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A Review of the Neurobiological Mechanisms and Treatment Options of ADHD Across Different Age Groups

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Abstract. This review paper synthesizes academic research to explore various aspects of ADHD, including its neurobiological mechanisms involving the basal ganglia, prefrontal cortex (PFC), and the roles of neurotransmitters such as dopamine and norepinephrine. It also examines how treatment approaches for ADHD vary across different age groups, emphasizing the need for special consideration in specific age groups, such as preschool children and older adults, due to factors like medication tolerability and physical condition. Additionally, the paper discusses emerging medications and non-pharmacological treatments, as well as established pharmacological treatments like stimulants and non-stimulants. Given the heterogeneity of symptoms and the individual responses to treatment, the significance of personalized treatment approaches in ADHD management is highlighted in this paper. Furthermore, it advocates for continued exploration into the pathophysiology of this disorder and the development of innovative therapeutic strategies to meet the specific needs of different individuals, thereby improving outcomes for affected individuals across the lifespan.

Keywords: ADHD; Age factors; Pharmacological approaches; non-pharmacological approaches; Emerging treatments.

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD), which originates in childhood and often persists into adulthood, is based on neurodevelopmental abnormalities. Behavioral manifestations of ADHD can include difficulty sustaining attention, impulsivity (e.g., engaging in risky behaviors), inappropriate behavior, and hyperactivity. These symptoms may not be present at the same time as individuals with ADHD vary from one another. The intensity of symptoms may be different in different individuals. Three types of diagnosis are classified based on the predominant symptoms: those predominantly characterized by inattentive features, those predominantly characterized by hyperactive or impulsive features, and those presenting combined features of both inattention and hyperactivity/impulsivity. Either one set of symptoms might be mainly observed, or both sets of symptoms may be present [1, 2].

The symptoms of ADHD negatively impact the quality of life of the affected individuals. ADHD interferes with normal executive functions needed during work and in daily life. This makes work that requires a high level of organization more difficult for individuals with ADHD. Time blindness, poor quality of working memory, and difficulty in maintaining continuous attention and diverging attention also add to the obstacles faced by individuals with ADHD. Those symptoms can also obstruct students with ADHD from performing well academically in school. The treatment of ADHD in older adults also faces obstacles, as some pharmacological treatments impact their physical condition. Doctors need to pay attention to the risk factors that medications might pose to their physical health.

According to the Centers for Disease Control and Prevention (CDC), data from the year 2022 showed that the diagnostic statistics of ADHD in children from the age of three to seventeen years old had reached 7 million in the United States in total. This statistic takes up 11.4% in children. More boys were diagnosed than girls [2].

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The statistics of diagnosis may vary from country to country as well. The percentage of children diagnosed with ADHD is different in developed and developing countries as well as in different continents, according to data from World Population Review. It showed that developed countries tend to have diagnosis rates that fluctuate within a moderate range, while developing countries had rates that vary largely from country to country. It is notable, though, that the five countries which had the highest diagnosis rates were all developing countries, including Haiti, Belize, Guyana, Dominican Republic, and Jamaica [3]. The explanation behind those phenomena awaits further research.

Considering the varying diagnosis rates across countries and the profound impact of ADHD on individuals' lives, there is a growing need for diverse therapeutic approaches and tailored treatment strategies. This review article talks mainly about the neurological mechanism of ADHD and the treatment options. The role of basal ganglia, prefrontal cortex (PFC), dopamine, and norepinephrine is included. This article also approaches treatment options from pharmacological and non-pharmacological perspectives, including stimulants, non-stimulants, and emerging treatments. It emphasizes aspects where age factors affect decisions of treatments, contributing to guiding future research and clinical practice towards optimal outcomes for patients.

2. The Neurological Mechanism behind ADHD

The neurobiological mechanism behind ADHD includes abnormalities in the prefrontal cortex (PFC), basal ganglia, and dysregulation in the dopamine and norepinephrine release systems [4, 5].

2.1. Basal Ganglia and Prefrontal Cortex

The basal ganglia work with the frontal cortex to perform higher cognitive functions such as the decision-making process and working memory. When it comes to the neurological foundation of ADHD, the places of abnormalities are very similar between adults and children, while these abnormalities are more inconsistent in adults. Dysfunction in the PFC would damage the ability to inhibit inappropriate behavior and random thoughts. This might cause an individual to be easily distracted by stimuli around with damaged executive function [4-6].

2.2. The Contribution of Dopamine and Norepinephrine in ADHD

ADHD is also related to dopamine and norepinephrine in the brain. A study proved that animal subjects exposed to small doses of dexamphetamine, which acts as a stimulant, had an increased amount of locomotor activity, and those exposed to large doses demonstrated behavior typical of ADHD. This was proof that the mechanism behind ADHD is related to dopamine, as this phenomenon can be explained by the Reversed-U effect that a disrupted stimulant level would lead to unpreferred cognitive functions. Reversed-U effect refers to the fact that behavior or cognitive function changes with the change of dopamine level in the brain. The correlation between cognitive function and dopamine level demonstrates a reversed-U pattern, indicating that cognitive function is preferred when the amount of dopamine available falls within a moderate range. Cognitive function would not be optimal if the level of dopamine is too high or too low. The dopamine level could be represented by dopamine receptor D1 stimulation, since when D1, α-1, and β-1 receptors are stimulated within a moderate range, the effectiveness of amygdala and posterior cortical functions might be strengthened. However, when those receptors were overstimulated, the working memory was damaged [4]. Since ADHD is linked to insufficiency of dopamine and norepinephrine levels, the levels in ADHD patients might not reach the optimal range for preferred cognitive function.

3. Pharmacological Treatment for ADHD for Different Age Groups

When it comes to the treatment for ADHD, it usually comes down to two categories, which are pharmacological treatments and nonpharmacological treatment options. Pharmacological treatments are further broken down into stimulants and non-stimulants.

3.1. Emerging Therapies

Monoaminergic reuptake inhibitors represent a promising emerging drug class for ADHD. One of the emerging pharmacological therapies-viloxazine, as a type of Noradrenergic reuptake inhibitor (NRI), has shown fewer side effects and comparable efficacy to other NRIs such as reboxetine and edivoxetine. Phase 1 and 2 trials suggested that it is potentially a good choice as a treatment for children with ADHD [7]. SPN-812, an extended-release viloxazine formulation, has been proven effective for children between the ages of six to twelve through randomized, double-blind trials. It is an emerging nonstimulant pharmacotherapy with the mechanism of inhibiting norepinephrine reuptake. Compared to the placebo, the emerging therapy SPN-812 was more effective in alleviating ADHD behavioral features while holding the possibility of causing intolerance in patients. It also may cause side effects such as somnolence, reduced appetite, and headache [8].

3.2. Stimulant Medication

Another category of pharmacological therapies is stimulants. They are generally considered the most useful first-line pharmacological treatments for children [9]. A study compared the three medications related to the treatment of ADHD, including norepinephrine-dopamine reuptake inhibitor (NDRI), a non-stimulant ADHD medication, selective norepinephrine reuptake inhibitor (sNRI), and a dopamine receptor modulator (DRA). These medications were tested by participants and were proven to be more effective than the placebo. The first one is a stimulant medication, while the other two are typically considered non-stimulant medications. According to the study, of the three ADHD medications, the most effective is the stimulant, which had a Standardized Mean difference (SMD) of 0.633, the dopamine receptor modulator, which showed a SMD of 0.402 went behind it, and then sNRI, which had a SMD of 0.386 followed [10]. This also indicates why stimulants are usually prescribed to patients with ADHD first, since the stimulants were proven to be more effective than the two non-stimulants. After all, stimulants are regarded as the first-choice pharmacological ADHD therapy. Since one of the mechanisms of the disorder is dysregulated release of dopamine, it is possible that stimulants can increase the tonic dopamine levels, decrease extreme phase responses, as well as regulate emotional processing and cognitive control [9].

While stimulants are considered effective and tolerable to a lot of people, stimulants have their limitations in preschool children and older adults. Intolerance and side effects are common reasons why stimulants might not be suitable as treatment in these age groups [11-12].

3.3. Non-stimulant Medication

Some common non-stimulant medications are Atomoxetine, Guanfacine, Clonidine, and Bupropion. A lot of double-blind and controlled trials showed that some non-stimulant medications are more effective for children and adolescents. For example, amphetamines had a better effect on patients of this age group than guanfacine. And methylphenidate was more effective than atomoxetine [13].

Double-blind and controlled trials have also proven that the four medications, amphetamines, methylphenidate, bupropion, and atomoxetine, are all effective in adults, while the effectiveness of guanfacine and clonidine is unsure. Among those medications, amphetamines and methylphenidate are stimulants, and the effects of atomoxetine, methylphenidate, and bupropion were better than that of modafinil for adults [13]. Another study found that Guanfacine extended release (GXR) was preferred by patients with ADHD and their caregivers compared to atomoxetine (ATX). According to the data in this experiment, GXR received better feedback on effectiveness from children and doctors. It took about 2-6 weeks less than ATX to be effective. It also has a lower percentage of causing some side effects compared to ATX [14].

Overall, amphetamines are more effective than modafinil, atomoxetine, and methylphenidate according to their results on individuals ranging from children to adults [13].

4. Limitation of ADHD Medication due to Age Factors

As mentioned above, the application of pharmacological treatment also needs to take age factors into consideration. When it comes to children under the age of five, pharmacological treatment should only be prescribed after consulting at least two specialists. Pharmacological treatments are not usually recommended, and behavioral therapy and other nonpharmacological treatments should be considered first [11].

In cases of older patients aged fifty or older with ADHD, the physical conditions of the patients should be taken into consideration when deciding the maximum dose of medication recommended by doctors. Physical comorbidities such as cardiovascular and endocrinological problems are present sometimes. They might become a risk factor for older people when using stimulants. The tolerability of medications such as stimulants might also change with age. Therefore, the specific dose of different older individuals and the choice of medication need special consideration and attention to physical conditions [12]. Side effects from ADHD medication for older individuals include increased heart rate, decreased weight, anxiety, depression, cardiovascular problems, and sleep problems [15].

5. Non-pharmacological Treatment for ADHD

Another option for treatment is non-pharmacological approaches. An emerging possible non-pharmacological treatment is Effective Deep Transcranial Magnetic Stimulation (dTMS), which is proven to be functional in relieving symptoms of ADHD, such as inattention and memory problems. dTMS in this study is an approach that avoids physical invasion, which operates by activating the right side of the prefrontal cortex (rPFC) with the intention to enhance functional engagement in the right dorsolateral prefrontal cortex (rDLPFC) as well as improve symptoms of inattention or memory in adults. The effectiveness of dTMS in rPFC was supported by functional magnetic resonance imaging (fMRI) results during working-memory tasks in a double-blind and randomized experiment with a control group. Conners' Adult ADHD Rating Scales (CAARS) was also used to determine that the results of the dTMS therapy on rPFC were positive [16].

According to Raz's study, comparing the cognitive performance of musicians and non-musicians diagnosed with ADHD through the Continuous Performance Test (CPT), musicians showed better performance in functions that are typically considered damaged in ADHD patients. This study indicates that music training is a candidate for non-medication treatment [17].

6. Conclusion

Every year, ADHD affects many people of all age groups across the globe. It is creating obstacles for students with ADHD in their academic life, relationships, and more. The symptoms of ADHD also make work and organization of life harder for adult patients. When symptoms go undiagnosed, they negatively impact the lives of individuals with ADHD to a large extent. Therefore, it is important to raise people's awareness of ADHD and promote a deeper understanding of the disorder to alleviate the stigma and misunderstanding amid ADHD within society. After diagnosis, getting suitable treatment also makes a great difference for individuals. More and more non-pharmacological treatment options are appearing, providing patients with ADHD additional options. Although stimulants are considered very effective in many cases, a lot of people with ADHD still choose to use non-stimulant medication or non-pharmacological treatment options. A variety of treatment approaches ensures that different approaches suit the specific needs of different individuals.

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