,35]

Several rating scales based on DSM-IV-TR were devised to confer objectivity and quantification to the subjective criteria listed in DSM-IV-TR. These rating scales are broadly classified as narrow band and broad band, depending on whether they test for the presence of a specific or a broad range of behavior/manifestations, respectively.[36] Whereas broad-band scales do provide a better overall clinical picture, the narrow band scales are used more often (especially for monitoring therapeutic efficacy) for their robustness and minimum time involved.[36] These narrow-band scales may be based on self-report (by adolescents) or those completed by parents, teachers, or caregivers assessing internalizing behaviors (eg, depression, anxiety, and eating disorders) and externalizing behaviors (eg, hyperactivity, impulsivity, and inattention), respectively. The adult-reported scales, therefore, offer a better measure of monitoring efficacy of a treatment. The more commonly used narrow-band scales in clinical practice include[37] the Conners Rating Scales–Revised; Inattention/Overactivity With Aggression (IOWA) Conners Teacher Rating Scale; Swanson, Nolan, and Pelham-IV (SNAP-IV) Questionnaire; Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale; ADHD Rating Scale-IV; Vanderbilt ADHD Rating Scale; and ADHD Symptom Rating Scale, each possessing its own strengths and limitations.[36]

It is imperative for clinicians to recognize that although these scales are based on DSM-IV-TR criteria for diagnosing ADHD, their limitations[36] and their questionable

specificity and sensitivity should preclude their use as sole diagnostic criteria for ADHD.[37] Lack of specificity in spite of high sensitivity of the Conners Teacher and Parent Rating Scales for determining ADHD was recently described,[38] leading to many false-positive diagnoses of ADHD. Thus, the results of these scales should be limited to document the subjective criteria listed in the DSM-IV-TR (and thus serve as a component of the diagnosis)[37] and for monitoring the efficacy of the treatment.

Treatment of ADHD

Treatment of ADHD may consist of drug therapy, behavioral therapy, or their combination. Regardless of the approach used, treatment is recommended for all children because early and effective treatment of ADHD has been reported to yield a better prognosis and fewer problems in adulthood[2] and provide a reprieve to parents and teachers.[39]

Initially, many psychologists believed that ADHD may be a result of poor parenting; this led to several behavioral approaches to treat ADHD.[40,41] However, these approaches were not universally effective in all patients. Following evidence for a neurochemical basis for ADHD, drug therapy was purported to be more effective than behavioral therapy. Many physicians combined drug therapy and behavioral therapy; however, the relative efficacy of behavioral treatment versus drug therapy, the benefit of adding them together, and the long-term benefit of either of the approaches used was unknown. These issues were addressed simultaneously in a landmark study called the Multimodal Treatment Study of Children with ADHD (MTA). The results of the study[42] and the follow-up results have been published[43-45] and extensively reviewed.[32,46-48] Although all approaches tested in the study were determined to provide a long-term benefit, drug therapy was superior to behavioral therapy in managing ADHD symptoms/manifestations and a combination of the 2 did not have an additive effect. Behavioral therapy was useful, but the effect was not as robust as for drug therapy. However, in other studies, behavioral therapy has been shown to be equally efficacious as stimulants administered at low doses.[49] Therefore, it may be useful for ADHD patients with mild symptoms and minimal impairment or when parents prefer it over drug therapy.[37] It may also be used in conjunction with drug therapy if a partial response is obtained to the drugs approved by the Food and Drug Administration (FDA) or when comorbid disorders are present concomitantly.[37]

Drugs approved by the FDA for treating ADHD include stimulants (considered first-line agents), such as methylphenidate and amphetamines, and nonstimulants (considered alternative agents), such as atomoxetine and extended-release α-2 agonists (guanfacine and clonidine). Tricyclic antidepressants (TCAs), immediate-release α-2 agonists, and bupropion have been used off-label to treat ADHD; however, these are used only if the above agents fail to show benefit or cannot be used. These drugs are discussed in more detail below. Common adverse events and drug interactions are summarized in Table 1, and the recommended dose for pediatric, adolescent, and adult patients is described in Table 2.

Stimulants

Two stimulant-based therapies are approved in the United States by the FDA for all age groups and include the amphetamines and methylphenidate. The FDA recommended dose for these drugs are listed in Table 2, but the effective dose needed for most adults surpass the FDA-approved maximum dose per day and is thus considered as off-label. However, the data on the efficacy and safety of these higher doses is limited.[50]

The stimulants interact with and inhibit DAT-1 and norepinephrine transporter (NET), thereby inhibiting the reuptake of DA and NE. However, amphetamine also gains access into the presynaptic terminal via DAT-1 and NET to release the stored NTs.[51-53] Both stimulants inhibit monoamine oxidase, the enzyme that metabolizes these catecholamines; however, amphetamine is the more potent of the two.[14] Thus, the net effect with either stimulant is to rectify the level of NTs such as DA and NE in the synapse. The slightly different mechanism of action between methylphenidate and amphetamine explains why some patients failing to respond to one stimulant show a better response with the other.

Methylphenidate and amphetamines are considered as equally efficacious for long-term treatment of ADHD.[54] Both immediate and extended-release forms are available and have shown equal efficacy in clinical trials.[55,56] Although extended-release formulations are more expensive than the immediate-delivery forms, they offer advantages of convenience, confidentiality at school/work, and greater compliance.[54] In adolescents, the long-acting forms may also improve driving performance[46] and are less likely to be abused or diverted.[57,58] However, only immediate-release forms that are available in small enough doses can be used in small children because of the risk of overdose with long-acting forms.[37]

The use of stimulants, often lifelong, has raised several concerns and controversies over the years because amphetamines and methylphenidate are ranked as 6th and 12th for substances known to cause physical harm (alcohol and tobacco are 11th and 14th) and 8th and 13th for substances known to cause dependence (cannabis and LSD are 11th and 14th).[59] However, stimulants do not seem to inhibit the NET and DAT-1 in nucleus accumbens (the area in the brain responsible for reward) when taken as prescribed.[60] In fact, studies have shown that treating ADHD with stimulants

Table 1. Adverse Effects and Drug-Drug Interactions of Therapeutic Agents Used for Treating ADHD.

Generic	Brand Name	ADR	DDI
Stimulants: (1) amphetamines and (2) methylphenidate	Dexedrine, ProCentra, Vyvanse, Adderall, Adderall XR, Ritalin, Methylin, Ritalin SR, Metadate ER, Methylin ER, Ritalin LA, Metadate CD, Concerta, Daytrana, Quillivant XR, Focalin, Focalin XR	Insomnia, anorexia, abdominal pain, weight loss, headache, irritability, emotional lability, anxiety, increased blood pressure, dry mouth, irritability, nausea, vomiting, diarrhea	• Both: MAOIs (contraindicated), ethanol, melatonin, meperidine, β-blockers, cardiac glycosides, bupropion, antihypertensives, TCAs, atomoxetine, anticonvulsants • Amphetamines: lithium carbonate, methylphenidate, dexmethylphenidate, antihistamines, alkalizing and acidifying agents, proton pump inhibitors • Methylphenidate: amphetamine, dexmethylphenidate, coumarin anticoagulants, SSRIs, anticonvulsants, caffeine, pseudoephedrine
Nonstimulants: (1) atomoxetine	Strattera	Decreased appetite, nausea, vomiting, fatigue, insomnia, abdominal pain, dry mouth, constipation, somnolence, urinary retention, dysuria, erectile dysfunction, dysmenorrhea	MAOIs (contraindicated), methylphenidate, dexmethylphenidate, amphetamine, dextroamphetamine, isoniazid, SSRIs, SNRIs, bupropion, albuterol, atropine, pseudoephedrine, antihypertensives
α-2 Agonists: (1) clonidine and (2) guanfacine	Kapvay, Intuniv	Somnolence, fatigue, upper-respiratory tract infection, dry mouth, bradycardia, irritability, midsleep awakenings, sore throat, insomnia, nightmares, constipation, increased body temperature, ear pain, nausea, lethargy, dizziness, hypotension, headache	MAOIs (contraindicated), β-blockers, methylphenidate, mirtazapine, dexmethylphenidate, TCAs, guanethidine, trazodone
Bupropion	Wellbutrin, Wellbutrin SR, Wellbutrin XL	Dizziness, tachycardia, anorexia, constipation, nausea, vomiting, irritability, sedation, rash, weight gain/loss, impotence, menstrual complaints, dry mouth, akinesia, bradykinesia, abnormal dreams, hyperhidrosis, headache, migraine, insomnia, tremor, agitation, confusion, hostility, fatigue, upper-respiratory complaints, blurry vision, auditory disturbance, anxiety, impaired concentration	Linezolid (contraindicated), methylene blue (contraindicated), MAOIs (contraindicated), amantadine, anticonvulsants, antipsychotics, cocaine, corticosteroids, efavirenz, ritonavir, Atripla (efavirenz, emtricitabine, tenofovir), ethanol, flecainide, furazolidone, isoniazid, mexiletine, psychostimulants, radio-plaque contrast agents, tamoxifen, theophylline, aminophylline, tramadol, trazodone, TCAs
TCAs: (1) desipramine and (2) imipramine	Norpramin, Tofranil	Hypotension, hypertension, palpitations, heart block, myocardial infarction, stroke, arrhythmias, tachycardia, ventricular tachycardia, ventricular fibrillation, sudden death, hallucinations, disorientation, delusions, anxiety, restlessness, agitation, nightmares, numbness, paresthesias of extremities, ataxia, tremors, extrapyramidal symptoms, peripheral neuropathy, dry mouth, blurred vision, urinary retention, suicidal ideation, manic episode, insomnia, panic attacks, constipation, nausea, vomiting, anorexia, diarrhea, dysgeusia, heartburn, weight gain, hyperhidrosis, erectile dysfunction, ejaculation dysfunction	Dronedarone, linezolid, maprotiline, mesoridazine, methylene blue, MAOIs, TCAs, ziprasidone, alfuzosin, amiodarone, amprenavir, apomorphine, arsenic trioxide, asenapine, atazanavir, bupropion, buspirone, chloroquine, chlorpromazine, clarithromycin, clonidine, clozapine, cocaine, cyclobenzaprine, dasatinib, delavirdine, dextromethorphan, dolasteron, erythromycin, ethanol, fentanyl, flecainide, fluconazole, fosphenytoin, guanfacine, halogenated anesthetics, haloperidol, imatinib, isoniazid, lapatinib, levofloxacin, lithium, lopinavir and ritonavir, methadone, mirtazapine, moxifloxacin, nilotinib, nefazodone, quetiapine, quinidine, radioplaque contrast agents, ritonavir, saquinavir, SSRIs, SNRIs, tacrolimus, telithromycin, trazodone, vardenafil, voriconazole

Abbreviations: ADHD, attention-deficit hyperactivity disorder; ADR, adverse reactions; MAOIs, monoamine oxidase inhibitors; DDI, drug-drug interactions; TCAs, tricyclic antidepressants; SNRI, serotonin/norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors.

Table 2. Available Formulations, Strengths, and Dosing Recommendations for Therapeutic Agents Used for ADHD.

Brand Name (Generic), Duration of Action	Formulations, Strengths, and Generic Availability	Dosing Recommendations
Adderall (amphetamine and dextroamphetamine salts), 4-6 hours	• Formulation: immediate-release tablet • Available strengths: 5, 7.5, 10, 12.5, 15, 20, and 30 mg • Generic availability: Yes	• Not approved by FDA for children <3 years of age; total daily dose can be given in divided doses, with the first dose given in the morning, and any following doses are given every 4 to 6 hours • Children 3-5: initial, 2.5 mg po daily; titrate dose by no greater than 2.5 mg/wk until the minimum effective dose is reached; maximum daily dose, 40 mg • Children 6-12, adolescents, and adults: initial, 5 mg po once or twice daily; titrate dose by no greater than 5 mg/wk until the minimum effective dose is reached; maximum daily dose, 40 mg
Adderall XR (amphetamine and dextroamphetamine salts), 10-12 hours	• Formulation: extended-release capsule • Available strengths: 5, 10, 15, 20, 30 mg • Generic availability: yes	• Not approved by FDA for children <6 years of age • Children 6-12: initial, 10 mg po QAM; titrate dose no greater than 5-10 mg/wk until the minimum effective dose is reached; maximum daily dose, 30 mg • Adults and adolescents: initial, 20 mg po QAM; titrate dose no greater than 5-10 mg/wk until the minimum effective dose is reached; maximum daily dose, 30 mg
Vyvanse (lisdexamfetamine), 12 hours	• Formulation: capsule • Available strengths: 20, 30, 40, 50, 70 mg • Generic availability: no	• Not approved by FDA for children <6 years of age • Children 6-12, adolescents, and adults: initial, 30 mg po QAM; titrate dose no greater than 10-20 mg/wk until the minimum effective dose is reached; maximum daily dose, 70 mg
Dexedrine (dextroamphetamine), 4-5 hours; ProCentra (dextroamphetamine), 4-5 hours	• Formulations: Immediate-release tablets and extended-release capsules • Available strengths: IR tablets: 5, 10 mg XR capsules: 5, 10, 15 mg • Generic availability: yes, except for 5 mg IR tablet • Formulation: oral solution • Available strengths: 5 mg/5 mL • Generic availability: no	• Not approved by FDA for <3 years of age; total daily dose can be given in divided doses, with the first dose given in the morning; any following doses are given every 4-6 hours. • Children 3-5: initial, 2.5 mg po daily; titrate dose no greater than 2.5 mg/wk until the minimum effective dose is reached; maximum daily dose: 40 mg • Children 6-12, adolescents, and adults: initial, 5 mg po daily (children 6-12), 5 mg po once or twice daily (adolescents and adults); titrate dose no greater than 5 mg/wk until the minimum effective dose is reached; maximum daily dose, 60 mg
Ritalin (methylphenidate), 3-4 hours; Methylin (methylphenidate), 3-4 hours	• Formulation: immediate-release tablet • Available strengths: 5, 10, 20 mg • Generic availability: yes • Formulations: immediate-release tablet, chewable tablet, oral solution • Available strengths: IR tablet, 5, 10, 20 mg; chew tablet: 2.5, 5, 10 mg; oral solution, 5 mg/5 mL, 10 mg/5 mL • Generic availability: IR tablet, yes; chew tablet, no; oral solution, yes	• Not approved by FDA for children <6 years of age • Children 6-12 and adolescents: initial, 5 mg po bid before meals; titrate dose no greater than 5-10 mg/wk until the minimum effective dose is reached; maximum daily dose, 60 mg • Adults: daily dose, 20-30 mg po in 2-3 divided doses taken 30-45 minutes before meals; maximum daily dose, 60 mg
Ritalin LA (methylphenidate), 8-10 hours	• Formulation: extended-release capsule • Available strengths: 10, 20, 30, 40 mg • Generic availability: yes, except for the 10 mg	• Not approved by FDA for <6 years of age • Children 6-12, adolescents, and adults: initial, 10-20 mg po QAM; titrate dose no greater than 10 mg/wk until the minimum effective dose is reached; maximum daily dose, 60 mg

(continued)

Table 2. (continued)

Brand Name (Generic), Duration of Action	Formulations, Strengths, and Generic Availability	Dosing Recommendations
Ritalin SR (methylphenidate), 8 hours	• Formulation: extended-release tablet • Available strengths: 20 mg • Generic availability: yes	• Not approved by FDA for children <6 years of age • Children 6-12, adolescents, and adults: 20 mg po tid; maximum daily dose, 60 mg
Concerta (methylphenidate), 12 hours	• Formulation: extended-release tablet • Available strengths: 18, 27, 36, 54 mg • Generic availability: yes	• Not approved by FDA for children <6 years of age or in the elderly; titrate dose no greater than 18 mg/wk until the minimum effective dose is reached. • Children 6-12, adolescents, and adults: initial, 18 mg po QAM (6-12 years and adolescents), 18-36 po QAM (adults); maximum daily dose, 54 mg (6-12 years), 72 mg (adolescents and adults)
Metadate CD (methylphenidate), 8 hours	• Formulation: extended-release capsule • Available strengths: 10, 20, 30, 40, 50, 60 mg • Generic availability: yes	• Not approved by FDA for children <6 years of age • Children 6-12 years, adolescents, and adults: initial, 20 mg po QAM; titrate dose no greater than 10-20 mg/wk until the minimum effective dose is reached; maximum daily dose, 60 mg
Metadate ER (methylphenidate), 8 hours	• Formulation: extended-release tablet • Available strengths: 20 mg • Generic availability: yes	• Not approved by FDA for children <6 years of age • Children 6-12 years, adolescents, and adults: 20 mg po TID; maximum daily dose, 60 mg
Methylin ER (methylphenidate), 8 hours	• Formulation: extended-release tablet • Available strengths: 10, 20 mg • Generic availability: yes	• Not approved by FDA for children <6 years of age • Children 6-12 years, adolescents, and adults: 20 mg po TID; maximum daily dose, 60 mg
Daytrana (methylphenidate), dependent on duration the patch is worn	• Formulation: transdermal patch • Available strengths: 10 mg/9 h, 15 mg/9 h, 20 mg/9 h, 30 mg/9 h • Generic availability: no	• Not approved by FDA for children <6 years of age; no indication for adults • Children 6-12 years and adolescents: apply to the hip once daily in the morning and leave on for 9 hours. The following schedule should be followed: week 1, 10 mg/9 h; week 2, 15 mg/9 h; week 3, 20 mg/9 h; weeks 4-7, 30 mg/9 h; there is no evidence of its effectiveness after 7 weeks of use
Quillivant XR (methylphenidate), 12 hours	• Formulation: extended-release powder for suspension • Available strengths: 25 mg/5 mL • Generic availability: no	• Not approved by FDA for children <6 years of age • Children 6-12 years, adolescents, and adults: initial, 20 mg po QAM with or without food; titrate dose no greater than 10-20 mg/wk until the minimum effective dose is reached; maximum daily dose, 60 mg
Focalin (dexmethylphenidate), 6 hours	• Formulation: immediate-release tablet • Available strengths: 2.5, 5, 10 mg • Generic availability: yes	• Not approved by FDA for children <6 years of age • Children 6-12 years, adolescents, and adults: initial, 2.5 mg po bid; titrate dose no more than 2.5-5 mg/wk until the minimum effective dose is reached; maximum daily dose, 20 mg
Focalin XR (dexmethylphenidate), 12 hours	• Formulation: extended-release capsule • Available strengths: 5, 10, 15, 20, 25, 30, 35, 45 mg • Generic availability: no	• Not approved by FDA for children <6 years of age • Children 6-12 and adolescents: initial, 5 mg po daily; titrate dose no more than 5 mg/wk until the minimum effective dose is reached; maximum daily dose, 30 mg • Adults: initial, 10 mg po daily; titrate dose no more than 10 mg/wk until the minimum effective dose is reached; maximum daily dose, 40 mg

(continued)

Table 2. (continued)

Brand Name (Generic), Duration of Action	Formulations, Strengths, and Generic Availability	Dosing Recommendations
Strattera (atomoxetine), 10-12 hours	• Formulation: immediate-release capsule • Available strengths: 10, 18, 25, 40, 60, 80, 100 mg • Generic availability: no	• Not approved by FDA for children <6 years of age • Children ≥6 years and ≤70 kg: initial, 0.5 mg/kg QAM or QPM or in 2 divided doses; after 3 days, the dose may be titrated to 1.2 mg/kg daily or in 2 divided doses • Children ≥6 years and >70 kg: initial, 40 mg po daily or in divided doses; after 3 days, the dose may be titrated to 80 mg daily or in 2 divided doses; after 2-4 weeks, the dose may be titrated to 100 mg po daily or in 2 divided doses; maximum daily dose, 100 mg • Adolescents ≤70 kg: initial, 0.5 mg/kg QAM or QPM or in 2 divided doses; after 3 days, the dose may be titrated to 1.2 mg/kg daily or in 2 divided doses • Adults and adolescents >70kg: initial, 40 mg po daily or in divided doses; after 3 days, the dose may be titrated to 80 mg daily or in 2 divided doses; after 2-4 weeks, the dose may be titrated to 100 mg po daily or in 2 divided doses; maximum daily dose, 100 mg
Kapvay (clonidine), 4-6 hours	• Formulation: extended-release tablet • Available strengths: 0.1 mg • Generic availability: no	• Not approved by FDA for children <6 years of age; no indication for adults • Children 6-12 years and adolescents: initial, 0.1 mg po at bedtime; titrate dose no greater than 0.1 mg/wk until minimum effective dose is reached; doses >0.1 mg/d should be given in 2 divided doses, QAM and at bedtime
Intuniv (guanfacine), 24 hours	• Formulation: extended-release tablet • Available strengths: 1, 2, 3, 4 mg • Generic availability: no	• Not approved by FDA for children <6 years of age; no indication for adults • Children 6-12 years and adolescents: initial, 1 mg po daily; titrate dose no greater than 1 mg/wk until minimum effective dose is reached; maximum daily dose, 4 mg
Wellbutrin (bupropion), 6-8 hours	• Formulation: immediate-release tablet • Available strengths: 75, 100 mg • Generic availability: yes	• Not approved by FDA for children <6 years of age, no indication for adults; black box warning for risk of suicide in pediatric patients • Children 6-12 years and adolescents: initial, 25 mg po daily; normal dosing is 1-2.5 mg/kg/d in divided doses; maximum daily dose, 2.5 mg/kg/d
Wellbutrin SR (bupropion), 8-12 hours	• Formulation: sustained-release tablet • Available strengths: 100, 150, 200 mg • Generic availability: yes	• No indication for children and adolescents • Adults: titrate to a maximum dose of 300 mg po daily
Wellbutrin XL (bupropion), 24 hours	• Formulation: extended-release tablet • Available strengths: 150, 300 mg • Generic availability: yes	• No indication for children and adolescents • Adults: initial, 150 mg po daily; maximum daily dose: 450 mg/d
Norpramin (desipramine), 8-12 hours	• Formulation: immediate-release tablet • Available strengths: 10, 25, 50, 75, 100, 150 mg • Generic availability: yes	• Not approved by FDA for children <5 years of age; no indication for adults • Children 5-12 years and adolescents: titrate up to a maximum daily dose of 3.5 mg/kg/d in 2 divided doses
Tofranil (imipramine), 8-12 hours	• Formulation: immediate-release tablet • Available strengths: 10, 25, 50 mg • Generic availability: yes	• Not approved by FDA for children <6 years of age, no indication for adults • Children 6-12 years and adolescents: initial, 25 mg po daily; titrate to a dose of 1-2.5 mg/kg/d in divided doses; maximum daily dose, 2.5 mg/kg/d

Abbreviations: FDA, Food and Drug Administration; QAM, every morning; QPM, every night.

may decrease the risk of substance abuse,[61,62] with a more robust effect apparent when initiated at an earlier age.[63] Imaging studies indicate a similar neurobiology between individuals suffering from ADHD and substance abusers[64]; thus, treating ADHD reduces substance abuse disorders concomitantly. Stimulant treatment has also been shown to decrease the likelihood for emergence of MDD, ODD, and anxiety disorders[65] and reduce aggression and antisocial behavior[66] in individuals with ADHD. Nevertheless, patients or their caregivers must be educated about the importance of using these as prescribed to ensure that drug diversion/abuse does not occur because at least 25% of adults and adolescents admitted to these behaviors in a survey.[67]

Because stimulants improved memory function in a control population,[68] concerns were raised that they may provide an unfair advantage to ADHD individuals by improving academic or occupational performance beyond normal. However, it has been reported that although stimulants do increase academic productivity as a result of increased attention and concentration, they do not seem to enhance learning or improve academic performance in children or occupational performance in adults diagnosed with ADHD.[69,70] Conversely, reports suggesting that high levels of DA and NE impair cognition[9] led to concerns about memory impairment by stimulants; but whereas high doses of stimulants are reported to impair PFC performance in animals,[71] they do not impair memory in the ADHD population if used as prescribed.[8] These data suggest that stimulants have the capacity to normalize attention in ADHD patients without adverse or enhanced effects on memory if used as prescribed and reiterate the importance of educating the patients/caregivers of using these drugs as prescribed.

Whether stimulants affect physical growth is also controversial because evidence refuting as well as supporting this premise exists. For example, some studies have reported that no clinically significant difference was observed on stimulant use.[37,72,73] However, other studies indicate that stimulant use is associated with initial reduced physical growth,[74,75] which is subsequently overcome.[76] In 2 studies,[77,78] it was determined that ADHD patients were taller and heavier to start with, and hence, it was hypothesized that slowed growth may not be obvious during treatment with stimulants.[78] However, others have hypothesized that ADHD itself may be associated with a slower growth rate that resolves in adulthood.[79] Thus, it is unclear at this time whether the reduced growth that has been observed in some studies actually exists and, if so, is a result of the ADHD itself or of the pharmacological/side effects of the medications (eg, anorexia). Regardless, it is recommended to evaluate children on stimulants every 6 months for height and weight.[37] A drug holiday (weekends, summer, and other holidays) is recommended in individuals on stimulants showing reduced physical growth because brief cessation of therapy seems to eliminate these effects.[80] The negative effects on growth had raised the concern that these medications may limit or hinder the growth of already compromised brain regions that is observed in ADHD, but stimulants have been shown to increase the gray matter volume in the PFC and other areas of the brain in ADHD patients.[11,81,82]

Controversy also arose over the association of sudden death with the use of stimulants, leading to black box warnings by the FDA. However, it was later determined that underlying cardiovascular problems may have been responsible. Hence, any cardiac structural abnormalities, cardiomyopathy, or abnormalities of the heart rhythm should preclude the use of stimulants.[83] It is reasonable to monitor the electrocardiogram (ECG) of children exhibiting chest pain, shortness of breath, and dizziness or those who have a family history of cardiovascular problems.[46]

Several side effects (Table 1) are also of concern with stimulants.[56,84-86] However, these are more prominent during initiation of therapy and do not seem to hinder adherence.[87] Gastrointestinal tract (GIT)-related side effects may be limited by taking medication with or after meals and encouraging patients to eat larger and more nutritious breakfasts and dinners,[87] when the plasma concentration of stimulants would be minimal. At this time, serving favorite food might also help.[46] For insomnia, reducing the dose of stimulants or administering them earlier during the day may help. α-2 Agonists, cyproheptadine, or melatonin may also help with insomnia. Anxiety and tics can be reduced by adding atomoxetine, or antidepressants and α-2 agonists, respectively.[87]

Methylphenidate. Methylphenidate can exist in 2 racemic pairs of 4 separate isomers (D, L-erythro pair and D, L-threo pair) because it contains 2 chiral centers. Although both enantiomers of the threo pair possess stimulant activity, the L-enantiomer is considered nonsignificant because it undergoes extensive first-pass metabolism.[88] Methylphenidate is generally preferred over amphetamine despite some reports that amphetamine possesses slightly better efficacy.[89] For example, because of its slower uptake and clearance,[90] it is much less likely to produce dependence and physical harm to the patient as compared with amphetamine.[59] Additionally, DA concentrations in the brain are increased by methylphenidate only when DA is being released actively in the brain, such as during complex cognitive tasks.[91] Finally, because methylphenidate is metabolized by hepatic and peripheral esterases,[92] drug interactions with other drugs that are metabolized by cytochrome P450 (CYP) enzymes are less likely.

The specific formulations of methylphenidate may contain a racemic mixture of the 2 isomers (Ritalin, Concerta, Metadate, and Daytrana) or may contain just the more active D-isomer (Focalin).[93-97] Daytrana is a transdermal

Table 3. Treatment Guidelines/Recommendations/Algorithms That May Be Followed to Treat ADHD.

Agency/Year	Guidelines/Recommendations/Algorithms	Notes
American Academy of Pediatrics (AAP), 2011	Preschool-aged children (4-5 years): parent- or teacher-administered behavior therapy; if not available or is not beneficial, methylphenidate may be used but only in moderate to severe dysfunction	Methylphenidate use in this population is off-label. Although dextroamphetamine is approved for use in this population, its use is not recommended because of lack of safety and efficacy data. Metabolism of stimulants in this population is slower; hence, a smaller initial dose and slower upward titration is recommended
	Elementary school-aged children (6-11 years): parent- or teacher-administered behavior therapy alone or in combination (preferable) with an FDA-approved medication	The evidence for use of FDA-approved medications is strongest for stimulants, followed by atomoxetine, extended-release guanfacine, and finally, extended-release clonidine; hence, most clinicians may use this sequential approach
	Adolescents (12-18 years): FDA-approved medication alone or in combination with behavior therapy (preferred)	If substance abuse or medication diversion is an issue in this age group, stimulants with less abuse potential (Vyvanse, Daytrana, or Concerta) or nonstimulants should be used
American Academy of Child and Adolescent Psychiatry (AACAP), 2007	For children (6-11 years) and adolescents (12-18 years): FDA-approved medication (stimulants or atomoxetine); if not beneficial, seek expert opinion for ADHD diagnosis; if diagnosis is confirmed, behavioral therapy alone or in combination with medications not approved by FDA should be used	Extended-release guanfacine and clonidine were approved by the FDA after these recommendations were published; hence, the recommendation for using an FDA-approved medication includes stimulants or atomoxetine only
Texas Department of State Health Services, 2006	• Stage 0: Nonmedication alternatives following diagnosis • Stage 1: Methylphenidate or amphetamine • Stage 2: Agent not used in stage 1 • Stage 3: Atomoxetine • Stage 4: Bupropion or TCAs • Stage 5: Agent not used in stage 4 • Stage 6: α-2 agonists	Any stage(s) can be skipped depending on the clinical picture. Note that extended-release α-2 agonists were approved years after this algorithm was published

Abbreviations: ADHD, attention-deficit hyperactivity disorder; FDA, Food and Drug Administration; TCAs, tricyclic antidepressants.

patch and, hence, may be preferred by patients who may find swallowing solid dosage forms difficult; additionally, it provides greater bioavailability than orally administered dosage forms because of the lack of a first-pass effect.[37] Oral dosage forms are available in immediate- as well as extended-release versions in multiple strengths with small increments of the dose of the drug. Manipulating the dose is thus easy for producing the desired effect with minimal side effects. Because individual differences exist between patients in their responsiveness to medications, the dose is titrated upward slowly every 1 to 3 weeks[37,87,98] from the recommended starting dose, often based on body weight.[99] If extended-release forms are to be used ultimately, titration should be conducted with them directly.[37]

Proprietary extended-release versions are formulated to release different amounts of drug over a 24-hour period. Thus, whereas Ritalin LA releases 50% of the dose in each of the 2 bursts, these values are 22% and 78% for Concerta and 30% and 70% for Metadate CD. The latter were designed following reports that a system delivering a higher concentration in the afternoon provided a superior treatment response than the one providing a steady-state concentration[100-102]; this may also explain why switching proprietary medications sometimes elucidates a better treatment response.

Regardless of the proprietary medication used, methylphenidate has similar pharmacological and side effects (Table 1), but the dosing recommendations may differ

(Table 2). All formulations carry a high risk for abuse and dependence if not used as prescribed. Various drug-drug interactions are also possible (Table 1)[93-97]; thus, dose adjustments may be needed for many drugs that may be prescribed concomitantly with stimulants. Daytrana can cause irritation at the application site, vomiting, tics, and emotional instability.[97] The patient should be advised to place the patch on a clean, dry, hairless area of the hip for a maximum of 9 hours, at least 2 hours before the benefits of this medication are needed. The patient should also be advised to rotate the site of application daily, not to share the patch, and dispose it carefully to avoid being ingested by pets or toddlers.[103]

Amphetamine Salts. The most commonly used amphetamine formulations include Adderall XR and Vyvanse containing amphetamine salts, and prodrug lisdexamfetamine, respectively. Both D- and L-optical isomers of amphetamine are active. Common side effects are similar to that of methylphenidate (Table 1).[104,105] Amphetamines are metabolized by CYP1A2, CYP2C9, CYP2D6, and CYP3A4[104]; hence, a multitude of drug interactions are possible (Table 2).[104,105] Additionally, CYP2D6 isoforms generate slow and fast metabolizers in the general population; thus, higher amphetamine concentrations may be observed in Latinos and African Americans and about 7% of Caucasians.[46] A slow upward titration of the dose as recommended for methylphenidate may, in part, avoid the precipitation of severe side effects and/or toxicity in these slow metabolizers. Both formulations containing amphetamines carry a potential risk for abuse and dependence as well as neurotoxicity if not used as prescribed.[106] However, the release and absorption of amphetamine is slower with lisdexamfetamine, thereby limiting the euphoria and, hence, its abuse potential.[57,58]

Nonstimulants

Although stimulants are considered first-line agents, they may not be suitable for nearly 30% of ADHD patients.[107,108] Nonresponsiveness or partial responsiveness to stimulants; intolerance to their side effects (eg, insomnia); presence of medical issues such as psychiatric, cardiovascular, or tic disorders; and family aversion to controlled substances may require alternative agents categorized as nonstimulants for either replacing stimulants or added as adjuncts to treat ADHD. The FDA approved nonstimulants for treating ADHD are atomoxetine (Strattera) and extended-release α-2 agonists clonidine (Kapvay) and guanafacine (Intuniv).

Nonstimulants are believed to possess a less-robust effect than stimulants.[37,46] However, well-controlled, head-to-head comparison trials do not exist, and the superior efficacy of stimulants (methylphenidate) over nonstimulants (atomoxetine) is based on several meta-analyses.[37,46,89,109,110] Some studies[87]and meta-analyses[111] have determined noninferiority or equal efficacy of these 2 drugs, but the study methodologies and different outcome measures used in meta-analyses may partly explain this discrepancy. It is argued, however, that because most studies are conducted short term, they favor the stimulants because nonstimulants generally take several weeks to show their full effect.[84,112,113] These issues underscore the need for long-term, randomized, double blind, placebo-controlled, head-to-head comparison trials between the 2 groups of drugs.

Atomoxetine (Strattera). Atomoxetine (Strattera) is approved by the FDA for treating ADHD in children, adolescents, and adults. Like stimulants, atomoxetine increases the availability of both NE and DA in the synapses of PFC[114] to improve the PFC function in ADHD patients.[115,116] However, because it lacks effects in the striatum and requires at least 4 to 6 weeks to show full effect, it is less likely to be abused than stimulants.[112,113,117] Hence, it may be preferred in patients where substance abuse is a problem/concern,[37,46] but the time lag observed with atomoxetine underscores the need to counsel patients/caregivers to exhibit patience with this drug. It may also reduce tics and anxiety[37,54] and may thus be useful in patients with these comorbidities.

Like stimulants, atomoxetine also produces the characteristic inverted U-shaped dose-response curve,[71] but the optimal dose varies between individuals.[118] Clinical trials have investigated 0.5-, 1.2-, and 1.8-mg/kg doses and determined that the highest doses correlated with better ADHD symptom control, ODD, mood symptoms, and family functioning.[108] The FDA-approved maximum recommended dose, however, is the lesser of 1.4 mg/kg or 100 mg daily. A slow upward titration from 0.5 mg/kg every 3 to 4 days to about 1.2 mg/kg is recommended and must be administered at bedtime for the first 7 to 10 days to overcome sedation.[87]

Atomoxetine can be administered once daily in the morning or twice daily in divided doses. Although the once-daily administration improves compliance with therapy, it is associated with more gastrointestinal tract side effects.[119] Atomoxetine is generally well tolerated because side effects are reported to be less problematic than for stimulants (Table 1). However, warnings regarding rare hepatotoxicity and suicidal ideation in children and adolescents were issued by the FDA in 2005. Liver function tests are not monitored routinely,[108] but if hepatic impairment is obvious, initial and target doses should be reduced.[120] Several drug interactions are also of concern and must be taken into account before prescribing/dispensing atomoxetine (Table 1). Like amphetamine, atomoxetine is metabolized by CYP2D6[120]; hence, a slow upward titration of atomoxetine as outlined above limits the concern for increased toxicity in slow metabolizers. Atomoxetine, like stimulants, should not be administered in patients with uncontrolled hypertension, structural cardiac abnormalities, cardiomyopathy, and abnormalities of the heart rhythm.[120]

α-2 Agonists. Immediate release α-2 agonists such as guanfacine (Intuniv) and clonidine (Kapvay) are FDA-approved agents to treat hypertension but were used off-label to treat ADHD.[121-123] Extended-release forms of these drugs were recently approved by the FDA to treat ADHD in children and adolescents. Like atomoxetine, these drugs (in addition to TCAs and bupropion) may possess inferior efficacy as compared with stimulants but may be as efficacious as behavioral therapy.[37,123] Thus, behavioral therapy is recommended before using these agents.[37]

Guanfacine and clonidine act on the presynaptic and postsynaptic α_2 receptors present in the neuronal cells. Because the amelioration of ADHD symptoms is believed to rely on stimulating postsynaptic α_{2A} receptors and guanfacine is more selective than clonidine at these receptors,[124] it may show better efficacy than clonidine. The selectivity of guanfacine toward postsynaptic α_{2A} receptors[46] in addition to a longer half-life[119] imparts advantages of lesser sedation and dizziness than that observed with clonidine.

Guanfacine and clonidine may be administered alone or in combination with stimulants to counteract comorbid aggression, tics, or insomnia.[37,87] Like atomoxetine, therapeutic benefit with these drugs is delayed and observed at about 4 weeks. Side effects are generally mild (Table 1) but may affect compliance. Hence, a gradual upward titration is recommended to determine the effective dose with minimal side effects. These drugs should not be withdrawn suddenly because of risk of hypertensive crisis, and hence, patients or their parents should be educated about the need for perfect adherence. A 1-to 2-week withdrawal is recommended for these drugs if they need to be discontinued,[37] and cardiac consultation should be performed in individuals with cardiovascular problems.[87] For both these drugs, dose reductions and monitoring are recommended if used in patients with compromised liver and/or kidney function.[121,122]

Bupropion. Bupropion is an FDA-approved antidepressant and a smoking cessation agent but has also been used off-label to treat ADHD based on several studies.[46,87,107] Like stimulants and atomoxetine, bupropion inhibits the reuptake of both DA and NE but does not carry the potential risk of abuse and dependence seen with stimulants. It generally shows faster onset of action than atomoxetine or α-2 agonists (~2 weeks) and seems to be as efficacious as these drugs. However, bupropion use has been associated with seizures and, hence, should not be used in patients with seizure or eating disorders.[46] Side effects are generally mild (Table 1) and can be minimized with administering bupropion in divided doses.[125]

Although both immediate- and extended-release forms of bupropion are available, twice-daily administration of the extended-release form is recommended for children and adolescents because of the shorter half-life in these individuals.[126] Bupropion is usually initiated at a dose of 3 mg/kg (100-150 mg for most individuals) and is titrated to 6 mg/kg (300 mg) in divided doses.[87] Any single dose of bupropion should not exceed 150 mg,[87] and the dose should be lowered in case of hepatic of renal impairment.[127]

Tricyclic Antidepressants. The TCAs have been the most widely used off-label medications to treat ADHD for monotherapy; the long duration of action (because of the long half-life), no risk of abuse potential, and ability to overcome depression and tics were touted as distinct advantages over stimulants.[39] However, they are generally not preferred nowadays because of a large number of cardiovascular, neurological, and anticholinergic side effects and drug interactions (Table 1) and because they have lesser efficacy than stimulants. These are, therefore, used only if individuals are nonresponsive to stimulants or alternative agents, cannot tolerate them, or have abuse potential, tics, or depression.

Imipramine, desipramine, and nortriptyline are the agents that have been used, but desipramine is least preferable because of reports of sudden death.[37] Additionally, the desipramine dose must be reduced in hepatic impairment. An ECG must be performed prior to initiating TCAs and after every dose increase to ensure cardiac safety.[37] Like every other drug discussed above, these drugs should also be titrated upward slowly to improve tolerability and like α-2 agonists, a slow withdrawal should be performed if these drugs are to be discontinued.[108] The slow upward titration may also limit the toxicity in slow metabolizers because TCAs are metabolized by CYP2D6.[108]

Therefore, although nonstimulants do not have abuse potential like stimulants do and are generally better tolerated than stimulants, they may possess inferior efficacy and a longer onset of action. Additional concerns with atomoxetine (hepatotoxicity and suicidal ideation) and TCAs (side effects and drug interactions) and the inability to use these drugs in patients with cardiovascular problems necessitates finding better drugs to treat ADHD. Recently, a selective D_4 agonist, A-412997, has been shown to improve ADHD symptoms in rats without the abuse and/or dependence potential.[128,129] Another drug that was well tolerated and seemed to show promise in clinical trials is a nicotinic receptor agonist ABT-418,[130] but it does not seem to be under development currently.

Treatment Guidelines

Given the extensive literature available with respect to the pathophysiology, etiology, and treatment of ADHD, it is surprising that the treatment guidelines are not well established. Physicians, therefore, may have to rely on their clinical experience, the patient or their family's preference, presence of comorbid disorders, and any other medical conditions that may preclude the use of the agents of choice.

The evidence-based clinical practice guidelines formulated and published by the American Academy of Pediatrics (AAP)[131] provides a brief overview for approaching treatment of ADHD (Table 3). Although these guidelines are useful in describing which approaches should be used, they do not describe an algorithmic approach to treatment if the stimulant/behavioral therapy fails to produce a desired response. A medication algorithm such as that designed in conjunction with the Texas Department of State Health Services[125] (Table 3) was instrumental in guiding pharmacotherapy but was deemed controversial. The American Academy of Child and Adolescent Psychiatry (AACAP), therefore, formulated a practice parameter for the assessment and treatment of ADHD in children and adolescents (Table 3).[37] Because extended-release guanfacine and clonidine were approved by the FDA for treating ADHD after the Texas Medication algorithm and the AACAP guidelines were published, it remains to be determined whether this will affect the subsequent algorithm or guidelines that may be developed. It is entirely possible that following FDA approval, these drugs may be prescribed more often and, therefore, may provide a more solid base of evidence for their use.

The AACAP guidelines also call for periodic assessment to determine continued efficacy, safety, and need for pharmacotherapy.[37] Efficacy of the drug can be rapidly assessed by the rating scales that have already been discussed. Safety and need for therapy is assessed by monitoring physical well-being (height, weight, blood pressure, pulse, etc) and the emergence of side effects or comorbid disorders several times a year.[37] Monitoring for efficacy and safety is generally not an issue during the slow upward titration phase but may become one once a patient achieves a stable dose that shows maximum efficacy with minimum side effects. A continuous monitoring not only ensures continuous efficacy and physical/mental well-being but may also provide evidence for cessation of therapy. This may be considered if the patient has been stable on a particular dose for a long time and/or a missed dose did not cause deterioration.[37] However, drug withdrawal must be done during low-stress times, such as summer vacations, and cognitively challenging tasks must be provided at this time to ensure that remission has indeed occurred.[37]

Conclusions

ADHD is a complex disorder associated with multiple issues leading to a lower quality of life. A chemical imbalance of NTs such as DA and NE in the PFC is believed to be responsible, and medications that correct this imbalance are broadly classified as stimulants (methylphenidate and amphetamines) and nonstimulants (atomoxetine, α-2 agonists, bupropion, and TCAs). These medications have multiple side effects and drug interactions, and stimulants have a potential for abuse if not correctly used. Hence, medications must be initiated at a low dose and gradually titrated upward, and patients must be monitored continuously for efficacy and emergence of side effects. Stimulants are considered as first-line therapy, but the first-line agent chosen is often patient specific, driven by the patient's age, preference, and comorbidities; side effects; and drug interactions.

Given the limitations of current drugs, those that are highly efficacious, long acting, and devoid of abuse potential, side effects, toxicity, or drug interactions need to be discovered. Additionally, well-planned comparison trials of different drugs available need to be conducted to facilitate the creation of a medication algorithm that may help standardization of therapy and care for this population. The discovery of a diagnostic marker of ADHD, although unlikely, would also aid tremendously in diagnosing this complex disorder.

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