Review Article

Pharmacologic management of attention deficit hyperactivity disorder in children and adolescents: a review for practitioners

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Abstract: Attention-deficit/hyperactivity disorder (ADHD) is a common neurobehavioral disorder in children and adolescents. ADHD affects multiple aspects of an individual's life and functioning in family, social, and academic realms. Effective management of ADHD is necessary for children and adolescents and may include non-pharmacologic treatments, pharmacologic therapy including use of stimulant and non-stimulant medications, or a combination of the different treatment modalities. In general, medications used to treat ADHD are safe and effective. Medical practitioners can follow a step-wise approach in the selection and adjustment of pharmacologic agents to treat ADHD, while working closely with families, caregivers, and other medical and educational professionals to form appropriate treatment plans. This article reviews practical aspects of pharmacological treatment of ADHD in children and adolescents.

Keywords: Attention-deficit/hyperactivity disorder (ADHD); stimulants; non-stimulant medication; methylphenidate; amphetamine; alpha-2-agonists

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder in children and adolescents. It is a complex chronic condition that begins in childhood, and individuals diagnosed with ADHD are considered children and youth with special healthcare needs. ADHD affects not just young children, but can continue into adolescents and adulthood (1). Medical practitioners should evaluate for ADHD in any child over age 4 years who presents with symptoms of inattention, hyperactivity, or impulsivity and academic or behavioral difficulties (1,2).

Over the past several years, the prevalence of ADHD has been increasing by an average of 5% annually, with approximately 6.4 million children and adolescents in the United States, between the ages of 4 and17 years, having ever received a diagnosis of ADHD based on parent or caregiver reports (3,4). This represents 11% of children and adolescents in this age range whose parents report ever having received an ADHD diagnosis (2-4). In the United States, two-thirds (3.5 million) of children and adolescents with ADHD were taking medication for treatment in 2011 (3,4). It is uncertain what the primary cause of the increased prevalence is, but factors such as changing diagnostic criteria, over- or misdiagnosis, or conversely heightened awareness and screening for ADHD may all play a role (1-8).

The underlying neuropathology of ADHD remains uncertain, but is likely multifactorial, including genetic causes, structural and functional differences in brain circuitry, and environmental and psychosocial factors. Commonly prescribed ADHD medications have dopaminergic and noradrenergic activities, suggesting this neurobiological role in etiology (9-13).

The diagnosis of ADHD is based on the criteria outlined

by The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) (8). ADHD is categorized into three subtypes: predominantly inattentive type ADHD, predominantly hyperactive/impulsive type ADHD, and combined type (8). The symptoms of inattention, hyperactivity, and impulsivity should be observed in at least two different settings, and must be present for 6 months or longer (8). The symptoms must also result in impairment of social, academic, or other functioning, and the symptoms must not be better explained or attributed to another physical condition, mental health condition, or social situation (6-8). In evaluating children and adolescents for ADHD, clinicians should use standardized assessment tools or questionnaires such as the Vanderbilt or Conner's rating scales (1,6,7). The ADHD rating scales should be used as part of the initial evaluation and for monitoring of symptoms in follow up after various treatments have been initiated (1,6,7).

The main categories of ADHD treatment are pharmacologic and non-pharmacologic treatments, including counseling, behavioral, and environmental modification strategies. Each treatment has been shown to be effective; however, a combination of treatment methods has been shown to be most effective (1,2,7). Behavioral therapy and parent behavioral training can potentially address core symptoms and functional impairments that occur in children with ADHD. Pharmacologic therapies can be useful in managing core symptoms of ADHD including reducing distractibility, improving sustained attention, reducing impulsive behaviors, and improving activity level, all of which can allow for improved performance across settings. Pharmacologic agents used to treat ADHD can be divided into two main classes: stimulant and non-stimulant medications (10-15).

Pharmacological agents

Stimulants

Mechanism of action

Stimulants work to enhance arousal in the prefrontal cortex (9). Specifically, preparations of methylphenidate and amphetamine (*Tables 1*,*2*) act to boost norepinephrine and dopamine neurotransmission in the prefrontal cortex (9,10,13). Methylphenidate exerts its effect from inhibiting presynaptic dopamine transporters of central adrenergic neurons. It also inhibits norepinephrine transporters to a much lesser degree. This increases synaptic cleft concentration of dopamine, amplifying the dopaminergic neurotransmission (13). Amphetamine is a competitive inhibitor of dopamine, acting directly on dopamine transporter and norepinephrine transporter binding sites as a pseudo-substrate (9). Amphetamines also increase catecholamine release as a primary mechanism and both, methylphenidate and amphetamine, increase dopamine release that enhances one's response to environmental stimuli (9-11). Amphetamines also have a peripheral sympathomimetic effect by stimulating β and α receptors (12).

Both, methylphenidate and amphetamine, have *d* and *l* isomers (9,10,13). The *d* isomer of methylphenidate is much more potent than the *l* isomer on norepinephrine transporter and dopamine transporter binding. Enantiomer *d*-methylphenidate is available in immediate-release and controlled-release preparations. Similarly, the *d* isomer of amphetamine is more potent than the *l* isomer for dopamine transporter binding; both the *d* and *l* isomers are equally potent on norepinephrine transporter binding (9). The preparations, dosing, and pharmacokinetics of stimulants are summarized in *Tables 1-4* (1,10-15).

Cardiovascular considerations and monitoring when prescribing stimulants

Although the heart rate and systemic blood pressure (BP) can elevate with the use of stimulants, the increase is not significant enough to reach abnormal range for age. The average increase in systolic BP is 3–4 mmHg, average increase in diastolic BP of 1–2 mmHg and average increase in heart rate 3–4 beats per minute (16-18).

Safety concerns, specifically regarding cardiac events, arose from reports of adverse effects of stimulant medications, including sudden unexpected death, leading to questions on what appropriate cardiovascular evaluation should be done prior initiation of stimulant drugs (19-21). While these reports raise concern, no large clinical trials have shown a correlation between the use of stimulants and sudden unexpected cardiac death. A United States Food and Drug Administration (FDA) study, included 2.5 million subjects including children and young adults (mean age 11.1 years), who were followed for an average of 2.1 years. In this study, no significant difference in risk for serious cardiovascular side effects (sudden death, acute myocardial infarction or stroke) was found between those using stimulants and those not using stimulant medications (22). The incidence of serious cardiovascular effects was 3.1 per 100,000 person-years (22). In a population-based study of 171,126 children between the ages of 6 and 21 years, no significant difference in risk was found between individuals

Table 1 Immediate release methylphenidate medications (10-15)

Drug brand	Formulation (mg)	Dosing	Peak (hrs)	Duration (hrs)	Comments
Ritalin (methylphenidate)	Tablet: 5, 10, 20	Initial: age 3–5 yr, 1.25 mg BID*; age >6 yr, 0.3 mg/kg/dose or 2.5–5 mg/dose twice daily. Titration: increase by 0.1 mg/kg/dose or 5–10 mg/week. Max (weight based, in divided doses): 2 mg/kg/day or <50 kg, 60 mg/day; 50 kg+, 100 mg/day	1–3	2–4	Doses typically divided 2–3×/day
Methylin (methylphenidate)	Tablet: 5, 10, 20; chewable: 2.5, 5, 10; solution: 5, 10 mg/mL				In children benefiting bid dosing may also benefit from a 3rd low afternoon dose
Focalin (dexmethylphenidate)	Tablet: 2.5, 5, 10	Initial: age >6 yr, 0.15 mg/kg/dose or 2.5 mg BID. Titration: increase by 2.5–5 mg/week. Max: 20 mg/day	1–3	3–5	D-isomer with more potent mechanism of action, therefore lower dose used

Drug brand names refer to United States brand names. *, not FDA approved in this age group, but recommended based on current evidence and guidelines. BID, twice daily; hrs, hours; kg, kilograms; max, maximum; mg, milligrams; mL, milliliters; yr, years old.

Table 2 Immediate release amphetamine medications (10-15)

Drug brand	Formulation (mg)	Dosing	Peak(hrs)	Duration (hrs)	Comments
Adderall (amphetamine)	Tablet: 5, 7.5, 10, 12.5, 15, 20, 30	Initial: age 3–5 yr, 2.5 mg daily*; age >6 yr, 5 mg daily or BID. Titration: age 3–5 yr, increase 2.5 mg/week*; age >6 yr, increase 5 mg/week. Max: 40 mg/day	1–3	4–6	Slightly longer duration for an immediate release preparation. Side effect: may increase aggressive behavior. Evekeo: expensive
Evekeo (contains d- and l-amphetamine in 1:1 ratio)	Tablet: 5, 10				
Dexedrine (dextroamphetamine)	Tablet: 5, 10	Initial: age 3–5 yr, 2.5 mg daily*; age >6 yr, 5 mg daily or BID. Titration: age 3–5 yr, increase by 2.5 mg/week*; age >6 yr, increase by 5 mg/week. Max: 40 mg/day	1–3	4–5	Side effects: may have more appetite suppression and sleep difficulties
Dextrostat (dextroamphetamine)	Tablet: 5, 10				
Procentra (dextroamphetamine)	Solution: 5 mg/5 mL				
Zenzedi (dextroamphetamine)	Tablet: 2.5, 5, 7.5, 10, 15, 20				

Drug brand names refer to United States brand names. *, not recommended in this age group. BID, twice daily; hrs, hours; kg, kilograms; max, maximum; mg, milligrams; mL, milliliters; yr, years old.

taking stimulants compared to matched controls, for adverse cardiovascular events such as angina pectoris, cardiac dysrhythmia, transient cerebral ischemia, tachycardia, palpitations, or syncope (23). The study did not include individuals with known cardiovascular risk factors (23). A nationwide cohort study of children ages 3–17 years, conducted in Denmark, reported no significant difference in the rate of sudden unexpected cardiac deaths between the children and adolescents using stimulants matched controls (23). Although infrequent, cardiovascular events were reported with stimulant treatment, with a 2.2-fold increased risk in children and adolescents with ADHD (24,25).

Children and adolescents should be evaluated for cardiac disease or risk factors for cardiac disease prior to initiation of stimulant as well as non-stimulant medications through complete medical history, family history (*Table 5*),

Table 3 Extended release methylphenidate medications (10-15)

Drug brand	Formulation (mg)	Dosing	Duration (hrs)	Comments
Methylin ER (methylphenidate) Metadate ER (methylphenidate)	Tablet: 10, 20	Initial: 10 mg/day. Titration: 10 mg/week. Max: 60 mg/day	4–6	Given shorter duration, may need 2nd dose of immediate release medication in afternoon
Ritalin SR (methylphenidate) Ritalin LA (methylphenidate) Metadate CD (methylphenidate)	Tablet: 20; capsule: 20, 30, 40	Initial: 20 mg/day. Titration: 20 mg/week. Max: 60 mg/day	6–8	Metadate CD and Ritalin LA capsule can be sprinkled
Quillivant XR (methylphenidate) Quillichew ER (methylphenidate)	Suspension: 25 mg/5 mL; tablet: 20, 30, 40		9–12	–
Concerta (methylphenidate)	Capsule: 18, 27, 36, 54	Initial: 18 mg daily. Titration: 18 mg/week. Max (age/weight based): 6–12 yr/<50 kg, 54 mg/day; >12 yr/>50 kg, 72 mg/day	9–12	Cannot crush, cut, chew OROS capsules
Daytrana (methylphenidate)	Patch: 10, 15, 20, 30	Initial: 10 mg patch applied daily (apply to hip 2 hrs before effect needed, remove 9 hours after application). Titration: increase to next transdermal patch dosage size no more frequently than every week	12	Can remove before 9 hrs for shorter duration of effect Potential for sensitization to methylphenidate due to topical route
Focalin XR (dexmethylphenidate)	Capsule: 5, 10, 15, 20, 30	Initial: 5 mg/day. Titration: 2.5–5 mg/week. Max: 30 mg/day	9–12	–

All preparations are methylphenidate except, Focalin XR, which is a dexmethylphenidate. Drug brand names refer to United States brand names. BID, twice daily; CD, controlled delivery; ER, extended release; hrs, hours; kg, kilograms; LA, long acting; max, maximum; mg, milligrams; mL, milliliters; OROS, osmotic controlled release oral delivery system; SR, sustained release; XR, extended release; yr, years old.

and physical examination (19,21-23). Current guidelines recommend that a medical practitioner considers performing an electrocardiogram (ECG) and in some circumstances, considers referral to a cardiology specialist in children and adolescents with findings suggestive of cardiac disease. Timely cardiac evaluation is indicated if children and adolescents develop any significant chest pain, unexplained syncope, or any other symptoms suggestive of cardiac disease (1,26,27).

Additional monitoring

Children and adolescents taking stimulants should be monitored clinically. No laboratory testing is indicated. Clinical monitoring should include, neurological examination, BP measurement, heart rate, sleep, appetite, behavior and mental health changes, and growth parameters (height, weight, body mass index). About one third of children and adolescents treated with therapeutic stimulant dosages of stimulants reports decreased appetite; however, in most children and adolescents this effect is transient or clinically insignificant. Strategies to manage low appetite and other potential side effects are summarized in *Table 6* (1,6,7,17). In a longitudinal study, findings suggested that treatment with stimulant medication was not associated with differences in final attained adult height between those who used stimulants and those who did not (28). A meta-analysis evaluating the effects of stimulant medications on quality of sleep in youth with ADHD found that stimulants

Table 4 Extended release amphetamine medications (10-15)

Drug brand	Formulation (mg)	Dosing	Duration (hrs)	Comments
Adderall XR (amphetamine and dextroamphetamine)	Capsule: 5, 10, 15, 20, 25, 30	Initial: 10 mg daily. Titration: 10 mg/week. Max: 30 mg/day	8–12	Can be sprinkled; side effects include insomnia, anorexia
Adzenys XR (amphetamine)	ODT: 3.1, 6.3, 9.4, 12.5, 15.7, 18.8	Initial: 3.1 mg daily. Max: 18.8 mg (ages 6–12 years); 12.5 mg (ages 13–17 years)	8–12	Expensive
Dexedrine SR (amphetamine)	Capsule: 5, 10, 15	Initial: 5 mg daily. Titration: 5 mg/week. Max:40 mg/day	8–10	Cannot be sprinkled; side effects: may see more anorexia, irritability
Vyvanse (lisdexamfetamine)	Capsule: 20, 30, 40, 50, 60, 70	Initial: 20–30 mg daily. Titration: 10–20 mg/week. Max: 70 mg/day	8–12	–
Dyanavel XR (amphetamine)	Suspension: 2.5 mg/mL	Initial: 2.5–5 mg daily. Titration: 2.5–10 mg/week. Max: 20 mg/day	8–12	Contains d-and l-amphetamine in a 3.2:1 ratio, very expensive

Adderall XR and Adzenys XR are amphetamines, Dexedrine SR, Vyvanse and Dyanavel XR are dextroamphetamines. Current long acting amphetamines/dextroamphetamines are approved for children ages 6 years and older. Drug brand names refer to United States brand names. hrs, hours; kg, kilograms; LA, long acting; max, maximum; mg, milligrams; mL, milliliters; ODT, oral disintegrating tablet; SR, sustained release; XR, extended release.

led to shorter sleep duration, longer length of time to transition from full wakefulness to sleep (sleep latency), and reduced sleep efficiency (29).

Stimulant dosing is typically adjusted on a weekly basis and initial follow up monthly is recommended. Once medication dosing is stable, clinical follow up appointments can be spaced to every 3 months for the first year. In children with long term stability, follow up visits every 6 months can be considered (1,6,15).

Contraindications

Children and adolescents should not take stimulants if also taking monoamine oxidase inhibitors (MAOIs) within 14 days or have a history of glaucoma (15). Amphetamines are not absolutely contraindicated, but should be avoided in children and adolescents with symptomatic cardiovascular disease, hyperthyroidism, and moderate to severe hypertension (15). Certain extended release formulations of methylphenidate should be avoided in children and adolescents with pre-existing severe gastrointestinal narrowing, due to concern regarding rare reports of intestinal obstruction (10,13,15). Caution is advised when prescribing methylphenidates to children and adolescents also taking anticoagulant medications, anticonvulsants, and tricyclic antidepressants (15). In children and adolescents with ADHD and seizure disorders, stimulants are not contraindicated; however, stimulants may lower seizure threshold (30).

Non-stimulant medications: atomoxetine

Mechanism of action

Atomoxetine is a selective norepinephrine reuptake inhibitor, which causes increased concentrations of norepinephrine and dopamine in the prefrontal cortex. Atomoxetine does not cause increased norepinephrine or dopamine in the nucleus accumbens and lacks abuse potential (9,10). The preparations, dosing, and pharmacokinetics of atomoxetine are summarized in *Table* 7. In children and adolescents with ADHD treated with atomoxetine, initial response may be slower than that seen with stimulant medications. ADHD symptoms may respond over the course of several weeks and after the dose is titrated up to the maximum daily dose; symptom improvement may continue over 2 months (10,11).

Monitoring

Atomoxetine carries the United States FDA warning for the potential to increase suicidal ideation in children and adolescents. Children and adolescents started on

Table 5 Cardiovascular screening history before starting pharmacotherapy

Screening parameters	Screening history
Symptoms*	Unusual fatigue associated with physical activity (more than or different from others)
	Pain, discomfort, or pressure in chest during exercise
	Pre-syncope or syncope during or after exercise, emotion, or startle
	Dizziness associated with exercise
	Shortness of breath associated with exercise (more than or different from others)
	Heart racing or skipped beats
Medical history and review of systems	Unexplained seizures*
	Detailed history of any congenital structural heart disease*
	Use of cardiac pacemaker or implanted cardiac defibrillator*
	History of Kawasaki disease*
	History of rheumatic fever*—known heart murmur
	Systemic hypertension
	Substance abuse, tobacco use
	Use of excessive caffeine or energy drinks
	Any previous recommendations to restrict physical activity
Family history*	Sudden or unexpected death of family members before age 50 years
	Coronary artery disease before age 50 years
	Family members using pacemaker or implanted cardiac defibrillator
	Family history of cardiomyopathies, long QT syndrome, short QT syndrome, or Brugada syndrome
	Family history of primary pulmonary hypertension

*, positive screening should warrant further cardiac evaluation.

atomoxetine should be monitored for mood and behavior changes and families should closely watch for symptoms such as irritability, agitation, or thoughts of suicide or self-harm (10,15). Data from recent meta-analyses suggest that there is no statistically significant association between atomoxetine and increased risk for suicidality (31).

No specific laboratory monitoring is recommended for children and adolescents taking atomoxetine. However, in children and adolescents with any symptoms of liver dysfunction, liver enzymes and/or transaminases should be evaluated prior to medication initiation (10). Atomoxetine is metabolized in the liver and a small percentage of the Caucasian population (7%) are poor metabolizers through the P450 pathway (CYP2D6) in which, atomoxetine is metabolized. Therefore, dose adjustments may be necessary in some children and adolescents (10). Children and adolescents should be assessed for risk of cardiac disease with follow up and screening as appropriate prior to medication initiation. Growth parameters, neurological examination, mental status examination, vital signs, and side effects should be monitored at regular intervals.

Contraindications

Atomoxetine should not be used in children and adolescents taking MAO inhibitors within the last 14 days, children and adolescents with glaucoma, history of pheochromocytoma, or any severe cardiac or vascular disorders in which the condition would be expected to worsen with increase in BP or heart rate (15,32).

Side effects and their management

Common side effects of atomoxetine include decreased

Table 6 Common side effects of stimulants and management strategies (6,10-15)

Side effect	Management strategies
Decreased appetite; nausea; stomachache; weight loss (less common)	Frequent snacks or additional "4th meal" at bedtime
	Dose medication with food or after meals
	Consider switch to short acting agent
	Drug holiday if significant change in growth
Sleep difficulties	Bedtime routine, reduce bedtime stimuli
	Reduce or eliminate afternoon dose (if on immediate release preparation)
	Move dosing regimen to earlier time
	Reduce or eliminate caffeine intake
	Consider addition of melatonin
Transient headache	Symptomatic management and observation
	Reduce dose, try another stimulant, or another class
	Consider alpha-agonist medication or atomoxetine
Behavioral rebound	Try sustained-release stimulant
	Add later afternoon dose of short acting stimulant
Exacerbation of tics (rare)	Reduce dose, try another stimulant, or another class
	Consider alpha-agonist medication or atomoxetine
Increased heart rate or blood pressure	Reduce dose, try another stimulant, or another class
	Consider alpha-agonist medication or atomoxetine
Irritability or dysphoria	Decrease dose, try another stimulant or class
	Consider coexisting conditions, especially depression
Psychosis, euphoria, mania, severe depression	Stop treatment with stimulants
	Refer to mental health specialist urgently

appetite, nausea, vomiting, diarrhea, fatigue, mood swings, and dizziness; most subside with continued use over several weeks. Insomnia may develop over time and can be a significant side effect. Elevation of heart rate and BP may also occur in some children and adolescents (10,15). Significant side effects such as suicidality, aggression, seizures, liver injury, and prolonged QT interval are rare in pediatric children and adolescents (32). However, significant changes in behavior, mood, or suicidal ideation should prompt immediate evaluation. Rare cases of severe liver injury have been reported. Therefore, in children and adolescents with any sign of urinary color change or jaundice or pruritus, atomoxetine should be immediately discontinued and liver function evaluated (32-37). In a placebo-controlled study, in otherwise healthy subjects who were CYP2D6 poor metabolizers, a statistically significant increase in QTc interval was reported as atomoxetine concentrations increased; case reports have also suggested that atomoxetine overdose may prolong the QT interval (33,34,37).

Non-psychostimulant medications: alpha-2-agonists

Mechanism of action

Clonidine stimulates alpha-2 adrenoceptors in the brain stem activating inhibitory neurons, which results in reduced sympathetic outflow from the central nervous system (CNS) (35). The reduced sympathetic outflow produces decreased peripheral resistance, renal vascular resistance, heart rate, and BP (35). In treatment of ADHD,

Table 7 Non-stimulant medications (10-15)

Drug brand	Formulation (mg)	Dosing	Duration (hrs)	Comments
Strattera (atomoxetine:norepinephrine reuptake inhibitor)	Capsule: 10, 18, 25, 40, 60	Initial: <70 kg, 0.5 mg/kg; >70 kg, 40 mg daily. Titration: <70 kg, increase after 1 week to 1.2 mg/kg as single or divided dose; >70 kg, increase to 80 mg over 1 week as single or divided dose. Max: 1.4 mg/kg/day up to 100 mg/day	10–12	Dose adjustment required in hepatic impairment. Takes several weeks to see effect. May be stopped without taper. Single daily dose recommended
Kapvay* (clonidine extended release; alpha-2-agonist)	Tablet: 0.1, 0.2	Initial: 0.1 mg/day at bedtime. Titration: 0.1 mg/week and divided BID. Max: 0.4 mg/day divided BID	12–24	If stopping therapy taper daily dose by ≤0.1 mg every 3 to 7 days
Intuniv* (guanfacine extended release; alpha-2-agonist)	Tablet: 1, 2, 3, 4	Initial: 0.05–0.08 mg/kg/dose or 1 mg daily. Titration: no more than 1 mg/week. Max: 6–12 yr: 4 mg/day	12–24	Taper the dose in decrement of ≤1 mg every 3 to 7 days

Drug brand names refer to United States brand names. *, approved for use in patients with ADHD ages 6 years and older. hrs, hours; max, maximum; mg, milligrams; yr, years old; BID, twice daily; ER, extended release; kg, kilograms; max, maximum; mg, milligrams.

the exact mechanism of action is unknown. There are many subtypes of alpha adrenergic receptors widely distributed in the CNS and the main theory proposes that postsynaptic alpha-2-agonist stimulation regulates subcortical activity in the prefrontal cortex, regulating symptoms of inattention, hyperactivity, and impulsivity (35). Clonidine is a relatively nonselective agonist at alpha 2 receptors; it also has actions on imidazoline receptors, which is thought to be responsible for some of its sedating and hypotensive actions. Guanfacine is a more selective alpha 2A adrenergic agonist, which is thought to contribute to less sedation and less hypotensive actions (10,11).

The preparations, dosing, and pharmacokinetics of alpha-2-agonists are summarized in *Table* 7 (10-15). Although not specifically studied, the immediate release clonidine and guanfacine have been used as second-line agents for ADHD or as adjunctive medications for children and adolescents with suboptimal results on stimulant medications. With the availability of extended release formulations specifically studied and approved for use in the treatment of ADHD, the use of immediate release alpha-2-agonists is not recommended. Extended-release clonidine (Kapvay) and extended-release guanfacine (Intuniv) have be approved by the US FDA for use as adjunctive therapy with stimulant medications in ADHD treatment (1). In some cases, these medications are used as primary or monotherapy for the treatment of ADHD. With the use of alpha-2-agonists, symptoms may respond over the course of 1–2 weeks (9-11,35). When comparing the use of alpha-agonists to stimulant medications as monotherapy, studies have shown that stimulant medications are relatively more effective in treatment of ADHD (35). Dose adjustment for guanfacine may be required in children and adolescents on strong CYP3A4 inducers or inhibitors (15).

Monitoring

Children and adolescents should be evaluated for cardiac disease or risk factors prior to starting alpha-2-agonists. Although not universally recommended, some practitioners obtain an ECG prior to starting an alpha-2-agonist. Given the mechanism of action to decrease peripheral vascular resistance, decrease heart rate, and BP, there is an increased risk of hypotension, orthostatic hypotension, and bradycardia. The heart rate and BP should be monitored closely at medication initiation and on follow up with each dose change. There is also risk for rebound hypertension if either of these alpha-2 agonist medications are abruptly discontinued, and when discontinuing these medications, the dose should be tapered over several days to weeks (15).

Contraindications

Alpha-2 agonists should not be used in children and adolescents with a history of significant depression as their physiologic effects may worsen depression symptoms. A hypersensitivity to the medication or component of formulation is a contraindication to clonidine or guanfacine use (15).

Side effects and their management

The most common side effects noted with use of clonidine

include dry mouth, sedation, somnolence, dizziness, headache, and constipation. The most common side effects reported with use of guanfacine include somnolence, fatigue, bradycardia, and hypotension. Somnolence and sedation tend to diminish over time and are less common side effects of guanfacine compared to clonidine. Guanfacine has also been noted to have less of an effect on BP compared to clonidine. In general, extended release formulations of clonidine and guanfacine tend to minimize the initial drop in BP and are better tolerated than the short acting preparations (10,15).

Clinical approach to pharmacotherapy

Step 1

Extended release stimulant medications are first line in pharmacologic management of ADHD symptoms. In general, stimulants improve core ADHD symptoms equally, but a child or adolescent may respond better to one stimulant over another. Stimulant medications are approximately equivalent in efficacy and side effects, but some children and adolescents respond better to one over another.

Step 2

Starting with the first stimulant medication (either methylphenidate or amphetamine) chosen, increased titration of dose should occur until maximum symptom benefit is achieved without significant side effects or to the dose at which side effects are tolerable and benefit outweighs risk (1).

Step 3

If one stimulant medication (either methylphenidate or amphetamine) does not work at the highest appropriate dose, a medical practitioner should then consider trying the other stimulant medication. Similarly, increased titration of dose of the other stimulant medication should occur until maximum symptom benefit is achieved without significant side effects.

Step 4

If both (methylphenidate and amphetamine) stimulants have been tried without producing benefit in ADHD symptoms or are not tolerated due to side effects, the next step in ADHD medication management should be to consider trying non-stimulant medications.

Along this step-wise pathway of medication management of ADHD, the family and child or adolescent should be fully involved in the decision-making process about use of medications. It is important to explore potential concerns and practice good collaboration and communication with the family, other medical providers, behavioral therapists, and school providers or other caregivers for the child. It is recommended that systematic rating scales be used to measure symptoms at baseline and throughout treatment to monitor symptoms, performance, and potential side effects (1,6,36).

Specific age-related considerations

Preschool-aged children

Management of ADHD in preschool-aged children (age 4–5 years) should start first with behavioral therapy. However, there is some evidence that preschool-aged children with moderate-to-severe dysfunction may benefit from pharmacologic therapy (1). In order for a clinician to consider initiation of stimulant medication in preschool-aged children, the following criteria should be met: symptoms that have persisted at least 9 months, dysfunction that is present in both the home and another setting such as daycare, and dysfunction that has not responded adequately to behavior therapy (1). The decision to initiate medication treatment for ADHD in preschool-aged children should also take into account a child or adolescent's developmental level or impairment, any potential safety risks, or consequences for school or social interactions (1,5).

Dextroamphetamine is the only medication approved by the US FDA for use in children younger than 6 years; however, there is a lack of evidence in the literature regarding safety and efficacy in this age group, and its use is not currently recommended. Most of the evidence in the literature regarding stimulant medication safety and efficacy in treating preschool-aged children has been in regards to the use of methylphenidate. There is reasonable evidence regarding safety and efficacy of methylphenidate for use in preschool-aged children; however, it is not specifically approved by the US FDA for use under the age of 6 years. A lower dose threshold for symptom response exists in preschool-aged children secondary to a slower rate of metabolism of stimulant medication. Therefore, it is advised

that when starting stimulant medication in preschool-aged children, the initial dose chosen should start low and be increased in smaller increments (1,5,14).

Adolescents 12 years of age and older

Prior to initiating stimulants for adolescents with newly diagnosed ADHD, clinicians should assess for symptoms of substance abuse and when substance use is identified, treatment of the underlying disorder should be evaluated and treated. Medical practitioners should monitor for signs of misuse or diversion of stimulants. Atomoxetine, extended-release guanfacine, or extended-release clonidine (medications with no abuse potential) may be considered when misuse of stimulant medications is a concern (1,6,10).

Limitations of pharmacotherapy

Data are limited on both long-term effectiveness and long-term adverse effects for all ADHD medications. Research is limited for stimulant use in the preschool age range (4–5 years) (5,14).

Medications alone do not change behaviors, teach social skills, build academic skills, and teach emotional regulation or how to cope with anger or frustration. Collaboration with caregivers, schools, and other behavioral interventions in conjunction with pharmacologic therapy can help with these essential skills for children and adolescents with ADHD.

Co-morbid conditions and ADHD

Up to half of children with ADHD may also have coexisting or comorbid psychological and developmental disorders. Among neurobehavioral disorders there are frequently overlapping symptoms of hyperactivity, impulsivity, and inattention. Learning disabilities, disruptive behavior disorders, anxiety, and mood disorders (depression or bipolar disorder) are the most common comorbid conditions in children with ADHD. ADHD can also co-occur with autism spectrum disorder and other neurodevelopmental disorders such as fetal alcohol syndrome, Tourette syndrome, trisomy 21, or other genetic syndromes (e.g., Prader-Willi syndrome, Williams syndrome, Turner syndrome (38).

A general principle in treating a child or adolescent with ADHD, as well as a comorbid mental health or medical disorders, is to treat the primary diagnosis or most urgent or impairing problem with indicated medication first (37,38). Specifically, in children with multiple comorbid conditions, one should try to minimize use of multiple medications when possible, and when changing medications, make only one change at a time, monitoring results carefully (38).

Conclusions

ADHD is common in children and adolescents, and can be impairing for the individual affected in numerous aspects of their daily lives. Effective treatment of ADHD symptoms is necessary for children and adolescents to achieve full potential and performance in social, academic, and family functioning. Existing medical evidence supports pharmacologic therapy for children and adolescents with ADHD and is continuing to evolve with new research in the field. Pharmacologic treatment of children and adolescents with ADHD should begin with long acting stimulant medications in most cases. Medical practitioners should ensure the use of an adequate dose and duration of medication before switching within the stimulant class of medications, or to alternate medication therapy. Rating scales are essential in diagnosis of ADHD, assessing baseline symptoms, and response to subsequent treatment. Behavioral interventions in addition to appropriate pharmacologic therapy, can be useful for children and adolescents and their families, and involvement of the community around a child in treatment is key. Appropriate, individually tailored treatment plans, working with behavioral, medical, and educational providers around children and adolescents with ADHD can help each individual succeed.

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Footnote

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