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ADHD - Treatment Options and Consequences of Neglect

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ABSTRACT

Purpose of Research: Attention Deficit Hyperactivity Disorder (ADHD) is one of the most frequently diagnosed neurodevelopmental disorders. It is estimated to occur in approximately 5-10% of children and adolescents. This paper aims to highlight the challenges faced by individuals suffering from ADHD, present risk factors, summarize current treatment methods, and outline the consequences of neglecting treatment.

Methods: Databases such as PubMed, Medline, and ResearchGate were used.

Basic Results: The goal of ADHD treatment is to reduce the severity of symptoms and improve the social, academic, and emotional functioning of children and adolescents. The choice of treatment and the selection of a specific medication depend on the patient's age and coexisting disorders.

Conclusions: ADHD often coexists with other mental disorders, complicating diagnosis and treatment. Lack of or ineffective treatment has consequences such as learning difficulties, disruptions in peer and family relationships. It correlates with higher rates of traffic accidents, accidental injuries, earlier onset, and higher rates of substance abuse.

KEYWORDS: ADHD, methylphenidate, atomoxetine, viloxazine, stimulants

INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most frequently diagnosed neurodevelopmental disorders. It is estimated to occur in about 5-10% of children and adolescents [1]. ADHD is associated with excessive impulsivity, hyperactivity, and attention deficits. This disorder negatively affects social functioning and is linked to emotional and adaptive disorders [1][2]. Individuals with ADHD often achieve poorer academic results, are more likely to use psychoactive substances, and have higher hospitalization rates (especially due to injuries) [3][4]. They also appear to be at increased risk of self-harm and suicide attempts [5]. ADHD is more commonly diagnosed in boys than in girls [6]. The onset of symptoms occurs in childhood and, in most cases, persists into adulthood. As individuals age, hyperactivity symptoms tend to subside, while attention-related symptoms persist [7][8].

ETIOLOGY AND PATHOGENESIS

The cause of ADHD remains unclear, but it appears that both genetic and environmental factors may influence the development of this disorder. Studies have shown that children whose parents have been diagnosed with ADHD are at a higher risk of developing the disorder [9]. In recent years, 27 significant loci across the genome associated with ADHD have been identified. Risk genes are linked to early brain development, brain-specific neurons, and midbrain dopaminergic neurons [10][11]. Some of the genes that may be associated with the development of ADHD include the dopamine receptor D4 gene (DRD4), the dopamine transporter gene 1 (DAT1, also known as SLC6A3), the serotonin transporter genes (SERT), the serotonin receptors 1B (5-HTR 1B) and 2A (5-HTR 2A), and the norepinephrine transporter gene (NET, SLC6A2) [10].

Factors related to pregnancy and perinatal circumstances also influence the occurrence of ADHD symptoms. Increased risk factors include alcohol consumption and smoking by the pregnant woman, maternal stress, exposure to air pollution during pregnancy, low birth weight, and prematurity. Additionally, other factors that may have an impact include gestational diabetes, hypothyroidism during pregnancy, and maternal overweight and obesity before pregnancy [1][10].

Environmental factors also encompass psychosocial variables. Family financial status and parental relationship status can affect the occurrence of ADHD symptoms. Children with ADHD subjected to improper educational techniques increasingly exhibit abnormal behavior patterns over time [10].

Studies have shown that cortical maturation in patients with ADHD is delayed. There is an observed delay in inhibitory and transfer functions [10].

A slight reduction in the total surface area of the cerebral cortex was noted. Subcortical areas were also affected by abnormalities. Among others, the hippocampus, basal ganglia, and amygdala were smaller in affected children compared to healthy ones. However, these differences were slight. They were observed in children but not in adolescents or adults [12].

TREATMENT OF ADHD

The inclusion of treatment should be preceded by a full diagnosis and introduced in patients meeting DSM V criteria. The aim is to improve patients' functioning, both in terms of subjective reduction in the severity and distress of symptoms and in terms of improved educational and academic performance or reduced injuries and accidents [13]. Lack or ineffectiveness of treatment carries a number of consequences, such as learning difficulties, disruption in peer and family relationships, and lowered self-esteem. It is correlated with higher rates of road traffic accidents and accidental injuries, increased psychiatric hospitalisation and earlier onset and higher rates of smoking, substance abuse, leading to increased mortality [14][15][16].

Recommendations for the type of treatment and choice of preparation vary according to the age of the patient:

1. **Treatment of ADHD in preschool children** starts with behavioural therapies such as parenting skills training (PTBM) and behavioural interventions in the classroom. If behavioural interventions are unsuccessful after at least three months and the dysfunction is moderate to severe, methylphenidate (MPH) is recommended. When using methylphenidate, start with low doses and aim to keep the doses low, using short-acting formulations, as the drug is metabolised more slowly in this age group.
2. **At school age**, therapy includes both pharmacotherapy and behavioural interventions. The primary behavioural interventions are parenting skills training for parents (PTBM), behavioural interventions in the classroom, educational interventions and individual learning support such as the Individual Learning Programme. In terms of pharmacotherapy, methylphenidate is considered a firstline drug, with both short- and long-acting formulations available for

consideration. The combination of these approaches aims to provide comprehensive support to the child.

3. **At the secondary school level**, treatment is based on a combination of pharmacotherapy and behavioural interventions. Primary behavioural interventions include parenting skills training (PTBM), behavioural interventions in the classroom, educational interventions and individual learning support such as the Individual Learning Programme. In terms of pharmacotherapy, methylphenidate (MPH) is considered a first-line medication, with long-acting formulations recommended to minimise the need for afternoon doses. This approach aims to provide stable control of ADHD symptoms, supporting students in their educational and social functioning [15][17].

ADHD often coexists with other psychiatric disorders, complicating the diagnosis and treatment of patients. Among the most common co-occurring disorders are oppositional defiant disorder (ODD) and conduct disorder (CD), which affect between 30% and 50% of people with ADHD. Anxiety disorders occur in 30%-40% of patients and depression in 20%-40%. Coexistence with substance use disorder is reported in 20%-30% of cases and with autism spectrum disorders in 10%-30%. Seizure disorders occur in 10%-20% of people with ADHD, while eating disorders can affect up to 20% of patients. Bipolar affective disorder occurs in 8%-10% of patients, Tourette's syndrome in 5%-10%, and mood dysregulation disorder, although its exact prevalence is not specified, is also frequently diagnosed [7][10][15].

1. Stimulant medication:

First-line drugs for the treatment of ADHD are psychostimulants, including methylphenidate and amphetamine [13]. Amphetamine acts by inhibiting dopamine and norepinephrine transporters, the monoamine transporter in the vesicles and monoamine oxidase activity. Methylphenidate acts by inhibiting dopamine and norepinephrine transporters, agonist activity at the serotonin type 1A receptor and redistribution of the vesicular monoamine transporter type 2 (VMAT2). Increasing the effects of dopamine and norepinephrine improves prefrontal cortex performance and enhances executive function and attentional focus in patients with ADHD (Table 1)[15][17].

Table 1. Side effects, their frequency and pathophysiology.

	Side effects	Pathophysiology	Frequency
General arrangement	Dry mouth, dizziness, nervousness, anxiety	Increased adrenergic receptor activity	Frequent >10%
Cardiovascular system	Tachycardia, Increase in blood pressure,	Increase in norepinephrine and dopamine, stimulation of adrenergic and dopaminergic receptors	Rare 1%10%,
	cardiovascular events	effects on conductivity and blood vessels	Very rare <1%
Gastrointestinal tract	Reduction in appetite, weight loss, abdominal pain	Increased gastric acid production, decreased appetite	Frequent >10%
Nervous system	Headache, insomnia, irritability, hyperactivity, mood changes	Increased neurotransmitter activity, impact on circadian rhythms	Frequent >10%, Rare 1%-10
	Hallucinations, hyperkinetic movements, mania	Effects on the central nervous system	Very rare <1%
	Serotonin syndrome	Effects on the central nervous system	Very rare <1%
	Seizures, transient, treatment-induced tics	Effects on the central nervous system	Very rare <1%
Reproductive system	Priapism	Increased levels of norepinephrine and dopamine	Very rare <1%

Vascular system	Peripheral vasculopathies (e.g. Raynaud's disease)	Abnormalities in blood flow to the extremities	Very rare <1%
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Interventions for complications of stimulant therapy. They require a multifaceted approach. Example strategies are outlined below:

1. **Reduced appetite, weight loss.** Track the patient's weight using centile and z-score grids, give high-calorie meals at times when the effect of the drug is least (e.g. at breakfast, before bed), and offer snacks throughout the day. It is worth considering breaks in stimulant use or the use of cyproheptadine when appropriate. Reassess stimulant treatment if the child deviates from the predicted growth trajectory and discontinue if appropriate.
2. **Abdominal pain.** Administration of stimulants on a full stomach.
3. **The headache** can be alleviated by splitting the dose, switching to a sustained-release product and administering the product with a meal.
4. **Insomnia:** earlier dosing during the day, reducing the last dose of the day or giving it earlier, and considering a sleep aid such as melatonin. If insomnia is associated with poorly managed ADHD symptoms, assess the need to optimise stimulant treatment.
5. **Dry mouth, dizziness.** These can be alleviated by hydration
6. **Nervousness, anxiety, irritability and hyperactivity.** Consider reducing dose, switching to a prolonged-acting product, considering non-stimulant treatment.
7. **Cardiovascular events.** Prevention of cardiovascular events requires routine monitoring of blood pressure and heart rate and consultation with a cardiologist if complications occur and consideration of discontinuing stimulants.
8. **Hallucinations, hyperkinetic movements, mania:** consultation with a neurologist or psychiatrist is crucial. Reassessment of the diagnosis and discontinuation of stimulants is worth considering, and MPH/d-MPH is preferred to AMP when introduced.

9. **Seizures.** For well-controlled seizures, initiation of treatment with a methylphenidate product is considered. For treatment-induced seizures, stimulants should be discontinued and a neurologist should be consulted.
10. **Peripheral vasculopathies (e.g. Raynaud's disease):** Peripheral vasculopathies, such as Raynaud's disease, especially with finger lesions, require immediate discontinuation of stimulants and urgent medical attention. Consideration of dose reduction or switching to an alternative drug is recommended.
11. **Priapism.** It requires education of patients and their carers about the symptoms, as well as urgent medical attention and discontinuation of stimulants.
12. **Serotonin syndrome.** Watch out for serotonergic drug interactions and educate patients and their caregivers about the symptoms of serotonin syndrome, including excessive sweating, hyperreflexia, clonus and pupil dilation.
13. **Transient treatment-induced tics.** Monitor tic symptoms after initiating stimulant treatment and assess whether the tic is related to the natural course of tic disorders (e.g. TS) or to stimulant treatment. An alternative treatment strategy should be considered, such as an alpha-2 receptor agonist (e.g. guanfacine).
14. **ADHD relapse symptoms.** Recommend switching to a long-acting or longer-acting stimulant product; add a dose of a short-acting stimulant in the afternoon [15][16].

2. Non-psychostimulants

Non-psychostimulants play an important role in the treatment of ADHD, especially when psychostimulants prove ineffective, when they are not tolerated by patients, which is the case in 10-30% of cases, or in patients with comorbid disorders, allowing a personalised treatment approach. Atomoxetine, a selective norepinephrine reuptake inhibitor, is one of the most commonly used non-psychostimulants. Others are tricyclic antidepressants (TCAs) and alpha2-adrenergic receptor agonists, also finding use in ADHD therapy, although their efficacy and tolerability vary. Experimental studies also suggest the potential of cholinergic drugs such as acetylcholinesterase inhibitors (tacrine, donepezil) and novel nicotinic analogues (ABT-418). New drugs currently in development may offer an even more

personalised approach to the treatment of ADHD, especially in cases with comorbid disorders (Table 2)[18][19][20].

Table 2. Comparative table of non-psychostimulants used in ADHD therapy

Drug	Mechanism of action	Effectiveness	Side effects	Comments
Atomoxetine	Selective norepinephrine reuptake inhibitor	High	Minimum	Approved by the FDA
Viloxazine XR	Selective norepinephrine reuptake inhibitor	High	Minimum	During the development phase
Clonidine XR	Alpha-2adrenergic receptor agonist	Average	Drowsiness, low blood pressure	Approved by the FDA
Guanfacine XR	Alpha-2adrenergic receptor agonist	Average	Drowsiness, low blood pressure	Approved by the FDA
Tricyclic antidepressants (TCAs)	Monoamine reuptake inhibitors	High	Numerous (e.g. dry mouth, weight gain)	Well researched
Acetylcholinesterase inhibitors	Increase acetylcholine levels	Experimental	Various, drugdependent	Potential in research
Nicotine analogues (ABT-418)	Nicotinic receptor agonist	Experimental	Various, drugdependent	Potential in research

Side effects of non-psycho stimulants. They can vary and depend on the specific drug. It is important that patients are monitored for these side effects and that therapy is tailored to their individual needs and tolerance (Table 3)[18][19][20].

Table 3. Comparative table of adverse effects of non-psycho stimulants

Drug	Main adverse effects	Frequency
Atomoxetine	Nausea, decreased appetite, fatigue, drowsiness, tachycardia, increased blood pressure	Rare - moderate
Viloxazine XR	Nausea, decreased appetite, drowsiness	Rare
Clonidine XR	Drowsiness, low blood pressure, dizziness, dry mouth, constipation	Moderate - frequent
Guanfacine XR	Drowsiness, low blood pressure, fatigue, dizziness, abdominal pain, dry mouth	Moderate - frequent
Tricyclic antidepressants (TCAs)	Dry mouth, weight gain, constipation, blurred vision, dizziness, arrhythmias, sleep problems, mood changes	Moderate - frequent
Acetylcholinesterase inhibitors	Nausea, vomiting, diarrhoea, muscle cramps, insomnia, liver damage (tacrine)	Moderate
Nicotine analogues (ABT-418)	Nausea, dizziness, headache, irritability, cardiovascular problems	Moderate

3. Innovative Treatment

Despite the availability of many drugs, more than 50% of adults discontinue treatment within 12 months of starting therapy, often due to tolerance or lack of effect. One of the latest innovations is the delayed and extended release methylphenidate (DR/ER MPH) formulation, which aims to provide more stable levels of the drug in the body throughout the day, minimising fluctuations in concentration and activity levels. This addresses the short-acting

nature of traditional formulations, which require multiple doses throughout the day. Another innovation is the methylphenidate prodrug, known as serdexmethylphenidate, which allows for a more controlled release of the active ingredient, which can lead to a lower incidence of side effects and a reduced risk of abuse.

Another major advance is amphetamine patches, which offer a convenient alternative to traditional tablets and capsules. These patches provide a steady release of the drug through the skin over a set period of time, which can be particularly beneficial for patients who have difficulty swallowing tablets or prefer a more discreet form of treatment.

In addition, atomoxetine and extended-release (ER) viloxazine are norepinephrine reuptake inhibitors approved for the treatment of ADHD in children and adults in the US, offering alternatives to stimulants. Clonidine ER and guanfacine ER are α_2A -adrenergic receptor agonists that are also used in the treatment of ADHD, offering different efficacy and side-effect profiles compared to stimulants (Table 4) [21][22][23][24][25].

Table 4. Overview of Innovative Treatment

Innovative Treatment	Type	Advantages	Challenges Addressed
DR/ER Methylphenidate	Stimulant	Stable concentration, reduced dosing frequency	Frequent dosing, peak/trough effects
Serdexmethylphenidate Prodrug	Stimulant	Controlled release, lower side effects	Side effects, abuse potential
Amphetamine Patches	Stimulant Patch	Convenient and steady release, lower abuse risk	Difficulty swallowing pills, abuse potential
Viloxazine ER	Non-stimulant	Alternative to stimulants, extended release	Limited non-stimulant options
Clonidine ER	Non-stimulant	Alternative to stimulants, specific receptor targeting	Limited non-stimulant options
Guanfacine ER	Non-stimulant	Alternative to stimulants, specific receptor targeting	Limited non-stimulant options

4. Drugs in the research phase:

Despite the availability of various drugs for ADHD, there is still a great need for new therapeutic options for patients who do not respond to current therapies. New substances in clinical trials, such as Centanafadine, Solriamfetol and L-Threonic Acid Magnesium Salt (LTAMS), promise to introduce a fresh approach to ADHD treatment [26].

Centanafadine is a norepinephrine, dopamine and serotonin reuptake inhibitor (NDSRI) that is being studied for efficacy in the treatment of ADHD in adults. In phase 2 studies, centanafadine at doses up to 400 mg/d was shown to improve ADHD-RS-IV scale scores, and effects were seen after the first week of treatment. The medication was generally well tolerated, with the most common side effects being decreased appetite, headache and nausea [27].

Solriamfetol is being investigated as a potential treatment for ADHD in adults. In a doubleblind placebo-controlled study, solriamfetol at doses of 75 mg or 150 mg was shown to improve scores on the AISRS, CGI and BRIEF-A scales. The drug was well tolerated and the most common side effects were decreased appetite, headache and insomnia. Solriamfetol may be particularly useful for patients who cannot tolerate or do not respond to current stimulant drugs [28].

L-Threonic Acid Magnesium Salt (LTAMS) has shown promising results in preclinical studies, associated with neurobiological and neurofunctional beneficial effects for the treatment of ADHD. In a study involving 15 adult patients with ADHD, LTAMS improved scores on the AISRS, CGI-I and the BRIEF sliding subscale. The drug was well tolerated, and almost half of the study participants met clinical response criteria. These results support further study of LTAMS in larger clinical trials [29].

5. Probiotics and prebiotics

Supplementation with the probiotic *Lactobacillus rhamnosus* GG (LGG) showed improvements in emotional, physical, social and school functioning and health-related quality of life in children with ADHD compared to the placebo group. In addition, Synbiotic 2000 reduced markers of intestinal and vascular inflammation in children with ADHD, in part by increasing levels of short-chain fatty acids (SCFAs). Further studies of longer duration, involving larger numbers of participants and different age groups, and using a variety of

assessment techniques are needed to thoroughly investigate the effects of prebiotics and probiotics on ADHD [30].

6. Psychological and behavioural therapies

Behavioural therapy for adolescents with ADHD uses a variety of interventions that have long-term benefits for both the adolescents themselves and their parents. The main types of interventions include developing organisational skills, maintaining motivation, improving self-awareness, increasing parental knowledge of ADHD, increasing the autonomy granted by parents, increasing parental involvement in the adolescent's life and improving the relationship between parents and adolescents. The development of organisational skills, present in 81.0% of participants, consists of an improvement in the ability to manage time, plan and complete tasks. An increase in motivation, reported by 57.1% of participants, represents an increase in intrinsic motivation to learn and perform daily duties. Improved self-awareness, also present in 57.1% of participants, involves better recognition of one's own emotions, behaviour and their impact on others. Educating parents about the mechanisms of ADHD and how to support their children is an intervention valued by 76.2% of participants. Increased autonomy granted by parents, reported by 61.9% of participants, is about giving children more independence and confidence in daily activities. Greater parental involvement in the child's education and emotional development is a benefit reported by 52.4% of participants. Improved relationships between parents and teenagers, also reported by 52.4% of participants, is an increase in the quality of communication and family relationships. In smaller subgroups of participants, benefits such as reduced need for medication were noted, which was the case for 3 of the 9 participants taking medication. Other important, although less common, themes included reduced family stress, improved school performance, increased social skills, reduced symptoms of depression and anxiety, improved stress management, improved general wellbeing and greater emotional stability [31][32][33][34].

CONCLUSIONS

Attention Deficit Hyperactivity Disorder (ADHD) is a common neurobehavioral disorder that affects children and adolescents worldwide. ADHD is associated with excessive impulsivity, hyperactivity, and attention deficits. The cause of this disorder remains unclear; however, factors contributing to its development include maternal alcohol consumption and smoking

during pregnancy, maternal stress, birth weight, and prematurity. Initiation of treatment should be preceded by a complete diagnosis and implemented in patients meeting the criteria according to DSM-5. The choice of treatment depends on the patient's age and coexisting disorders. Both pharmacological medications and behavioral therapies are used in the treatment of ADHD. First-line medications are psychostimulants (methylphenidate, amphetamine). Non-stimulants also play a significant role in the treatment of ADHD, especially when psychostimulants are ineffective or not tolerated, and in individuals with coexisting disorders.

Despite the availability of many medications, over 50% of adults discontinue therapy within a year due to lack of efficacy or tolerability. A new innovation is delayed-release and extended-release methylphenidate (DR/ER MPH), which stabilizes the drug level throughout the day, reducing fluctuations in concentration and activity. Another modern solution is serdexmethylphenidate, a prodrug of methylphenidate, which controls the release of the active substance, reducing the risk of side effects and abuse. An important advancement is also the development of amphetamine patches, offering consistent drug release through the skin, which is beneficial for patients who have difficulty swallowing pills or prefer a discreet form of therapy. These innovations expand the available therapeutic options, allowing for a more personalized approach to ADHD treatment.

Despite the availability of various medications, there is still a need for new therapeutic options. Currently, substances such as centanafadine, solriamfetol, and L-threonic acid magnesium salt (LTAMS) are in clinical trials.

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