WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 15, 412-425. Review Article ISSN 2277–7105

A REVIEW ON PHARMACOLOGICAL MANAGEMENT OF ADHD IN CHILDREN AND ADOLESCENTS

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Article Received on
09 June 2024,

Revised on 29 June 2024,
Accepted on 18 July 2024

DOI: 10.20959/wjpr202415-33361

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ABSTRACT

Attention deficit hyperactivity disorder (ADHD) is a neurocognitive behavioural developmental disorder most common in childhood and adolescence, often persisting into adulthood. Compared to a decade ago, extensive research has been conducted to understand the underlying factors of ADHD, which has led to more treatment options for the disorder. New formulations of stimulant medications have helped tailor treatment to the effective duration that patients require and have helped minimize the risks of misuse, abuse and diversion. In recent years, several new non-stimulant options have also emerged. Stimulants, including methylphenidate and amphetamine, are the main treatment for ADHD. This review summarizes currently available pharmacological treatment options for ADHD in children and adolescents.

KEYWORDS: Attention-deficit hyperactivity disorder, childhood, adolescents, treatment, stimulants, non-stimulants.

INTRODUCTION

Approximately 5% of people worldwide have attention-deficit/hyperactivity disorder (ADHD), a heterogeneous neurodevelopmental disorder. The disease affects more men than women, and in nearly half of cases, it persists into adulthood in those diagnosed. Furthermore, ADHD is not limited to childhood or adolescence but persists into adulthood, with an estimated prevalence of 2.5% in adults.[1]

It is associated with several genetic and environmental risk factors, and its high comorbidity with other neurodevelopmental and psychiatric disorders supports its polygenic origin.[2] Attentional deficiencies, impulsivity, and hyperactivity are characteristic symptoms that are frequently associated with neurophysiological anomalies in the front striatal and prefrontal cortex (PFC) brain circuits.[3]

Patients diagnosed with ADHD demonstrate executive function impairments in various cognitive domains such as visuospatial and verbal working memory, inhibitory control, vigilance, planning, and adjusting reward mechanisms. These deficits are supported by atypical findings from structural and functional brain imaging investigations, primarily in larger brain networks such as the frontostriatal, frontoparietal, and ventral attention networks. Consistent with the diversity of research findings, ADHD symptoms also demonstrate considerable variation at both the individual and intra-individual levels, which should be considered in the context of persistent neurodevelopmental disease. Core manifestations of ADHD are often associated with other symptoms, such as sleep disturbances, feelings of depression, or challenging behavior, all of which contribute to reduced psychosocial abilities. In general, ADHD is associated with a high frequency of co-occurring psychological disorders (for instance, conduct disorder) and physical diseases (e.g. obesity) occurring simultaneously.[1,4]

Due to the described features of ADHD, establishing the diagnosis is challenging. The diagnostic process is supported by assessment tools (semi-structured interviews, rating scales) and guided by classification systems (e.g., DSM-5 or ICD-10), but primarily relies on the classical skills of a psychiatrist. As (undertreated) ADHD negatively affects many long-term outcomes (e.g., academic achievements, traffic accidents, employment status,), timely and adequate treatment is essential.[5]

Current clinical guidelines recommend an individualized multimodal and multidisciplinary treatment approach. Based on the extensive psychoeducation, a framework of pharmacological and/or non-pharmacological interventions should be established, considering the age, severity of symptoms, and individual needs of the patient. In adult ADHD, treatment typically follows the same multimodal and multidisciplinary approach, ideally involving the patient's partner, family, or relatives.[6]

The main objective of this review is to summarize the pharmacological treatment options available for ADHD in children and adolescents, and to provide an overview of ongoing efforts to develop new drugs to treat ADHD in children and adolescents.

Psychostimulants

Psychostimulants have been the drugs of choice for treating ADHD for more than 60 years. Stimulants were the first class of compounds reported to be effective in treating disruptive behaviors and hyperactivity in ADHD.[16] Different delivery mechanisms are available. Physicians may choose from different delivery mechanisms for these stimulants (liquid, sprinkle, tablet, capsule, or patch); from active isomer, mixtures of active and pro-drug or less active isomers, or; from, intermediate-release, extended-release or immediate-release formulations.[45]

Psychostimulants, including methylphenidate and amphetamine, are the first-line therapy for patients with ADHD (Table 1). They have similar clinical benefits; However, pharmacokinetic and pharmacodynamic characteristics vary significantly. Psychostimulants will optimize executive function and attention in ADHD patients, by enhancing the effects of norepinephrine and dopamine.

In general, psychostimulants cause similar common adverse effects, including decreased appetite, gastric irritation, sleep disturbances, headaches, tachycardia, and hypertension. Stimulants are associated with statistically significant increase in heart rate and blood pressure. Although these effects were small at the group level, they may be clinically significant in subgroups of patients, especially those with preexisting cardiovascular disease.

Therefore, clinical guidelines generally recommend pulse and blood pressure monitoring when prescribing psychostimulants. Additionally, it is still debated controversially, whether stimulant medication might increase the risk of serious adverse effects such as sudden death or suicidality.[7]

Greenhill *et al*., in a longitudinal study, showed that consistent treatment with stimulants over 16 years was associated with changes in height trajectory, with reduced adult height as well as increased weight and BMI. To date, it is unclear whether the effects on height should be considered reversible. Clinicians should engage in discussions with families to determine whether the potential changes in height and increased risk of obesity outweigh the risks of not

treating the child`s ADHD. Further research is needed to replicate these findings and explore the impact of planned interruptions in medication on growth trajectories.[21]

Methylphenidate and amphetamine

Psychostimulants, especially methylphenidate and amphetamine, are the mainstay of treatment for ADHD.[46] Effects of amphetamine include the inhibition of dopamine and norepinephrine transporters, vesicular monoamine transporter 2, and monoamine oxidase activity. Effects of methylphenidate include inhibition of transporters like norepinephrine and dopamine, agonist activity at the serotonin type 1A receptors, and redistribution of the vesicular monoamine transporter 2.[16] Amphetamines and methylphenidate medications have distinct pharmacological properties. The half-life of amphetamine is significantly longer than that of methylphenidate; immediate and extended-release formulations of amphetamine have an average half-life of 9– 15 hours, compared with 2–7 hours for methylphenidate formulations.[46]

Methylphenidate and amphetamine are associated with a range of adverse effects, which are usually tolerable because most are mild and/or temporary. Common adverse effects include loss of appetite, sleep disturbances, increased blood pressure and heart rate, headache, irritability, and stomach pain.[47]

Table 1: Approved stimulant drugs used in the treatment of ADHD.[45,49,50]

Drugs	Dose	Mode of Action
Methylphenidate	**Immediate-release/short-acting:** Initial 5-18 mg. **Intermediate-acting:** One to two times daily. **Extended-release/long-acting:** Once daily (Patch left on for 9 hrs).	norepinephrine and dopamine transporter inhibition, agonist activity at the serotonin type 1A receptor, and redistribution of the vesicular monoamine transporter 2.
Amphetamines	**Immediate-release/short-acting:** Initial dose half IR MPH; two to three times daily. **Intermediate-acting:** One to two times daily. **Extended-release/long-acting:** Once daily.	Dopamine inhibition and norepinephrine transporter, vesicular monoamine transporter 2, and monoamine oxidase activity.

Non-stimulants

While stimulants are quite effective in the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD), it is estimated that at least 30% of affected individuals do not adequately respond or cannot tolerate stimulants or significant comorbidities that interfere with treatment.[41] The first generation of stimulants were short-acting drugs that required multiple administrations during the day with their attendant impact on compliance and the need to take treatment during school or work hours. While this problem may be offset by the new generation of long-acting stimulants, there may be other issues with this class of medication that affect their use. Usage of stimulants includes the potential for insomnia that may prevent administration in the evening. In addition, stimulants are controlled substances, posing legal concerns that may worsen the barriers to treatment.[42] In this case, non-stimulants are a good option.

The non-stimulants used in the treatment of ADHD are classified into Tricyclic antidepressants, Non-tricyclic antidepressants, Specific norepinephrine reuptake inhibitors, Alpha-2 noradrenergic agonists, and Non-schedule stimulants.[16] (Table 2).

Atomoxetine (Specific Norepinephrine Reuptake Inhibitors)

It is a selective NRI and the first non-stimulant drug to treat ADHD.[11] It highly selectively binds to the presynaptic membrane NE reuptake transporter and inhibits NE reuptake, but has low affinity with other neurotransmitters.[12,13] Therefore, it can increase the level of NE in the synaptic cleft and dopamine levels in the PFC, enhance children's memory and attention, and significantly improve ADHD symptoms.[14]

Atomoxetine is administered orally and is primarily metabolized by the cytochrome P450 2D6 (CYP2D6) pathway. This should be considered because some selective serotonin reuptake inhibitors may increase serum atomoxetine. Atomoxetine is currently approved in many countries, including the United States and Europe, to treat ADHD in children, adolescents as well as adults.

The most common adverse effects of atomoxetine in child and adolescent clinical trials were nausea, vomiting, fatigue, decreased appetite, abdominal pain, and somnolence.[22] 7% of the population have been estimated to be poor metabolizers of atomoxetine, with significantly higher plasma levels and longer half-lives. This may lead to an increase in adverse effects.

If methylphenidate is ineffective or the patient has contraindications or comorbidities such as depression or anxiety disorders, commonly used alternative medications include atomoxetine or antidepressants such as venlafaxine, reboxetine, and desipramine. As regards significant efficacy in adult ADHD, however, so far only the selective noradrenaline reuptake inhibitor atomoxetine has been evaluated – also in larger studies.[15]

Tricyclic antidepressants (TCAs)

Numerous open-label and controlled trials of TCAs, such as desipramine, imipramine, and nortriptyline have demonstrated the efficacy of these compounds in the treatment of ADHD. It is assumed that their activity in ADHD stems from their actions on catecholamine (noradrenaline and dopamine) reuptake.[25] Up to 70 % of children showed significant improvement in behavioral symptoms when treated with TCAs compared to 10 % with placebo.[26]

In patients with comorbid tics, desipramine was found to be more effective than clonidine on the symptoms of ADHD.[48] The TCAs shown to have the greatest effect on ADHD are desipramine and, to a lesser degree, imipramine, nortriptyline, and amitriptyline.[27] In contrast, clomipramine and protriptyline do not seem to have been successful in the treatment of ADHD because of their efficacy and a high rate of intolerable side effects.[28,29] Desipramine was shown to be superior to placebo in the treatment of ADHD with an effect size similar to that of stimulants in 62 clinically referred children with ADHD, most of whom had not previously responded to psychostimulant treatment. Imipramine can be used as an alternative to desipramine.

Advantages of the TCAs include their relatively long half-life (approximately 12 hours) eliminating the need to administer medication during school hours, absence of abuse potential, and putative positive effects on mood and anxiety, sleep, and tics.[30] However, TCAs demonstrate a narrower margin of safety than stimulants, along with a wider range of potential side effects.

They have a significant affinity for adrenergic, cholinergic, and histaminergic receptors potentially resulting in drowsiness, sleep disturbances, anxiety, headache, dizziness, dry mouth, sweating, blurred vision, constipation, sedation, weight gain, changes in heart rate and blood pressure, tremor, lowering seizure threshold, and cognitive impairment. More seriously, TCAs are also associated with quinidine-like effects, i.e. the potential for delayed cardiac

conduction and repolarization, which can occur even two years after the start of the treatment.[31,32]

Bupropion (Non-TCA Antidepressants)

Bupropion hydrochloride is a novel-structured antidepressant of the aminoketone class, which is related to the phenylisopropylamine class but pharmacologically distinct from known antidepressants.[42] It is metabolized to three pharmacologically active substrates and may be used as a second-line agent in the treatment of ADHD. Bupropion has noradrenergic, anticholinergic, and indirect dopaminergic effects. Several open and controlled trials have shown bupropion's efficacy in improving ADHD symptoms.[25,35]

Based on the NNT, one in every five adults with ADHD have a positive response to bupropion treatment. Bupropion is an alternative for patients who are not responding to the treatment or cannot tolerate the side effects of stimulants.[36]

Bupropion found to be well tolerated in most of the children and adolescents.[38] Bupropion's side effects include irritability, insomnia, drowsiness, fatigue, headache, dry mouth, sweating, constipation, nausea, and dermatological reactions. While it does not have the cardiovascular risks associated with the tricyclic antidepressants or the substance abuse potential of the stimulants, concerns remain about an increased risk of seizures.

Therefore, regular control examinations of the EEG are recommended. Bupropion may also exacerbate tic disorder.[39] Thus, it may not be an appropriate alternative to stimulants in the treatment of ADHD in Tourette's syndrome. Bupropion is contraindicated in patients with seizure disorders or bulimia nervosa. Side effects may become worse if bupropion is combined with fluoxetine. Increased incidence of side effects may be associated with increased levels of the metabolite hydroxybupropion.[40]

Clonidine and Guanfacine (Alpha-2 agonists)

Clonidine and guanfacine are very similar in pharmacology, and their primary mechanism of action is an agonist effect on alpha-2 adrenergic receptors in the brain. They differ in their potency and also with respect to metabolization, with clonidine being primarily metabolized via CYP2D6 and excreted renally and hepatically in equal shares, and guanfacine being primarily metabolized via CYP3A4 and excreted predominantly renally. Since clonidine is often quite sedative, guanfacine has been explored as an alternative. Guanfacine is an a2-

agonist that shows greater specificity for the a2A receptor, which is found to a greater degree in the cortex, while clonidine shows a similar affinity for the a2A, a2B, and a2C subtypes. The a2A subtypes are prominent in the brainstem, where they mediate clonidine`s sedative effect.[31]

Several small open trials of guanfacine have suggested it might be helpful in ADHD and recently the results of a small double-blind, placebo-controlled trial of guanfacine have been presented.[43]

Clonidine and guanfacine were approved for monotherapy, as extended-release formulations for the treatment of ADHD or as an adjunctive therapy to stimulants in many countries.[4]

Adverse effects of clonidine and guanfacine are generally considered very similar and are most commonly somnolence, fatigue, irritability, insomnia, and nightmares4, sedation, drowsiness, and depression.[25] Guanfacine causes less sedation than clonidine.[33] Impairment of glucose tolerance can occur. It should be noted that clonidine stimulates growth hormone (GH) release.[34] Orthostatic hypotension and cardiac arrhythmias are rare but potentially serious. For clonidine, dry mouth, bradycardia, sedation and syncope have also been reported. Warnings are also existed in the approvals/labels of both clonidine and guanfacine and refer to hypotension/bradycardia, somnolence/sedation, discontinuation, and allergic reactions, and cardiac conduction abnormalities.[4]

Table 2: Approved Non-stimulant drugs used in the treatment of ADHD.[4,43,50]

Drugs	Dose	Mode of Action
Atomoxetine	Initial 0.5 mg/Kg; Increase to 1.2-1.8 mg/Kg one to 2 times a day.	Norepinephrine reuptake inhibition
Bupropion	Initial: less than 3 mg/Kg/d or 150 mg; Maximum: Lesser than 6 mg/Kg/d or 450 mg; No single dose greater than 150 mg; 2 to 3 times a day.	Non-TCA Antidepressants
Clonidine	**Immediate release:** Initial dose 0.05-0.1 mg at night; titrate to max 0.4 mg/ per day. **Extended-release:** Initial 0.1 mg qhs; titrate to max 0.4 mg qhs; once daily. **Transdermal patch:** 0.1, 0.2 and 0.3 mg.	Agonism at alpha-2 adrenergic receptors (leading to enhanced Noradrenergic neurotransmission)
Guanfacine	**Immediate release:** Initial 1 mg daily; titrate as needed up to 4 mg MDD; twice daily.	Agonism at alpha-2 adrenergic receptors (leading to enhanced noradrenergic

	Extended-release: Initial 1 mg; up to 4 mg; once daily.	neurotransmission)
Imipramine	Initial: 1 mg/Kg/d; Maximum: Lesser of 4 mg/Kg/d or 200 mg; 1 to 2 times per day.	Tricyclic antidepressants

Comparative efficacy of stimulants

Most research conducted so far shows that psychostimulants and non-psychostimulants are both effective in treating ADHD. However, it has been found that psychostimulation therapy provides better and faster results.[8] Medical treatment for ADHD is represented by psychostimulants—Methylphenidate, and non psychostimulants—Atomoxetine.[17] If not adequately treated, ADHD has a poor prognosis and can lead to complications. In a comparative analysis by Cojocaru A et al., it was shown that psychostimulation therapy in particular, significantly reduces the main symptoms of ADHD, giving better results compared to non-psychostimulant treatment in improving the clinical condition of ADHD patients.[20]

Although both therapies are effective in reducing the frequency of ADHD symptoms, psychostimulants have been shown to significantly reduce ADHD symptoms. There was a significant reduction in the severity of ADHD symptoms at six months and one year from the start of treatment in the case of the psychostimulant group, whereas, in the non-psychostimulants, the significant reductions in symptoms severity occurred only at six months after the start of treatment.[20]

Therefore, psychostimulants—Methylphenidate, appears to be more effective than non-psychostimulants in the treatment of ADHD.[17,18,19]

CONCLUSION

ADHD is a chronic neurodevelopmental disorder that persists into adulthood. It has a high incidence in childhood and adolescence, causing significant functional impairment and social burden. Research has explored various treatments, including stimulants (methylphenidate, amphetamines) and non-stimulants (atomoxetine, bupropion, guanfacine, clonidine). Stimulants are often the first choice, but concerns about misuse, abuse, and cardiovascular side effects exist. Non-stimulant medications are also effective. Regular follow-ups should monitor height, weight, heart rate, blood pressure, symptoms, mood, and treatment compliance. More trials are needed to compare stimulants and non-stimulants and to investigate combined treatments. ADHD in adults can be effectively treated with medication, but further research is needed on the long-term course and treatment strategies.

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