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ADHD (G KULKARNI, SECTION EDITOR)

ADHD and Its Therapeutics

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Abstract

Purpose of Review Attention deficit hyperactivity disorder (ADHD) is a chronic neurobehavioral disorder that is characterized by inattention, hyperactivity, and impulsivity along with a troubled functioning in family, social, occupational, and academic settings. A brief discussion of the management of ADHD including pharmacotherapy, behavioral interventions, multidisciplinary approach, and new advances in treatment is described.

Recent Findings New developments in the management of ADHD including atypical drugs, neurostimulation, and druggable genomes.

Summary The outline of the article includes dynamic advances in the treatment of ADHD with an emphasis on a multidisciplinary approach.

Keywords Therapeutics · ADHD · Amphetamines · Atomoxetine · Multidisciplinary · Neurostimulation

Introduction

Attention deficit hyperactivity disorder (ADHD) is a common neurobehavioral disorder that presents with either symptoms of inattention or hyperactivity or both affecting the individual in social, family, and academic settings for a minimum period of 6 months (Diagnostic and Statistical Manual of Mental Disorders(DSM), Fifth Edition). Most of the children diagnosed with ADHD meet the DSM 5 criteria, even as adults [1, 2]. The review aims to describe the therapeutic approach, address the treatment-related adverse effects and limitations, and also discuss new advances in the management of ADHD.

Racemic alpha-methylphenethylamine was discovered in 1910 and synthesized in 1927. It was marketed as Benzedrine, and the generic name amphetamine was coined several years later by the Council on Pharmacy and Chemistry by American Medical Association. In 1937, Benzedrine was first reported to have a positive effect on children that had problems with concentration and hyperactivity by Charles Bradley, who noticed a modest improvement in behavior and school performance [3]. Benzedrine is the first stimulant drug to be used in children with behavioral problems and is no longer in use. A group of 30 children who suffered from behavioral issues was started on a trial of Benzedrine, the most potent stimulant known during that time, after a positive correlation, with improvement in symptoms in half of the children [3, 4]. Methylphenidate, another member of the amphetamine group, is piperazine-substituted phenylisopropylamine. It was first synthesized as Ritalin in 1944 by Leandro Panizzon and patented in 1954 by Ciba-Geigy Pharmaceutical company which remains as one of the first-line medications of ADHD even to this day [3]. Atomoxetine is an aromatic ether and a member of toluenes. It is a secondary amine compound with methyl and 3-(2-methyl phenoxy)-3-phenylpropane-1-yl substituents [5]. It is a non-stimulant option that was approved by the Federal Drug Association (FDA) in 2003 for use in patients with ADHD [6]. Lisdexamfetamine became available as the first prodrug by FDA in 2007 [7]. Adhansia XR has received approval in March 2019 and is an extended-release preparation of Methylphenidate [8].

This article is part of the Topical Collection on *ADHD*

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Therapeutic Approach

Stimulants are usually the first-line agents in school-aged children and adolescents because of the rapid onset of action and better safety and efficacy [9, 10••, 11]. Methylphenidate and amphetamine salts (dextroamphetamine, mixed dextroamphetamine-amphetamine salts) are the two major drugs in this class. Stimulants work by increasing the release of catecholamines and acting at the noradrenergic and dopaminergic receptors in the CNS synapses [12]. Methylphenidate is available in short-acting, intermediate-acting, and long-acting forms. Short-acting forms are preferred as initial management options before switching to a long-acting formulation. Older kids (> 6 years) are usually started with a low dose of long-acting form and then titrated accordingly. Intermediate-acting or long-acting forms are generally started in children who require the drug for more than 4 h or in whom multiple doses cannot be administered due to stigma or inconvenience (e.g., School) [13, 14]. The addictive potential and the chance of being misused or diverted (transfer of drugs to other individuals through selling, trading, or giving away prescription medications) is less with long-acting formulations [15]. In some cases, a combination of short-acting and long-acting medications is used to cover the evening hours for homework or driving [10••].

Amphetamines are available as single or mixed salt preparations. Individual preparations include dextroamphetamine and amphetamine sulfate, whereas dextroamphetamine-amphetamine salts are the mixed type. Lisdexamfetamine is the newer, safer drug developed to target abuse, which is a prodrug of dextroamphetamine [11, 16]. It requires conversion to dextroamphetamine in red blood cells, which delays the onset of action regardless of the route of administration [17].

The decision regarding which stimulant to choose depends on the clinician and family, duration of action of the drug, ability of the child to swallow, time of the day when symptoms occur, comorbidities, history of substance abuse in the patient or household members, preferred medications if any, and the cost of the drug [9, 10••]. Phenotypic heterogeneity (meaning ADHD types and comorbidities, genetics, environment, neurocognitive processes) of ADHD interferes with the treatment response prediction and medication efficacy. Multiple studies are performed to decipher the interindividual variability in medication efficacy and adverse effects using genetic variants. Pharmacogenetic data has shown variance in treatment response, which is not substantial [18•].

Drug therapy, when initiated in patients by the physician, has to be managed in three stages—titration, maintenance, and termination.

Titration Phase

The optimal dose and frequency of the medication are decided during the titration phase (3–6 months). The frequency is determined based on the subtype of ADHD and domains in which improvement is needed. Stimulants are started at a low dose and continued until the core symptoms improve by at least 50%, or the side effects are intolerable [19]. The therapeutic effects of stimulants are evident after 30 to 40 min of drug intake. Appetite suppression should be monitored as it indicates treatment response [20, 21]. According to the Preschool ADHD Treatment Study (PATS), preschool children should be titrated at a lower dose with smaller increments as the metabolism of methylphenidate is slower in them compared with older children and adolescents [22]. Treatment response is evaluated weekly, along with adverse effects. They are monitored with combined feedback from parent and teacher, along with ADHD rating scales. Follow-ups are scheduled monthly to notice any changes in growth (height and weight), heart rate, and blood pressure [9, 10••].

Maintenance Phase

Patients are followed up every 3 to 6 months to monitor the progression, dosing adjustments, treatment adherence, and side effect profile [10••]. Drug holidays can be advised if the patient has a predominantly inattentive type of ADHD or poor physical growth due to stimulants.

Termination Phase

Termination of medication should be considered after there is a stable improvement in core symptoms. Closely supervised off medication trials can be done to evaluate if medication adjustment is necessary (Fig. 1) [10••].

Adverse Effects

The adverse effects of stimulant medications are mild and usually reversible with dose adjustments. But it is necessary to delineate the timing of the adverse event with the drug administration because of confounding factors like comorbidities and stress [21]. Mixed salts have a greater reduction in weight and increased irritability over time compared with methylphenidate [23]. The most common adverse effects are appetite suppression, poor growth, dizziness, insomnia, mood lability, rebound, tics, psychosis, diversion, and misuse [15]. Growth is most commonly affected, but normalization of the growth percentiles and no relation to the final adult height are seen after the cessation of the treatment. Drug holidays are advised for patients with greater than a two percentile drop of growth trajectories [9]. Sensitization and hypopigmented

Table 1 Types of methylphenidate formulations

Type	Brand name	Onset of action	Duration of action	Formulation
Short-acting	Ritalin	20 to 60 min	3–5 h	Tablet, chewable tablet, or liquid
Long-acting	Metadate-ER	20 to 60 min	Up to 8 h	Tablet
	Concerta	20 to 60 min	Up to 12 h	Tablet
	Cotempla-XR ODT	Within 1 h	12 h	Orally disintegrating tablet
	Aptensio XR Adhansia XR Focalin XR Metadate CD Ritalin-LA	Within 1 h	12 h Up to 16 h for Adhansia	Capsule
	Quillivant XR	Within 1 h	Up to 8 h	Oral suspension
	Quillichew ER	Within 1 h	Up to 8 h	Chewable tablet
	Daytrana	Within 1 h	Up to 12 h	Transdermal patch

lesions are observed with transdermal methylphenidate. The occurrence of hypopigmented dermatosis after a chemical insult is termed as chemical leukoderma. Among the 51 reported cases between 2006 and 2014, the time of onset of chemical leukoderma ranged from 2 months to 4 years. The methylphenidate patch should be discontinued and transitioned to other long-acting preparation in such cases [18•, 24]. Regular monitoring for cardiovascular side effects is recommended before and during the treatment. Even though priapism is a rare complication with methylphenidate, there were 15 reported cases from 1997 to 2012. Increased dose, longer dosing interval, and discontinuation either temporarily or permanently were associated with this event. Four of the 15 reported cases had priapism even after the discontinuation of the drug, thought to be due to the short-acting, immediate-release methylphenidate. Priapism was resolved in some of the patients who were restarted on the drug [25]. Children with a family history of mental illness had an increased risk of developing psychosis after starting stimulants [26•]. Tic disorder commonly coexists with ADHD, and stimulants can cause worsening or appearance of new tics altogether [27]. A study that compared the diversion and misuse of psychotropic medications like stimulants, tricyclic antidepressants, selective serotonin reuptake inhibitors, and alpha-adrenergic agonists reported that stimulants were the most frequent cause of diversion and misuse among ADHD patients when compared with patients with other conditions (11 vs 0% for diversion, 22 vs 5% for misuse) [28].

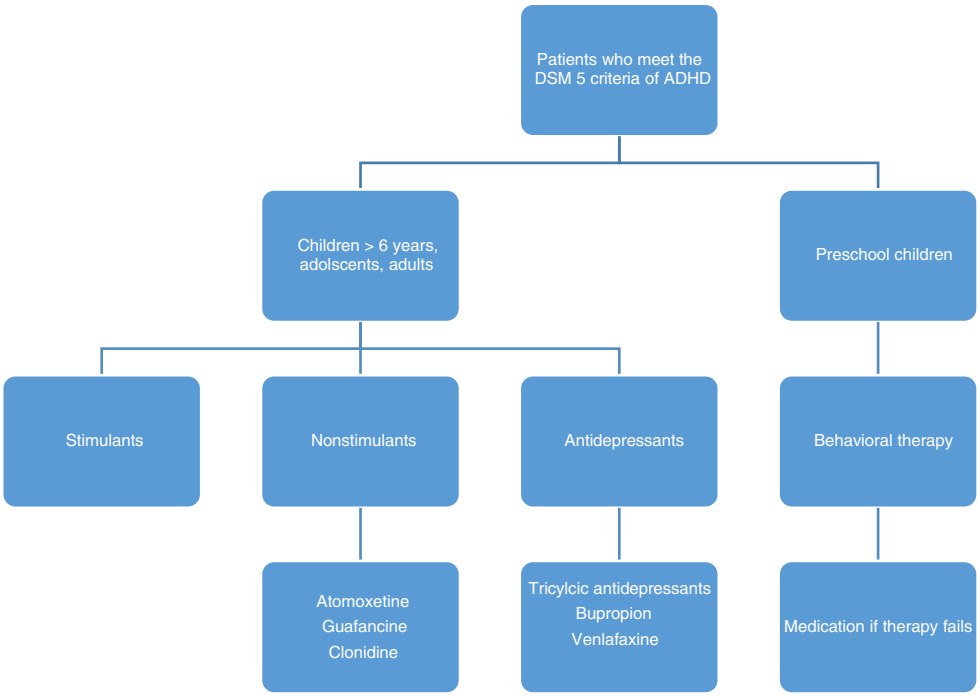

Fig. 1 Approach to the management of ADHD

Stimulants should be avoided in symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, history of drug abuse, anxiety, agitation, known hypersensitivity, glaucoma, and concurrent use of monoamine oxidase inhibitors [19].

Atomoxetine

Atomoxetine is a non-stimulant that is used as an alternative in patients with a history of substance abuse, a family member with substance abuse, or intolerable side effects with stimulants. It is a selective, presynaptic norepinephrine reuptake inhibitor that is well tolerated but less effective than stimulants [29••]. Dosing adjustments are needed if CYP2D6 inhibitors (paroxetine, fluoxetine, etc.) are used concurrently as atomoxetine is metabolized through the same CYP2D6 cytochrome P450pathway [11, 30].

The side effects associated with atomoxetine use include weight loss, decreased appetite, irritability, and cardiovascular events, including sudden death, which is a rare but serious side effect [31, 32]. A pooled analysis of 12 short-term placebo-controlled trials (6 to 18 weeks) in 2208 patients showed increased suicidal ideation in pediatric patients (0.4% vs. none of the controls). Suicidal ideation is increased in pediatric patients, which is substantiated by a combined analysis of 12 short-term placebo-controlled trials (6 to 18 weeks) in 2208 patients (0.4% vs. none of the controls) [33].

Alpha 2 Adrenergic Agonists

Alpha 2 agonists act on presynaptic, inhibitory alpha 2A receptors, which are predominant in the brain, especially the prefrontal cortex. Moderate activation of alpha 2A receptors causes improved prefrontal cortex regulation of memory, attention, and emotion regulation. Their role in ADHD is supposed to be due to the norepinephrine-mimicking actions in the prefrontal cortex. Clonidine has a high affinity for all the adrenergic receptors (A, B, C), whereas guanfacine acts specifically on the presynaptic alpha 2A receptors attenuating the prefrontal cortical function. They were used as off-label medications, and recently in 2009, guanfacine XR has been approved by the FDA. Clonidine hydrochloride was the first drug used, which is an imidazoline derivative synthesized in 1966 [34]. It has been used as an antihypertensive since then [35]. Guanfacine is a phenyl acetyl guanidine derivative that was produced in the late 1970s and used as an antihypertensive. Guanfacine and clonidine are used either due to a lack of response or side effects from stimulants and atomoxetine [10••]. These medications have delayed onset of action and can take up to 2 weeks for the initial response [36]. Clonidine is usually titrated from 0.05 mg and increased up to 0.4 mg [37]. Dosing of extended-release clonidine is 0.1 mg at bedtime, which can be titrated to increments of 0.1 mg at weekly intervals with a maximum of 0.4 mg/day. The duration of actions lasts for 10 to 12 h. Common side effects include sedation, bradycardia, headache, and hypotension [38]. Immediate-release guanfacine is started at 0.25–0.5 mg at bedtime and increased to 0.5 mg bid. It can also be increased by 0.5 mg every 3–4 days up to 2 mg or until the desired effect is attained [39]. Extended-release guanfacine is dosed at 1 mg per day and can be titrated to 1 mg increment at weekly intervals up to a maximum recommended dose of 4 mg/day. Side effects include headache, fatigue, abdominal pain, and sedation [40].

Role of Antidepressants

Tricyclic antidepressants (TCAs) and dopamine reuptake inhibitors (e.g., bupropion) are usually used after an inadequate response from all the above medications. TCAs act by inhibiting the reuptake of serotonin and norepinephrine. The cardiovascular profile should be investigated before starting TCAs as they can cause side effects like long QT syndrome and arrhythmias in patients with a personal or family history of heart disease [41].

Bupropion is a dopamine, norepinephrine reuptake inhibitor that has more stimulant properties than TCAs [42]. Clinical response with bupropion is slow and takes several weeks. When compared with placebo, bupropion had a 30% reduction in ADHD symptoms [43]. Side effects include insomnia, irritability, motor tics, and decreased seizure threshold. Extended-release formulations are associated with low peak levels, making seizures less likely [11].

Table 2 Various formulations of amphetamines

Type	Brand name	Onset of action	Duration of action	Formulation
Short-acting	Adderall	Within an hour	Up to 6 h	Tablets
Long-acting	Adderall XR	60 min	Up to 10 h	Sustained-release capsules
	Mydayis	60 min	Up to 16 h	capsules
	Adzenys	1 h	Up to 10 h	Liquid suspension
	Vyvanse	1 h	Up to 10 h	Capsule or chewable tablet
	Dyanavel	1 h	Up to 13 h	Liquid suspension

Venlafaxine is a serotonin-norepinephrine reuptake inhibitor antidepressant that has mild efficacy in decreasing ADHD symptoms. Twenty-five percent reduction in symptoms than placebo was noted in patients receiving venlafaxine [44].

Comparison of Various Medications

In a randomized control trial (RCT), stimulants proved to have increased benefit over atomoxetine and alpha 2 adrenergic agonists. Stimulants improved the core symptoms of ADHD, parent-child interactions, aggressive behavior, academic productivity, and self-esteem [45]. Few studies concluded that these medications are well tolerated over 12 months and effective for 5 years. But, regardless of the treatment, ADHD symptoms generally improve over time [46].

New Advances

Cholinesterase inhibitors like tacrine, donepezil, and other nicotinic analogs are being tested for the management of ADHD. Nicotinic dysregulation is thought to activate the dopaminergic transmission in the brain, contributing to the pathophysiology of ADHD. This is also substantiated by the increased risk of ADHD in the offspring because of maternal smoking during pregnancy in animal models. Improved memory, cognitive vigilance, executive functioning, and attention are noted in non-ADHD subjects with nicotinic stimulation [47]. Modafinil is a benzhydrylsulfinyl compound invented in the late 1970s and has been used since for the treatment of excessive daytime sleepiness in narcolepsy, shift work sleep disorder, and obstructive sleep apnea [48, 49]. It is a weak dopamine reuptake inhibitor with stimulant properties. Modafinil has shown improvement in symptoms of inattention, impulsivity, and hyperactivity in a 9-week study period in children and adolescents [50]. It is not approved for use in children because of the serious side effects like erythema multiforme and Steven-Johnson syndrome with a higher rate (12/650 vs. 1–2/million/year) than the usual [51]. Other common side effects include headache, decreased appetite, nausea, and anxiety [50].

Neurostimulation comprises of either electrical or magnetic stimulation of the brain to control the symptoms of ADHD. Transcranial magnetic stimulation, transcranial direct current stimulation, has shown some benefits. Other methods include deep brain stimulation, ultrasound stimulation, electroconvulsive therapy, vagal nerve stimulation, or trigeminal nerve stimulation. Repetitive transcranial magnetic stimulation focused in the dorsolateral prefrontal cortex caused improvement in hyperactive symptoms for 4 weeks. In some small studies, transcranial direct stimulation caused permanent changes to the cortical excitability with a reduction in the inattentive and hyperactive symptoms. The problem with these studies was small sample sizes, thereby decreasing the power of the study and the heterogeneity of the population, some including children, whereas some included adults. Also, different scales have been used to measure the outcomes after the treatment. More studies need to be conducted with a large sample size before attributing benefit to neurostimulation [52••].

Based on a genome-wide association study, the druggable genome in ADHD and its comorbidities have been explored. The druggable genes identified so far are PTPRF, SLC6A9, KCNH3, KCNJ13, MANBA, LEPRE1, and SEMA3F. PTPRF is located on chromosome 1, which encodes tyrosine phosphate, and has a role in axonal growth and hyperactivity [53]. SLC6A9 encodes glycine transporter targeted by sarcosine, glycine, and bitopertin. Glycine supplementation as a potential treatment for ADHD is under study [54]. Sarcosine was studied to have an effect on oppositional symptoms only [55•]. KCNH3 and KCNJ13 genes encode voltage-dependent potassium channels. Knocking out of these genes in mice enhanced cognitive skills like attention supporting the role of dalfampridine-like drugs in ADHD [56]. LEPRE1 has been associated with collagen synthesis and regeneration of neurons. This gene is targeted by nutraceutical ascorbate, succinic acid, and L-proline, which helped in the treatment of comorbidities and enhance the quality of life [57••]. Drug repurposing and the use of signal transduction, and cell adhesion (including negative signaling) are also proposed as a means of treatment [58••].

Interventions in Psychotherapy

Psychological intervention is directed towards emotional status and thought patterns. Though psychotherapy does not address the core symptoms, there is no noted change in core symptoms with psychotherapy [59••]. Organizational skills and coexisting psychiatric conditions in adolescents with ADHD tend to improve with cognitive-behavioral therapy [60].

Behavioral Therapy

Behavioral intervention is the first-line management for preschool children and used as an adjunct to pharmacotherapy in older children and adolescents. It includes physical and social environment changes which cause behavioral modifications using positive reinforcement, time-out, response cost, and token economy [61]. Positive reinforcement is a method of providing rewards or privileges depending on the child's performance, whereas the problematic behavior is corrected with a time-out to sit still for 5 min. Response cost is the withdrawal of rewards due to unwanted behavior. Token economy is a combination of positive reinforcement and response cost

concerning the situation. Combined parent-child behavioral therapy is a relationship enhancement technique making a parent understand how behavioral therapy works. A few examples include self-discipline, rewarding positive behavior, setting goals, limiting choices, charts, and checklists to help with attention, specific places for schoolwork, toys, and clothes. Behavioral therapy alone has no proven benefit to reduce the core symptoms of ADHD according to most systematic reviews, but has shown improvement of other behavioral problems like aggression and helped with the parent-child relationship [62].

Other Interventions

Daily physical activity improves the core symptoms of ADHD and neurocognitive function and also showed increased efficacy of stimulants [63]. The elimination diet is a controversial method in which some children with ADHD showed improvement of behavioral symptoms after eliminating specific food colors and additives [64]. In a series of experiments conducted by McCann and colleagues, two groups of children are studied (3 years old vs. 8–9 years old). Symptoms of hyperactivity increased when children had food additives (dyes) and artificial coloring in a 1-week crossover challenge period in both groups. While some children had episodes of hyperactivity, others had none. The individual differences noted substantiate the high sensitivity of children to food additives manifesting as hyperactivity. Measures of hyperactive behavior should be recorded by parents, teachers, and health professionals during such food sensitivity testing sessions. Restricted foods are added, one per week, to identify the culprit. This process should be monitored by the dietician and primary care physician to prevent malnutrition [65].

Combined Therapy

Behavioral therapy combined with medications is the most common and effective approach to control core symptoms and to achieve target outcomes. Target behaviors like academics, self-esteem, driving, and social function have shown remarkable change over some time with combined therapy. Pharmacotherapy is considered an adjunct to behavioral therapy in patients with ADHD. Comorbid conditions should always be kept in mind when treating patients. Kids usually need follow-ups at least twice a year, of which once during the transition phase (shift from elementary school into middle school or middle school to high school) is mandatory.

Combined therapy is superior in preschool children who do not respond to behavioral therapy alone. Older school-going children (6–12 years) and adolescents, however, have a similar response with combined therapy or with medications [66]. Adults with comorbidities like depression and anxiety showed improved benefit with combined therapy (cognitive-behavioral therapy and medications) [67]. Children undergoing combination therapy required relatively low doses of medications with noticeable changes in oppositional/aggressive symptoms, parent-child relations, and teacher-rated social skills [68]. School-based interventions comprise of tutoring and resource room support along with behavior management programs. Enhanced academic skills and improved achievement scores in various domains are noted with combined therapy [11].

Multidisciplinary Approach

Primary care physicians play an essential role in educating the patients and family members about the disease, setting treatment goals, and assisting with local support groups. A weekly communication book or a daily report card helps in correlating between the home and school behavior. Target goals that are achievable and realistic are needed on a day-to-day basis. Examples of achievable targets include an improved relationship with parents, teachers, and peers and improved academic performance and discipline. Primary care physicians (PCP) usually take care of the children with ADHD unless the child needs consultation due to coexisting psychiatric, neurologic, or medical conditions along with a lack of improvement with a trial of stimulants.

Conduct disorder, oppositional defiant disorder, and other coexisting conditions should be addressed simultaneously to improve the treatment outcome of ADHD. Sleep disorders are also commonly seen in kids with ADHD and should be addressed. In a randomized trial of 244 children with ADHD, each child met the diagnostic criteria for at least one sleep disorder. Both groups were taking medications for ADHD. Sleep interventions are done in half of the children who showed improvement in the follow-up compared with the other group (56% vs. 30% in a 3-month follow-up) (46% vs. 34% in a 6-month follow-up) [69•].

Conclusion

ADHD is a chronic neurobehavioral disorder that can be manageable. Side effect profile of the medications currently used and their risk for abuse is a challenge that needs to be tackled during their use. Even though there are new formulations that are long-acting and with lesser abuse potential, failure of adherence can be a problem. ADHD is a complex condition that requires a multidisciplinary approach that encompasses not only pharmacological options but also psychotherapy. A well-rounded multidisciplinary approach is key to optimally addressing this complex neurobehavioral disorder.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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