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REVIEW

Pharmacological Treatment of Attention Deficit Hyperactivity Disorder in Children and Adolescents: Clinical Strategies

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Abstract: Attention deficit hyperactivity disorder (ADHD) is a common neurobehavioral disorder of childhood that can result in significant functional impairment, and if not adequately treated can lead to impaired quality of life. Pharmacotherapy is considered the first-line treatment for ADHD in children and adolescents. We review both recent literature and seminal studies regarding the pharmacological treatment of ADHD in children and adolescents. There is ample evidence for the efficacy and safety of both stimulants and non-stimulants in the treatment of ADHD. We review important aspects of evaluation and assessment and discuss first-line pharmacological treatments and as well as when to consider using alternative pharmacological agents. Treatment approaches to manage frequently seen comorbid disorders with ADHD are also covered.

Keywords: children, adolescents, ADHD, stimulants, non-stimulants, clinical strategies

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Introduction

ADHD is one of the most commonly diagnosed neurobehavioral disorders of childhood with an estimated prevalence of 6.7% to 12% in the United States.[1] Children with ADHD exhibit developmentally inappropriate levels of inattention, hyperactivity, and impulsivity resulting in functional impairment and negative outcomes in academic, family, occupational and social settings, and increased risk for substance abuse disorders.[2–4] Validated treatments for ADHD include pharmacological, psychosocial/behavioral and combined treatments.

The primary objective of this paper is to discuss clinical strategies for pharmacological treatment of ADHD in children and adolescents. We provide a brief overview of the neurobiological basis of ADHD, diagnosis, assessment and treatment process of the disorder. The clinical strategies for the first line psychopharmacological treatments are also discussed, as well as when to consider alternate psychopharmacological treatments, and strategies to manage adverse effects and comorbid disorders in children and adolescents with ADHD.

Neurobiological Basis of ADHD

ADHD is among the most heritable of psychiatric disorders with a mean heritability estimate of 76%; children with parents or siblings of children with ADHD have two- to eight-fold increased risk for being diagnosed with ADHD.[5,6] Even though the exact cause and mechanisms underlying ADHD are not yet completely understood, several etiologically heterogeneous animal models have been proposed. These include genetic models (the spontaneously hypertensive rat [SHR], dopamine transporter knockout mouse, Naples High Excitability rat and the SNAP-25 deficient mutant coloboma mouse), chemically induced models such as prenatal or early postnatal exposure to ethanol or nicotine, and environmental vulnerability models such as rat pups reared in isolation or with neonatal anoxia.[7] The most widely studied animal model of ADHD is the SHR, however it has not shown treatment response to methylphenidate in behavioral tests for ADHD.[8,9] Moreover due to heterogeneity of the current animal models, no one animal model best represents ADHD.[8]

Dysfunction in the fronto-subcortical pathways and imbalances in the dopaminergic and noradrenergic systems have been implicated in ADHD and form the basis for pharmacological treatment with dopamine and norepinephrine transporter blockers. For example, structural brain differences in the form of a 3–5 year delay in the peak of cortical thickness maturation, with greatest delays in frontal and temporal brain regions[10] and global thinning of the cortex most prominently in the medial and superior prefrontal and precentral regions have been reported in ADHD individuals compared to normal controls.[11] Recently, a significant reduction of gray matter volume in the right basal ganglia and reduction of right globus pallidus and putamen volumes was reported in children and adolescents with ADHD.[12,13] Diffusion tensor imaging studies of ADHD have indicated alterations in white matter integrity in widespread areas, most often in the right anterior corona radiata, right forceps minor, bilateral internal capsule and left cerebellum; areas which have previously been implicated in ADHD.[14] Paralleling the structural brain findings, magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI) studies have reported significant hypoactivity in frontal regions including anterior cingulate, dorsolateral prefrontal, inferior prefrontal, and orbitofrontal cortices as well as in related regions such as portions of the basal ganglia, thalamus, and parietal cortices in ADHD individuals compared to controls.[15,16]

Psychostimulant treatment was reported to normalize the rate of cortical thinning seen in children and adolescents with ADHD compared to a more rapid cortical thinning in unmedicated ADHD patients.[17] Similarly, normalizing effects of stimulant treatment were seen with larger right anterior cingulate volume in psychostimulant treated children (medial age = 9–10.6 years)[18] and adolescents (median age = 12.75–15 years)[19] with ADHD and age-matched healthy controls compared to smaller right anterior cingulate volume in unmedicated ADHD patients. Clinically-effective doses of stimulants strengthened connectivity of some frontoparietal regions on fMRI compared to placebo in 18 children and adolescents with ADHD (mean age = 14.6 + 2, age range = 11–17 years); the changes in functional connectivity were associated with improvements in a working memory performance task.[20] Methylphenidate increased activation in left ventrolateral, dorsomedial frontal, and parietal cortices and the fronto-striatal regions compared to placebo in

twelve medication-naïve boys with ADHD and normalized the brain activation levels similar to that of healthy age-matched controls.[21]

Various MEG studies have indicated that treatment with a stimulant affects alpha, gamma, and theta activity in the brain. Alpha activity has been shown to lessen when attention is directed toward a stimulus[22,23] and it has been hypothesized that gamma activity is crucial in coordinating information processing.[24] A MEG study by Wienbruch et al[25] found that methylphenidate had greatest effects in frontal regions of the brain. In particular, theta activity increased over the left hemisphere with complimentary improvement in the performance of the D2 test of attention, and alpha activity decreased in both hemispheres with treatment.[25] Another MEG study reported that gamma activity significantly increased following stimulant administration in adults with ADHD bringing their gamma activity levels closer to the non-ADHD controls.[26]

Diagnosis and Assessment

The Diagnostic and Statistical Manual of Mental Disorders Fourth Edition-Text Revision (DSM-IV-TR) criteria for ADHD diagnosis requires that patients must show a minimum of 6 of the 9 inattentive or hyperactive/impulsive symptoms for at least 6 months.[27] Psychiatric evaluation for a DSM-IV-TR diagnosis of ADHD includes a comprehensive psychiatric history from the caregiver(s) and a mental status examination of the patient. Detailed information should be obtained from the caregiver(s) to review symptoms and behaviors related to inattentive and/or hyperactive/impulsive symptoms, the context in which the symptoms occur, the degree to which these behaviors are inconsistent with the patient's age, and have led to functional impairment in 2 or more settings, eg, social, school, and/or home. In addition to the ADHD symptoms, a detailed history regarding presence or absence of any existing co-morbid disorders and the patient's developmental and medical history are required to rule out any developmental and medical conditions and/or medications that may predispose, mimic, or exacerbate ADHD symptoms should be obtained. Any social issues that may have an impact on the child's ADHD symptom presentation, as well as impact of ADHD symptoms on the child's social relationships should be explored. Family history for genetic loading of ADHD or other psychiatric disorders should also be obtained.

Collateral information should be gathered from school teachers regarding inattentive and/or hyperactive/impulsive symptoms in the classroom, behavioral problems at school, problems with peer-relations, and level of academic performance and achievement. Furthermore, information should be collected from parents and teachers through rating scales or questionnaires. Information obtained from rating scales is used to complement clinical information and provides objective data to aid in confirming diagnosis of ADHD and in monitoring treatment response. Some examples of the parent and teacher ADHD rating scales include commercially-available Conners' Rating Scales-Revised,[28] publically available ADHD Rating Scale-IV,[29] the National Initiative for Children's Healthcare Quality Vanderbilt Assessment Scale,[30] the Swanson, Kotkin, Atkins, M-Phlynn, and Pellham Rating Scale,[31] and the Swanson, Nolan, and Pellham-IV Rating Scale.[32]

ADHD is diagnosed more frequently in boys than in girls. Girls with ADHD often do not exhibit impulsive, hyperactive, and disruptive rule-breaking behaviors and may be less likely to be referred for evaluation. Another reason may be that inattention and difficulty completing tasks in girls may be overlooked or misdiagnosed as a learning disorder.[33] It is important to keep in mind, however, that girls with ADHD suffer significant impairment and disability and are at high risk for disruptive, mood, anxiety, eating and substance abuse disorders.[34]

Pharmacologic Treatment of ADHD

After a DSM-IV-TR diagnosis of ADHD is confirmed, a thoughtful exploration of treatment recommendations may begin. Pharmacological and psychosocial treatments in the form of parent behavioral training and school behavioral interventions have empirical support for treatment of ADHD in children and adolescents and can be used alone or in combination.[18] Pharmacotherapy combined with non-pharmacologic interventions is indicated for moderate to severe ADHD in children and adolescents.[35] Pharmacological treatment of ADHD has been found to be positively associated with improved academic achievement in elementary school children,[36] and improved health-related quality of life in children and

adolescents,[37] and improved brain dysfunction as previously mentioned.

Due to abuse and addiction potential of stimulants, the first-line pharmacological agents for ADHD, many caregivers are reluctant to consider such treatment for their child or adolescent. However it is important to note that most long-term follow-up studies of stimulant treatment of ADHD in children and adolescents did not find an increased risk for substance use, abuse or dependence by adulthood.[38–42] On the other hand, stimulant therapy in childhood was found to be associated with a reduced risk of subsequent cigarette smoking and alcohol and substance use disorders compared to untreated patients.[41,43–45] Association of ADHD treatment and reduced risk for substance abuse is further bolstered by PET and fMRI findings pointing to neurobiological similarities in ADHD and substance abuse type cravings which suggest that treatment of ADHD may potentially reduce craving for substances and may also reduce the risk for relapse.[46] In the following sections we discuss clinical strategies for first line psychopharmacological treatments, when to consider alternate psychopharmacological treatments, and strategies to manage adverse effects and comorbid disorders in children and adolescents with ADHD.

First line psychopharmacological agents

Stimulants are approved by the Food and Drug Administration (FDA) to treat ADHD in children and adolescents and are considered first-line pharmacological agents in the treatment of ADHD.[4] Stimulants (methylphenidate and amphetamines) increase levels of norepinephrine and dopamine by facilitating their release in the prefrontal cortex. Methylphenidate binds to the dopamine transporter and blocks the reuptake of dopamine from the synaptic cleft, whereas amphetamines increase the availability of norepinephrine and dopamine at the synaptic cleft by displacing them from the pre-synaptic terminal storage sites and by blocking the action of a degradative enzyme, catechol-*o*-methyltransferase.

Stimulants have over 50 years of history of clinical use in the treatment of ADHD and are the most commonly prescribed psychotropic medications in children; 2.8 million children were estimated to be receiving stimulant medications in 2008.[47] Stimulants are also the most researched psychotropic medications with over 250 controlled stimulant trials for treatment of ADHD involving over 6000 children.[48]

The National Institute of Mental Health (NIMH) sponsored the well-known Collaborative NIMH Multisite Multimodal Treatment Study of Children with ADHD (MTA),[49] conducted a study in which a group of 579 children with ADHD Combined Type, aged 7 to 9.9 years, were randomly assigned to 14 months of either (1) carefully monitored medication management consisting of a 28-day initial titration phase with double-blind random-order daily switches of three doses of immediate release (IR) methylphenidate (low dose = 5 mg AM, lunch and afternoon, medium dose = 10 mg AM and lunch and 5 mg in the afternoon, and high dose = 15 mg AM and lunch and 10 mg in the afternoon) and placebo followed by a 13-month maintenance phase consisting of monthly medication management visits, (2) weekly intensive behavioral treatment sessions with parent, school, and child components (therapist involvement was gradually reduced over time), (3) combination of (1) and (2), or (4) standard community care. After the initial 28-day titration phase, 10.4% of the study participants in the medication management group were openly titrated and maintained on IR-dextroamphetamine as they did not obtain an adequate response to IR-methylphenidate. The study results indicated that at the end of 14 months of treatment, children in all four groups showed improvement from baseline. However, the medication management and the combination groups were superior to the intensive behavioral treatment and to standard community care groups in improving ADHD symptom ratings.[49]

A follow up of the MTA sample at 8 years showed that improvement in ADHD symptoms was maintained over baseline. Compared to their non-ADHD classmates, however, significant impairment was still evident in the MTA sample. Additionally, no differences were observed in the MTA sample based on the initial randomization group assignment. Sociodemographically-advantaged children showing the best response to initial treatment, regardless of the randomization group assignment, had the best long-term prognosis.[50] Improvement in teacher ratings of ADHD symptoms was reported at the 5-year follow up assessment in children adherent to stimulants.[51]

Both methylphenidate and amphetamines are available in once or twice daily long-acting formulations

and have empirical support for short-term efficacy and safety and long-term effectiveness and tolerability.[52] See Tables 1 and 2 for a listing of the available methylphenidate and amphetamine formulations.

Clinical strategies

Which stimulant to use first?

Currently there is no empirical evidence that indicates a clear advantage of the use of methylphenidate over amphetamine or vice versa and there are no guidelines to help decide which stimulant to use first. Thus, selecting one stimulant over the other remains a clinical decision and requires collaboration with caregivers regarding their preference.[4,53] Elia and colleagues[54] treated 48 boys with ADHD with dextroamphetamine, methylphenidate and placebo in a double-blind crossover study.[54] Both dextroamphetamine and methylphenidate were found to be highly and equally efficacious for the group as a whole, even though individual children responded better to one drug or the other, and experienced treatment-emergent adverse events (TEAE) only on one of the stimulants. A review of the published methylphenidate and amphetamine double blind crossover trials showed that 41% of the subjects enrolled in these studies responded equally to both methylphenidate and amphetamine and 44% responded better to either methylphenidate or amphetamine.[55] Hence, the initial stimulant response rate may be as high as 85% if trials of both methylphenidate and amphetamine medications are performed.[4]

Treatment with short-acting versus long-acting stimulant formulations

In the current clinical practice, it is much more common to use long-acting formulations administered as a single daily dose to treat ADHD in children and adolescents. Compared to the need for a noon-time dose of short-acting IR stimulant formulations disrupting a child's school day, single daily dosing with long-acting formulations offers increased convenience and confidentiality and increases likelihood of compliance.[56] Another advantage is the continued efficacy of long-acting formulations through the end of the day when the children and adolescents will likely need to focus on completing their home work. On the other hand, there may be situations when short-acting formulations may be more desirable. For example, (i) if children and adolescents experience TEAEs with long-acting formulations, eg, poor appetite throughout the day, (ii) parental preference as we have seen in our clinical practice, that their children take medication during school hours only, and (iii) young age of the children. Pre-school age children have been shown to develop more TEAEs at higher doses and have a unique adverse effect profile including more irritability and proneness to crying when treated with stimulants.[57–62] When treating ADHD in children of pre-school age, short-acting agents have an advantage as they can be dosed lower and with more precision.

Medication titration and monitoring

Treatment can be initiated with long-acting formulations without the need to titrate first with a short-acting formulation and then to switch to a long-acting equivalent dose.[4] In our clinical practice, we recommend visits or telephone contact every week or every other week during initial titration period of 1 to 2 months, followed by monthly visits until a child's dose is stabilized and optimal response is achieved. Medications are started at the lowest dose available to decrease the risk of TEAEs and titrated upward (as tolerated) every 1–3 weeks until either the maximum recommended dose is reached or symptoms are adequately controlled with minimal TEAEs[63] IR stimulant formulations are usually prescribed bid or tid (AM dose and noon/lunch-time dose for bid dosing and an additional after school dose around 4 PM for tid dosing), and long-acting once-daily formulations are usually prescribed in the morning. See Tables 1 and 2 for initiating doses, rate of dose increment and FDA-approved maximum doses of stimulants. The patient may remain on this dose for maintenance with follow up visits every 1–3 months to monitor progress and TEAEs and for dose adjustment as needed.[4] If there is poor response or TEAEs, switching between different formulations in the same class of stimulants may be appropriate to achieve medication effect for the desired duration, for example switching from IR-methylphenidate to Osmotic-controlled Release Oral delivery System (OROS)-methylphenidate to achieve medication effect throughout the day.[4] If there is poor response with the FDA-approved maximum doses, some clinicians prescribe higher, off-label doses before proceeding to the next step of trying the class of stimulant not yet prescribed (ie, if not responding to methylphenidate formulations then switching to

Table 1. Available methylphenidate formulations.

Medication (brand name)*	Initial dose*	Maximum dose (FDA)/ day*	Off-label maximum dose*	Formulation type**	Maximum duration of activity (h)**	Comments**
Ritalin^	5 mg twice a day	60 mg	>50 kg: 100 mg	IR	3–4	
Methylin^	5 mg twice a day	60 mg	>50 kg: 100 mg	IR	3–4	Chewable tablets and oral solution available Take with at least 8 oz liquid per package insert
Focalin^ (dexmethylphenidate)	2.5 twice a day	20 mg	50 mg	IR	6	Half the equivalent of racemic methylphenidate
Ritalin SR«	10 mg qAM	60 mg	>50 kg: 100 mg		8	Contains a waxbased matrix May require an additional morning and/or early afternoon IR dose
Methylin ER«	10 mg qAM	60 mg	>50 kg: 100 mg		8	Contains a dissolution controlling polymer for extended release action May require an additional morning and/or early afternoon IR dose
Metadate ER«	10 mg qAM	60 mg	>50 kg: 100 mg		8	Contains a waxbased matrix
Metadate CD«	10 mg qAM	60 mg	>50 kg: 100 mg		8	30% IR beads and 70% ER beads with a biphasic release pattern Capsule may be opened and sprinkled onto soft foods*
Ritalin LA«	20 mg qAM	60 mg	>50 kg: 100 mg	SODAS	8–10	50% IR and 50% entericcoated delayedrelease beads with a biphasic release pattern Capsule may be opened and sprinkled onto soft foods*
Focalin XR¶	5 mg qAM	30 mg	50 mg	SODAS	12	50% IR and 50% entericcoated delayedrelease beads
Concerta¶	18 mg qAM	72 mg	108 mg	OROS	12	Delivers MPH at a controlled rate with a triphasic release pattern
Daytrana Patch¶	10 mg patch daily on hip	30 mg	Not yet known	Transdermal	Dependent on wear time	Effects last 3 hours after removal Releases MPH continuously May use during swimming/exercise

Notes: *Information based on Pliszka S. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;46(7):894–921; **information based on Chavez et al 2009; ^short acting; «intermediate acting; ¶long acting.
Abbreviations: FDA, food and drug administration; h, hours; IR, immediate release; XR, extended release; qAM, every morning; SODAS, spheroidal oral drug absorption system; OROS, OROS Osmotic-controlled release oral delivery system; SR, sustained release; ER, extended release; CD, controlled delivery; MPH, Methylphenidate.

Table 2. Available amphetamine formulations.

Medication*	Initial dose*	Maximum dose (FDA)/day*	Off-label maximum dose*	Maximum duration of Activity (h)**	Comments**
Adderall^	3–5 y: 2.5 mg qAM 6 y and older: 5 mg qAM to twice a day	40 mg	>50 kg: 60 mg	4–6	3:1 d-amphetamine to l-amphetamine ratio approved for 3 y and older
Dexedrine^	3–5 y: 2.5 mg qAM 6 y and older: 5 mg qAM to twice a day	40 mg	>50 kg: 60 mg	4–5	Approved for 3 y and older
Dextrostat^	3–5 y: 2.5 mg qAM 6 y and older: 5 mg qAM to twice a day	40 mg	>50 kg: 60 mg	4–5	Approved for 3 y and older
Dexedrine¶ Spansules	6 y and older: 5–10 mg qAM to twice a day	40 mg	>50 kg: 60 mg	8	50:50 of immediate release and sustained release of d-amphetamine
Adderall XR¶	6 y and older: 10 mg qAM	30 mg	>50 kg: 60 mg	10–12	50:50 IR and delayed release beads 3:1 d-amphetamine to l-amphetamine ratio Capsule may be opened and sprinkled onto soft foods*
Vyvanse¶	30 mg qAM	70 mg	Not yet known	12	Capsules of l-lysine and d-amphetamine requiring hydrolysis to release d-amphetamine

Notes: *Information based on Pliszka S. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;46(7):894–921; **information based on Chavez et al 2009; ^short acting; ¶long acting.
Abbreviations: FDA, food and drug administration; h, hours; qAM, every morning; y, years; d, dex; l, lis; XR, extended release; IR, immediate release.

amphetamine formulations). However, it is important to remember that there is very limited empirical information regarding efficacy and safety of higher off-label doses in the treatment of ADHD in children and adolescents.[64] If there is poor response even after switching the stimulant class, the medications described in the alternative pharmacological agents section may be considered.[4,65]

Adverse effects of stimulant medications

Common stimulant TEAEs include appetite suppression, stomachache, insomnia, and headache.[4,66] Less common side effects of stimulants include tics, emotional lability, irritability, and increases in heart rate and blood pressure.[4] The TEAEs are usually more severe when first initiating the medication trial and may abate over time. Charach et al[51] evaluated the effectiveness and tolerability of methylphenidate use over 5 years in 6- to 12-year-old children who initially participated in a 12-month randomized controlled trial (RCT) of methylphenidate. Yearly follow up after the initial RCT revealed that clinically significant TEAEs were persistent for 5 years, and although half of the children who were adherent to medication reported at least one TEAE (eg, appetite loss) at the end of five years, they continued the medication implying acceptability of the TEAEs.[51]

Findings for stimulant effects on growth have been mixed. In the MTA study, the children treated with stimulants showed decreased growth rate without evidence of growth rebound at 3 year follow up.[49,67] Poulton[68] performed a review of 29 studies focusing on the effects of stimulant medications on growth and reported approximately 1 cm/year height deficit in children during the first 1–3 years of treatment.[68] Faraone et al[69] found that growth was slightly less than expected after 6–30 months of extended-release mixed amphetamine salt treatment for ADHD in children. A later review by Faraone et al[70] concluded that the transient delay in growth after stimulant treatment can be caught up later, either on or off medications.[43] Conversely a more recent 10-year prospective study did not find an association between deficits in growth outcomes and psychostimulant treatment for ADHD during childhood.[71]

There have been reports of sudden deaths in individuals taking stimulants that led to the FDA's "black-box warning" for all stimulants.[72,73] A subsequent

FDA review of the Adverse Events Reporting System data for marketed safety experience with therapeutic use of stimulants (for the period of January 1, 1992 to December 31, 2004) reported that the base rate of sudden death in children treated for ADHD is below the rate of sudden death in the general population.[74] Regardless, stimulants generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems. Additionally, it is important to obtain a careful targeted cardiac history including history of cardiac problems and family history of sudden death in children or young adults.[60]

In general, methylphenidate and amphetamines have similar TEAEs. In a medical record review study to examine outcome of long-term stimulant treatment during childhood in a population-based birth cohort, dexamphetamine was more likely to be associated with adverse effects than methylphenidate (10% vs. 6%; $P < 0.05$).[66]

Strategies to manage stimulant adverse effects

Caregivers should be instructed to administer the stimulant medications with or after a meal to allow the child to eat prior to the onset of the stimulant's appetite suppressant effect. Additionally, we routinely instruct the caregivers to allow the child to eat large meals in the morning and evening and extra after-dinner nutritious snacks to prevent weight loss. The children's weight, height, blood pressure and heart rate should be monitored regularly. To minimize sleep difficulties, IR stimulant should not be administered late in the evening. If insomnia is problematic with IR or long-acting preparations, the stimulant dose may need to be lowered and/or administered at an earlier time.

Alternative psychopharmacological agents

Non-stimulant medications are not usually considered first-line agents in the treatment of ADHD due to less robust response than stimulants. A meta-analysis report of double-blind placebo-controlled ADHD treatment trials indicated effect sizes of 0.6 to 0.7 for most non-stimulant studies compared to effect size of 0.95 for stimulant studies.[75,76] Non-stimulant medications are usually considered if a child fails to achieve an adequate response to or experiences TEAEs with stimulants.[4] However, under certain circumstances, one may consider initiating treatment with non-stimulant medications without a stimulant trial first, for example, with comorbid tic, substance abuse, anxiety and depressive disorders, and parental preference. In the following section, we briefly review four non-stimulant medications, atomoxetine, alpha agonists, buproprion and modafinil for the treatment of ADHD in children and adolescents. Special circumstances when non-stimulants may be considered first will be addressed in the section on comorbidity.

Atomoxetine

Atomoxetine is a selective presynaptic norepinephrine reuptake inhibitor. It acts to increase levels of extracellular norepinephrine and dopamine in the prefrontal cortex but has limited effect in the striatum. Atomoxetine is approved by the FDA for treatment of ADHD in children, adolescents and adults. There is evidence of short-term efficacy and long-term effectiveness of atomoxetine[77–79] when used in younger children,[80,81] in children with comorbid oppositional defiant disorder,[82] comorbid anxiety disorders,[83] and in children with PDD.[84] Atomoxetine is usually well tolerated and youth show good long-term adherence.[85] Open-label combination treatment with atomoxetine and stimulant medications was shown to improve ADHD symptoms in atomoxetine partial responders.[86] However, higher frequency of insomnia, irritability and appetite loss, and increases in diastolic pressure were observed with the combination treatment compared to atomoxetine alone.[87]

Atomoxetine response is reported to be less robust than stimulants, previously mentioned meta-analysis reported atomoxetine effect size of 0.7 compared to stimulant effect size of 0.95.[88] Some atomoxetine and methylphenidate comparative studies and meta-analysis have reported equivalent efficacy between atomoxetine and methylphenidate[89,90] however concerns regarding study methodologies have been expressed.[91] Hence, atomoxetine is usually considered in children and adolescents who do not respond adequately to stimulants and/or have TEAEs, have comorbid tics, or have a potential for drug abuse.

Adverse effects of atomoxetine

Common atomoxetine TEAEs include abdominal pain, vomiting, decreased appetite, somnolence,

dizziness, fatigue, and irritability. Weight loss and decrease in expected height were reported in children treated with atomoxetine for 15 to 18 months, but no significant growth impairment was reported at the end of a 5-year atomoxetine treatment study.[92] Due to noradrenergic effects of atomoxetine, children can experience increases in heart rate and blood pressure. Atomoxetine should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, and serious heart rhythm abnormalities.[93] Atomoxetine has been shown to lead to rare hepatic injury,[94] and apparently due to its molecular similarity to fluoxetine, has been associated with suicidal ideation which led to the FDA "black box" warning in 2005.[95]

Clinical strategies, medication titration and monitoring, and management of adverse effects

Dosing of atomoxetine is determined by the child's weight with a 3 to 5 day starting dose of 0.5 mg/kg/day and increasing to 1.2 to 1.8 mg/kg/day for individuals who weigh less than 70 kg. It is common to start this medication at bedtime for the first 7 to 10 days to prevent daytime sedation which can occur when initiating treatment with atomoxetine. Doses higher than 1.8 mg/kg/day did not lead to further improvement in ADHD symptoms and only led to more side effects.[96] On the other hand, atomoxetine dose of 1.8 mg/kg/day was shown to be more effective than the dose of 1.2 mg/kg/day in treating youth with comorbid oppositional defiant disorder.[82] Youth over 70 kg can be started at a dose of 40 mg/day and then titrated to 80 mg/day with a maximum dose of 100 mg/day. Atomoxetine can be dosed with a single dosing in the morning or evening[97] or as a split dose in the morning and afternoon[98] to decrease sedation and gastrointestinal side effects.[99] Clinicians must show patience with this medication as the time to improvement in symptoms is approximately 1 month but remission of symptoms often does not occur until over 3 months.[100] This medication can be abruptly discontinued without a need for a tapering off.[101]

Atomoxetine is metabolized by the hepatic cytochrome P450 2D6 enzyme and can lead to an increase in atomoxetine blood level with concomitant use of fluoxetine and paroxetine. Thus, a lower dose of 0.5 mg/kg/day for the first month and a slower and cautious titration to a target dose of 1.2 mg/kg/day should be used if atomoxetine is prescribed concomitantly with fluoxetine or paroxetine. Additionally, lower doses of 0.5 mg/kg/day should be used in slow metabolizers, which are 7% of Caucasian and 2% of African-American youth, to prevent cardiac and gastrointestinal side effects that can become severe when the blood level reaches steady state.[102]

Alpha-2 adrenergic agonists

Alpha-2 adrenergic agonists, guanfacine, and clonidine are antihypertensive agents that act on presynaptic alpha-2 adrenoreceptors (alpha-2A, 2B and 2C) in the prefrontal cortex to inhibit norepinephrine release and downregulate the noradrenergic system. Guanfacine, is a selective alpha-2A adrenoreceptor agonist, whereas clonidine has relatively high affinity for all three alpha-2 adrenoreceptors.

Immediate-release clonidine and guanfacine are not approved by the FDA for use in children and adolescents with ADHD, however have a long history of "off-label" use in treating youth with ADHD. IR-guanfacine was found to improve teacher-rated ADHD symptoms in children with ADHD comorbid with tic disorder[103] and in children with pervasive developmental disorders accompanied by hyperactivity and impulsivity.[104] IR-clonidine has shown efficacy in placebo-controlled trials when used alone,[105] in combination with stimulants,[106] to treat ADHD comorbid with tics,[107,108] and with aggression.[106,109] On the other hand, a recent IR-clonidine treatment study failed to show improvement in teacher ratings of ADHD symptoms, but benefit on parent ratings of ADHD symptoms and increased frequency of sedation were observed.[110]

Given the need for repeated dosing with IR guanfacine and clonidine, extended release (ER) formulations have been developed and are approved by the FDA for treatment of ADHD in children and adolescents as once daily monotherapy and as adjunctive therapy to stimulants. ER-guanfacine was found to have short-term efficacy and 2-year effectiveness as monotherapy, in children with ADHD and comorbid ODD, and in combination with a stimulant.[111–116] ER-clonidine was shown to significantly improve ADHD symptoms over 5 weeks of treatment in pediatric patients as monotherapy and as adjunctive therapy to stimulants.[117,118] Though these 2 extended-release

alpha agonists are approved by the FDA for treatment of ADHD, they have not been researched or used extensively.

Response to alpha-2 agonists has been shown to be less robust than stimulants. A meta-analysis of ADHD treatment studies showed an effect size of 0.58 for clonidine compared to 0.82 for stimulants,[119] hence alpha agonists are usually not considered as first line treatment agents for ADHD. Alpha agonists can be considered in children who do not respond adequately to stimulants or atomoxetine, and/or have adverse effects associated with these agents, such as severe insomnia or loss of appetite, have comorbid tics, aggression, eating disorders, or a potential for drug abuse.

Alpha-2 agonist adverse effects

TEAEs with clonidine and guanfacine have usually been mild and include sedation, fatigue, headache, dry mouth, constipation, upper abdominal pain, mid-sleep awakening, irritability, dizziness, bradycardia, orthostatic hypotension, and withdrawal hypertension. Somnolence can be significant and may require a slower rate of titration. Guanfacine is generally less sedating than clonidine.

As alpha-2 agonists are antihypertensive agents, blood pressure and heart rate should be monitored routinely and they should not be discontinued abruptly to prevent a hypertensive crisis. There were several case reports of sudden death in children taking a combination of clonidine and methylphenidate.[120] However, extensive exploration of these cases did not establish a definite causal link between this combination and sudden death,[121] and there have not been further reports of this nature. Nevertheless, cardiac consultation should be obtained prior to considering treatment with alpha-2 agonists alone or in combination with stimulants in children who have a history of preexisting myocardial or structural heart disease or renal disease that can increase a child's risk for developing hypertension and cardiovascular disease.

Clinical strategies, medication titration and monitoring, and management of adverse effects

IR-clonidine is usually initiated at a dose of 0.05 mg at night to minimize adverse effects, especially sedation. Depending on the age and weight of the patient and to avoid excessive sedation, IR-clonidine may be started at a dose of 0.025 mg at night. A morning dose of 0.05 mg can then be added 3–7 days later followed by a mid-day dose of 0.05 mg 3–7 days later. The dosage can be titrated in this manner in increments of 0.05 mg bid or tid (may also be given qid) to a total daily dose of 0.4 mg. ER-clonidine can be initiated at a dose of 0.1 mg at bedtime and increased, as needed to obtain optimal response, by 0.1 mg at weekly intervals to a maximum total daily dose of 0.4 mg. ER-clonidine should be administered twice daily with equal or higher dose at bedtime.

IR-guanfacine is usually initiated at a dose of 0.25 mg to 0.5 mg at night to minimize sedation.[122] The dosage can be titrated every 3–7 days in increments of 0.5 mg first with addition of a morning dose of 0.5 mg followed by an after school dose of 0.5 mg 3–7 days later. The dose can be titrated in the this manner to a total daily dose of 4 mg. Somnolence and fatigue are the most common TEAEs especially during early titration and can be managed by a slower titration or lowering the dose. ER-guanfacine is usually started at 1 mg in the morning and can be titrated weekly to a maximum dose of 4 mg. It may take 2–3 weeks to see response.[115]

Abrupt discontinuation of alpha agonists can lead to withdrawal hypertension and can result in a hypertensive crisis, making compliance with alpha agonists especially important. IR-clonidine should be tapered gradually by 0.05 mg, ER-clonidine by 0.1 mg, IR-guanfacine by 0.5 mg, and ER-guanfacine by 1 mg every 3–7 days.

Bupropion

Bupropion is an atypical antidepressant with actions involving inhibition of norepinephrine and dopamine reuptake. Study results have been inconsistent with bupropion treatment of ADHD in youth. A multisite, placebo-controlled trial using dosages of 3 to 6 mg/kg/day showed improvement in hyperactivity, conduct problems, and on parent and teacher ratings, however the effect size was smaller than that typically found with stimulant medication.[123] It has also been found to be effective in substance abusing youth with comorbid ADHD and a mood disorder[124] and in youth with ADHD and comorbid depression.[125] However in the latter study only parent ratings of ADHD symptoms showed improvement with bupropion, improvement was not seen on teacher ratings.

Bupropion can be considered if stimulants and atomoxetine trials fail to provide adequate control of ADHD symptoms or lead to intolerable adverse effects, or in patients with history of substance abuse or mood disorder. Due to the shorter half-life of slow release bupropion and its metabolites in children and adolescents,[126] bid dosing is recommended. Bupropion is usually initiated at a dose of 100 mg to 150 mg (3 mg/kg) and titrated to a maximum dose of 300 mg (6 mg/kg) daily in divided doses; any single dose should not exceed 150 mg. Response to buproprion is usually seen within 2 weeks of starting a therapeutic dose. Bupropion is usually well tolerated, possible TEAEs include dry mouth, nausea, vomiting, urticaria and rash, sedation, constipation and irritability. Bupropion can lower the seizure threshold and can lead to seizures at higher doses and in patients with a comorbid eating disorder.[127]

Modafinil

Modafinil is a promising new non-stimulant medication approved by the FDA for treatment of narcolepsy. It appears to have effects on dopamine and norepinephrine as well as increasing levels of hypothalamic histamine, however the mechanism of action is unclear. Even though modafinil is not approved for treatment of ADHD, its use for treatment of ADHD in children and adolescents has been explored. A 6-week placebo-controlled trial in 7 to 14 year old children with ADHD showed a response rate of 78% with modafinil compared to 0% for placebo.[128] Similarly, modafinil has shown improvement in ADHD symptoms in children and adolescents when compared to placebo, in inattentive and combined ADHD subtypes and whether or not the patient had previously received stimulant medication.[128–131] The dosages ranged from 170 mg to 425 mg daily. Adverse effects were mild with insomnia, headache and decreased appetite being the most common. However, there have been cases of serious skin rashes and this medicine is not approved for children under 17 years old.[132]

Comorbidity

Comorbidity has been shown to moderate treatment response in ADHD,[133–135] therefore assessing for and incorporating treatment of comorbid disorders in the overall treatment plan are vitally important. ADHD is frequently associated with 1 or more comorbid disorders in as much as 69% of cases.[49] The most frequent comorbid disorder in children and adolescents with ADHD is oppositional defiant disorder (ODD) and conduct disorder and occurs in more than half of patients with ADHD.[49] Depressive and anxiety disorders, such as post traumatic stress disorder and obsessive compulsive disorder, are present in about one third of patients with ADHD.[49,136] Approximately 20% to 25% of the children with ADHD have comorbid learning disorders,[137] about 23% children develop substance abuse disorders,[138] and approximately 11% of the ADHD participants in the MTA study had tic disorders.[49] Comorbidity of bipolar disorder with ADHD continues to be highly controversial. As recommended in the AACAP Practice Parameters for the assessment and treatment of ADHD, the diagnosis of mania should only be considered in youth who exhibit severe mood lability/elation, grandiosity, hypersexuality, and a decreased need for sleep.[4]

Clinical strategies for management of comorbid disorders

The presence of learning disorders can confound the diagnosis of ADHD and vice versa. Careful evaluation for the presence of learning disorders and specific classroom interventions to address learning issues should be implemented in the child's school setting. Pharmacological treatment of ADHD can often reduce the severity of or, even, lead to resolution of ODD symptoms. Psychosocial interventions including behavior therapy should be considered in order to optimize positive outcomes. For persistent ODD and conduct disorder, additional individual, group and family therapies can be effective.

For depressive, bipolar, anxiety, and tic disorders it is important to determine which disorder is causing the greatest impairment for the child. For instance, if comorbid depressive disorder or bipolar disorder is severe and is associated with suicidality, it would be most important to treat the mood disorder first. In an open-label sustained-release bupropion trial, improvements in both depressive and ADHD symptoms were seen in adolescents with ADHD and comorbid depressive disorder.[125] For children and adolescents with ADHD and comorbid bipolar disorder with manic symptoms, mood stabilization is recommended prior to treating ADHD.[139] If ADHD

symptoms are causing the most impairment in a child with comorbid mood disorder, treatment for ADHD should be initiated. However, a word of caution is in order since stimulants have been associated with induction of psychosis and manic symptoms.[140,141] Once adequate control of ADHD symptoms is achieved and there are residual depressive or bipolar disorder symptoms severe enough to warrant specific treatment, an algorithm for the treatment of depressive or bipolar disorders can be instituted.[142] Similar strategy can be used for treatment of comorbid anxiety and tic disorders.

Youth with comorbid anxiety and tic disorders disorders can respond well to a stimulant without exacerbation of anxiety or tic symptoms.[143,144] However if anxiety or tic symptoms are severe or worsen with stimulants, use of a non-stimulant agent is recommended. Atomoxetine improved ADHD and anxiety ratings relative to placebo in 6–17 year old patients with ADHD and cormorbid anxiety disorders[83] and thus atomoxetine can be considered as a first line treatment in such cases.

There have been case reports of tics worsening with atomoxetine,[145] however recent placebo-controlled trials have shown atomoxetine to reduce both ADHD and tic symptoms in children and adolescents with ADHD and comorbid Tourette's syndrome or chronic motor tic disorder.[146,147] Guanfacine and clonidine have been shown to improve tic and ADHD symptoms when used alone[103] or as adjunct to stimulants.[108] Hence, families and providers may prefer non-stimulants to treat ADHD in patients with moderate to severe comorbid tic disorder.

Children and adolescents diagnosed with ADHD and comorbid substance abuse disorder should first participate in substance abuse treatment. Treatment for ADHD should begin once they are drug free and continue to abstain from drugs. Given the risk of abuse potential and diversion of stimulants, ADHD is best treated with a non-stimulant in youth with comorbid substance abuse disorders. However, the option of using lisdexamfetamine or OROS-methylphenidate, which have a lower potential of abuse and diversion, can also be appropriate options. If it is decided to prescribe stimulants (for example due to severity of ADHD symptoms), a careful monitoring and accurate documentation of frequency of prescriptions dispensed and duration between prescription renewals should be maintained.

Summary

ADHD is one the most researched and written about psychiatric disorder of childhood and adolescence and so is the psychopharmacological treatment of ADHD. Clinical approach to ADHD treatment starts with a comprehensive assessment that includes a careful history with information obtained from caregivers and teachers as well as an interview of the child in order to make correct diagnosis and to institute an appropriate treatment plan.

Number of well-controlled pharmacological trials provide evidence of short term efficacy and safety, and long-term effectiveness and tolerability of stimulants. Stimulants are considered drugs of choice in the treatment of ADHD in reducing core symptoms of ADHD and which in turn results in improving academic performance and behavior at school and at home. The major challenge for clinicians is how to translate and apply research knowledge in the treatment of an individual patient with his/her unique socio-family context. Long acting preparations of stimulants have resulted in better compliance and steady effect on child's symptoms. To minimize possible untoward TEAEs, there is need to titrate the dosages gradually with the goal of finding the most effective lowest dose of medication.

There are some children who do not benefit from stimulants or experience significant TEAEs and some parents are against use of any stimulants. There are a number of non-stimulant medications including atomoxetine, bupropion, alpha-adrenergic agonists, and modafnil that can provide viable alternatives.

ADHD is often associated with comorbid disorders and complex family and social problems. This is particularly true for children seen in community clinics. Preference should be given if one medication can treat both ADHD and the associated comorbid disorder. Care should be taken to minimize polypharmacy. Psychosocial interventions including behavior therapy should be considered in all children with ADHD in order to optimize positive outcomes and possibly decrease need for higher dosages of medications.[148,149] It is important to emphasize to caregivers that proper supervision and monitoring should be provided when the child takes the medication.

Author Contributions

Conceived and designed the experiments: JKG and HSG. Analysed the data: ACS, TR, JKG and HSG. Wrote the first draft of the manuscript: ACS, TR, JKG and HSG. Contributed to the writing of the manuscript: ACS, TR, JKG and HSG. Agree with manuscript results and conclusions: ACS, TR, JKG and HSG. Jointly developed the structure and arguments for the paper: ACS, TR, JKG and HSG. Made critical revisions and approved final version: ACS, TR, JKG and HSG. All authors reviewed and approved of the final manuscript.

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