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Treatment of ADHD in Adults: Efficacy and Safety of Stimulants and Non-Stimulants

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Abstract:

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental condition with a complex etiology involving neurobiological, neuropsychological, and genetic factors. It is associated with brain structural and functional abnormalities, particularly in areas linked to executive functions, such as the prefrontal cortex and cerebellum. Disruptions in neurotransmission, particularly involving dopamine, norepinephrine, and serotonin, contribute to symptoms like impulsivity, hyperactivity, and inattention. Genetic studies reveal a strong hereditary basis, with variants related to dopaminergic and serotonergic systems. Although no single biomarker can definitively diagnose ADHD, a comprehensive diagnostic approach integrating clinical, neurophysiological, and neuroimaging data is necessary.

Treatment strategies for ADHD in adults include pharmacological and non-pharmacological approaches. First-line medications are stimulants like methylphenidate and amphetamines, which improve attention and impulse control by increasing dopamine and norepinephrine levels. Non-stimulants, such as atomoxetine and guanfacine, are used when stimulants are contraindicated. While stimulants are more effective, non-stimulants may benefit patients with comorbid conditions. Treatment should be personalized, considering symptom severity, comorbidities, and treatment adherence. Neuroimaging shows that stimulants increase brain activity in areas related to cognitive control, while non-stimulants provide a more stable pharmacokinetic profile. A combined approach is essential for optimal ADHD management.

Introduction:

Aim of study: The aim of this review paper is to analyze the effectiveness and safety of stimulant and non-stimulant treatments for adult ADHD. By reviewing the available literature, this study seeks to assess existing research on the impact of these therapies on symptom management, side effects, and overall treatment outcomes. Additionally, the paper aims to compare current clinical recommendations and identify areas requiring further research to optimize ADHD treatment in adults

Key words: ADHD, Stimulants, Non-stimulants, Atomoxetine, ADHD treatment, ADHD managment, Neurobiology of ADHD, Dopamine.

Pathophysiology of ADHD

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder with a complex and multifactorial etiology, involving neurobiological, neuropsychological, neurophysiological, and genetic factors. Research shows that ADHD is not a single, coherent clinical entity but rather a syndrome characterized by

significant biological and cognitive diversity, with symptoms that may arise from different pathophysiological mechanisms.

The neurobiological foundations of ADHD primarily refer to abnormalities in brain structure and function. Neuroimaging studies using magnetic resonance imaging (MRI) have highlighted delayed cortical maturation, particularly in areas responsible for executive functions, such as the prefrontal cortex, cingulate gyrus, caudate nucleus, and cerebellum. ADHD symptoms correlate with reduced brain volume and decreased white matter integrity in pathways connecting key areas involved in attention and impulse control. Structural changes are most visible in children, although some may persist into adulthood. Functional brain studies (fMRI) have shown changes in white matter integrity, especially in pathways connecting the prefrontal cortex with the basal ganglia and cerebellum. Diffusion tensor imaging (DTI) studies have revealed abnormalities in the frontostriatal and fronto-cerebellar tracts, which are responsible for attention, response inhibition, reward processing, and cognitive control. Individuals with ADHD often exhibit disrupted synchronization between the default mode network and the executive network, which may lead to frequent "attention lapses" and reduced activity in the reward system, contributing to impulsivity and difficulty with delayed gratification. [1]

In the pathophysiology of ADHD, disrupted neurotransmission plays a crucial role, particularly involving monoamines: dopamine, norepinephrine, and serotonin. These neurotransmitters are derivatives of aromatic amino acids—tyrosine and tryptophan—and their proper synthesis, release, reuptake, and metabolism are tightly regulated at multiple levels. Disruptions at any of these stages can lead to symptoms typical of ADHD, such as impulsivity, hyperactivity, and difficulties with concentration. The synthesis of dopamine and norepinephrine begins with the hydroxylation of tyrosine, a process involving the enzyme tyrosine hydroxylase (TH), which is the rate-limiting enzyme in the reaction. Its activity depends on the presence of the cofactor BH4 (tetrahydrobiopterin), oxygen, and the availability of substrate. TH activity is also influenced by signaling pathways, such as phosphorylation by protein kinases (e.g., PKA, PKG, CaMKII), as well as oxidative stress and nitric oxide (NO), which can further modify TH through nitrosylation or phosphorylation. After synthesis, neurotransmitters are transported into synaptic vesicles by the VMAT2 transporter and released into the synaptic cleft in response to a nerve impulse. The duration of neurotransmitter action in the synaptic cleft depends primarily on the activity of reuptake transporters: DAT (for dopamine), NET (for norepinephrine), and SERT (for serotonin). These are also the main targets of ADHD medications, such as methylphenidate or atomoxetine. After reuptake, neurotransmitters can be stored again or broken down by enzymes, mainly monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT). Disturbances in these pathways may result from genetic mutations, enzyme or cofactor (e.g., BH4) deficiencies, or problems with amino acid transport across the blood–brain barrier, which affects the availability of substrates for monoamine synthesis. In neurometabolic disorders such as

phenylketonuria (PKU) or tyrosinemia, excess of certain amino acids can inhibit the transport of others, leading to neurotransmitter deficiency in the central nervous system. This imbalance in neurotransmission can directly contribute to the manifestation of ADHD symptoms. [2]

Neuropsychological aspects of ADHD are also highly relevant. The disorder is associated with deficits in executive functions—particularly response inhibition, working memory, planning, time processing, and motivational control. However, not every individual with ADHD exhibits the same deficits, leading to the concept of ADHD as a spectrum of cognitive difficulties. Some individuals show prominent deficits in one domain, while others experience more diffuse or unstable impairments. Many children and adults with ADHD function cognitively within the normal range, indicating that behavioral symptoms may result from dynamic interactions between biological and environmental factors. [1]

Neurophysiological studies using EEG and ERP provide insights into the timing and processing of information in the brains of individuals with ADHD. Earlier theories proposed a characteristic EEG pattern, such as an elevated theta-to-beta ratio (TBR), but more recent studies indicate significant individual variability and a lack of consistent results. Event-related potentials (ERPs) in individuals with ADHD show weakened activation in areas associated with response preparation and cognitive control, suggesting difficulties in effectively processing stimuli and adapting to changing environmental demands. These changes are also observed in first-degree relatives, indicating a possible hereditary basis. [1, 3]

The genetics of ADHD support a strong biological basis for the disorder. Heritability of ADHD is estimated at 75–90%, meaning that most of the variability in ADHD symptoms is genetically determined. ADHD is polygenic—meaning that many genetic variants with small effects contribute to its development. Many of these variants are associated with the dopaminergic, noradrenergic, and serotonergic systems. Genome-wide association studies (GWAS) have identified numerous genetic loci associated with ADHD, including genes involved in brain development and neurotransmission. Importantly, many of these genetic variants are also present in other psychiatric disorders, such as depression, schizophrenia, or bipolar disorder, supporting the concept of a shared genetic background among various mental disorders. [1, 4]

Despite extensive research into the biological mechanisms of ADHD, there is still no single biomarker that can definitively confirm a diagnosis. Instead, researchers emphasize the need to integrate genetic, neurophysiological, neuroimaging, and clinical data to better understand individual differences and develop personalized diagnostic and therapeutic approaches. ADHD thus remains an example of a complex neurodevelopmental disorder that requires an interdisciplinary approach combining neurobiology, psychology, and genetics. [1]

Methods of treating ADHD

The treatment of ADHD in adults necessitates a multifaceted approach, which can be categorized into pharmacological and non-pharmacological interventions. The selection of treatment for patients with ADHD should primarily be based on efficacy concerning functional outcomes, which encompass the reduction of symptoms as well as improvements in daily functioning, interpersonal relationships, and quality of life [6]. Within the realm of pharmacological treatment, psychostimulant medications, such as amphetamine derivatives, are utilized, along with non-stimulant medications, including atomoxetine. Furthermore, off-label medications such as modafinil, as well as antidepressants like venlafaxine, bupropion, desipramine, paroxetine, nomifensine, reboxetine, and duloxetine, may also be employed in the management of ADHD [4].

Non-pharmacological treatment encompasses a range of approaches, including cognitive-behavioral therapy, dialectical behavior therapy, mindfulness-based therapy, hypnotherapy, psychoeducation, neurofeedback, cognitive remediation, as well as other forms of "brain training" and interventions focused on learning skills [4,5].

It is important to note that the guidelines for the treatment of ADHD may vary depending on the country. The majority of scientific research focuses on psychostimulant medications, with numerous guidelines advocating for methylphenidate as the first-line pharmacological treatment for Attention Deficit Hyperactivity Disorder (ADHD). A systematic review conducted by Castells et al. demonstrated that methylphenidate is significantly more effective than placebo in reducing ADHD symptoms, achieving a moderately large effect size in the short term, regardless of the formulation and dosage employed. Among the non-stimulant medications, atomoxetine stands out, as studies on its efficacy have shown a significant reduction in ADHD symptoms compared to placebo. Atomoxetine serves as an alternative for patients who are intolerant to psychostimulants; however, it may induce noradrenergic side effects that must be appropriately considered, and its efficacy in treating symptoms is comparatively lower [4,6].

Pharmacological treatment of ADHD in adults is associated with lower acceptance and poorer tolerance compared to placebo. Retrospective studies indicate a variable level of adherence to therapy within this age group. Meta-analyses suggest that adults are more prone to discontinuation of treatment over extended periods compared to children. Consequently, the implementation of a PRN (pro re nata) regimen is proposed, which entails administering medication only as needed. This approach may contribute to improved treatment adherence, increased patient independence, and a reduction in the risk of adverse effects and treatment costs [4].

Due to the demonstrated efficacy of amphetamine derivatives, they are currently recommended as the first line of treatment according to the "European Consensus on the Diagnosis and Treatment of ADHD in Adults." Prior to initiating pharmacotherapy, it is essential to thoroughly discuss the benefits and potential adverse effects of

available treatment options with each patient. It is also important to emphasize the significance of healthy habits, such as regular physical activity, a balanced diet, and proper sleep hygiene, as well as the presence of other symptoms that may accompany ADHD [6].

Stimulants in the treatment of ADHD

Treatment of Attention Deficit Hyperactivity Disorder (ADHD) offers multiple clinical benefits, including symptom reduction, improved daily functioning, enhanced concentration and academic performance, as well as reduced risk of accidents, injuries, and mood disorders. The most effective pharmacological interventions are central nervous system stimulants, particularly amphetamine derivatives and methylphenidate. Amphetamines exert their effects by increasing the levels of dopamine and norepinephrine through release from presynaptic neurons and inhibition of reuptake, demonstrating slightly greater efficacy than methylphenidate, which only blocks reuptake. Non-stimulant medications such as atomoxetine and guanfacine serve as alternative treatments but are associated with lower clinical efficacy [7].

According to current clinical guidelines, stimulants are considered first-line pharmacological therapy. Their use has increased markedly in developed countries in recent decades. Initial research focused on high-dose stimulant administration in rodents, which induced hyperlocomotion and elevated dopamine levels in the striatum. These findings contributed to hypotheses regarding addiction mechanisms and schizophrenia, with emphasis on sensitization phenomena. However, in individuals with ADHD, stimulants exert the opposite effect—reducing hyperactivity and improving attention. This was long considered paradoxical until studies demonstrated that stimulants also enhance attention in healthy individuals, albeit to a lesser extent. A breakthrough study by Kuczenski and Segal (2002) revealed that low, orally administered doses of methylphenidate—comparable to those used in children—also decreased locomotor activity in young rats, thereby challenging the interspecies difference hypothesis and highlighting the importance of dosing in animal models. The neurobiological basis of ADHD includes dysfunction of the prefrontal cortex, particularly on the right side. Neuroimaging studies show reduced volume of this region, along with abnormalities in the cerebellum and corpus callosum, which correlate with impaired cognitive performance. These alterations have been observed even in individuals never treated with medication, supporting the biological origin of the disorder. Neuropsychological assessments frequently reveal deficits in executive functions—such as response inhibition, cognitive flexibility, and working memory—although some inconsistencies in findings may be attributed to the use of inadequate diagnostic tools. [8,9]

To further understand the effects of stimulants on brain function, an fMRI study was conducted in stimulant-naïve adolescents with ADHD, comparing the effects of methylphenidate to placebo during tasks requiring response inhibition, working

memory, and time estimation. Additionally, a meta-analysis of previous fMRI studies on the acute effects of stimulants was performed. Results showed that methylphenidate significantly increased activation in the inferior frontal cortex (IFC) and insula during response control and time estimation tasks, but had no significant effect on working memory networks. The meta-analysis confirmed that stimulants—especially methylphenidate—most commonly activate the right IFC and insula, and in some cases the putamen. Increased activity in these regions, which are critical for cognitive control, may underlie the clinical efficacy of stimulant medications. [9]

Pharmacoepidemiological studies suggest that ADHD medications offer short-term benefits, such as reducing the risk of injuries and accidents, improving academic outcomes, and lowering the risk of substance use disorders, without increasing the incidence of seizures or suicide attempts. Increasingly, within-subject study designs are employed to limit confounding variables related to treatment initiation. However, long-term outcomes—such as those related to depression, criminal behavior, or psychosis—remain inconclusive and warrant further investigation. Interpretation of such findings is complicated by time-varying confounders and methodological limitations. Therefore, potential benefits of pharmacological treatment must always be weighed against associated risks, including health concerns and societal issues such as misuse or diversion of stimulant medications. [8]

Non-stimulants in the treatment of ADHD

In the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD), non-stimulant pharmacological agents are increasingly being used alongside traditional stimulant medications [11]. The pharmacotherapy of ADHD is based on the use of both stimulant and non-stimulant drugs. These substances exert their effects through complex pharmacokinetic and pharmacodynamic mechanisms, which can lead to therapeutic benefits in improving patient functioning, but may also result in adverse effects that complicate treatment adherence and efficacy [12].

Non-stimulant agents used in ADHD management can be categorized into several pharmacological classes: tricyclic antidepressants, non-tricyclic antidepressants, selective norepinephrine reuptake inhibitors, α2-adrenergic receptor agonists, and so-called off-schedule stimulants that do not belong to classical stimulant groups. Each class has a distinct mechanism of action and efficacy profile, allowing for a more individualized therapeutic approach to symptom management [12, 13].

First-line pharmacological treatment of ADHD typically involves stimulant medications, particularly methylphenidate, followed by amphetamine-based compounds such as dextroamphetamine and lisdexamfetamine. These drugs act by inhibiting dopamine transporters, thereby increasing synaptic concentrations of dopamine and norepinephrine in the central nervous system (Faraone et al., 2018).

When stimulant therapy proves ineffective or poorly tolerated, second-line treatment options include non-stimulant agents, particularly those that act as norepinephrine system agonists. Among the most commonly used are atomoxetine, guanfacine, and clonidine. These medications enhance noradrenergic transmission, and indirectly dopaminergic signaling, particularly in cortical and prefrontal brain regions (Groom & Cortese, 2022) [11,14].

Atomoxetine, a selective norepinephrine reuptake inhibitor, is a non-stimulant option approved for the treatment of ADHD (classified in ICD-10 as a hyperkinetic disorder) in children, adolescents, and adults [15]. It demonstrates efficacy in reducing core symptoms such as inattention, impulsivity, and hyperactivity. Its mechanism involves modulation of noradrenergic neurotransmission, leading to improved executive function without the risk of substance dependence [17]. Atomoxetine's efficacy has been validated in numerous clinical trials, and it is included in international treatment guidelines for ADHD [15].

Additional therapeutic benefit may be provided by α2-adrenergic receptor agonists, such as clonidine and guanfacine. These agents reduce sympathetic nervous system activity and are particularly useful in patients with comorbid symptoms, including sleep disturbances, anxiety, and tic disorders. Their sedative properties can also aid in emotional regulation [17].

Clonidine and guanfacine act centrally as non-stimulant agonists of α2-adrenergic receptors, attenuating noradrenergic activity in the brain. In Poland, only clonidine is currently available and is primarily used to manage mild to moderate tics, as well as an adjunct in ADHD treatment—especially in cases accompanied by sleep disorders or heightened anxiety. Although clonidine is generally less effective in tic reduction compared to antipsychotics, it offers notable benefits due to its sedative, anxiolytic, and hypnotic properties, while also contributing to the reduction of hyperactivity and impulsivity. The most frequently reported adverse effects include somnolence and hypotension [16].

Overall, non-stimulant pharmacological agents represent a valuable alternative in adult ADHD treatment, especially when stimulants are contraindicated, insufficiently effective, or associated with intolerable side effects. Their diverse mechanisms of action and unique safety profiles make them important components of personalized ADHD pharmacotherapy [17].

Comparison of Stimulants and Non-Stimulants in ADHD Treatment

Stimulants and non-stimulants differ fundamentally in their mechanisms of action, therapeutic effectiveness, onset of effects, and side effect profiles, making them suited for distinct clinical scenarios. Stimulants, such as methylphenidate and amphetamines, act directly by increasing dopamine and norepinephrine levels in brain regions like the prefrontal cortex, enhancing attention, impulse control, and executive functioning. This

dual mechanism—blocking reuptake transporters (e.g., dopamine transporter, DAT) and, in the case of amphetamines, promoting neurotransmitter release—accounts for their robust efficacy in reducing ADHD symptoms [21, 22]. Non-stimulants, such as atomoxetine, work indirectly, modulating norepinephrine pathways and secondarily affecting dopamine levels, with a slower onset of therapeutic benefits [20,23].

Research consistently demonstrates that stimulants are more effective than non-stimulants for ADHD symptom control. Meta-analyses show moderate-to-large effect sizes for stimulants, highlighting their superior ability to improve attention, reduce hyperactivity, and enhance overall functioning [18, 19]. Neuroimaging studies confirm that stimulants enhance activation in key regions for cognitive control, such as the inferior frontal gyrus, insula, and putamen, further supporting their efficacy. In contrast, non-stimulants are associated with smaller effect sizes, although they provide significant benefits in areas like emotional regulation and sleep disturbances, especially in patients with comorbid conditions [20].

Side effect profiles are another important differentiating factor. Stimulants often cause side effects such as insomnia, decreased appetite, weight loss, and cardiovascular issues, limiting their use in patients with preexisting heart conditions or significant anxiety [22, 23]. Non-stimulants, while less potent, are generally better tolerated and have fewer cardiovascular side effects, making them safer for long-term use in populations with medical vulnerabilities [20]. Additionally, the abuse potential of stimulants necessitates close monitoring, whereas non-stimulants like atomoxetine and guanfacine present minimal risk of misuse [24].

Another key distinction is the onset of action. Stimulants provide rapid symptom relief, often within hours, making them ideal for acute management. Non-stimulants, on the other hand, typically require several weeks to achieve noticeable effects, which may delay symptom improvement but allow for a steadier and more predictable pharmacodynamic profile [23]. This characteristic can benefit patients who prefer stable, long-term symptom management over rapid but variable responses.

The role of comorbid conditions also informs treatment decisions. Non-stimulants, particularly alpha-2 adrenergic agonists like guanfacine and clonidine, are especially beneficial in patients with ADHD and concurrent anxiety, tics, or sleep disturbances, given their sedative and anxiolytic properties [20, 22]. Stimulants, while effective for core ADHD symptoms, may exacerbate these comorbidities, necessitating alternative options or adjunctive therapies.

In summary, stimulants remain the gold standard for ADHD treatment due to their superior efficacy and rapid onset of action, while non-stimulants provide a safer alternative for individuals with specific contraindications, comorbidities, or concerns about stimulant misuse. The choice between these medications should be individualized, taking into account patient-specific factors such as symptom severity, medical history, and personal preferences. A comprehensive, multimodal treatment plan

combining pharmacological and non-pharmacological interventions often yields the best outcomes [18,24]

Conclusions:

The pharmacological treatment of adult ADHD encompasses both stimulant and non-stimulant medications, each characterized by distinct mechanisms of action, efficacy, and safety profiles. Stimulants, such as methylphenidate and amphetamine derivatives, are considered the first-line therapy due to their ability to enhance dopamine and norepinephrine levels, thereby improving attention regulation, impulse control, and executive function. Methylphenidate primarily acts by inhibiting the reuptake of these neurotransmitters, while amphetamines not only block reuptake but also stimulate their release, contributing to their superior therapeutic effectiveness. Despite their efficacy, stimulants pose potential adverse effects, including insomnia, appetite suppression, elevated blood pressure, and the risk of misuse, necessitating careful monitoring, particularly in patients with cardiovascular conditions or heightened anxiety susceptibility.

Non-stimulants, such as atomoxetine and guanfacine, serve as viable alternatives for individuals who either do not tolerate stimulants or require a treatment with a more stable pharmacokinetic profile and minimal abuse potential. Atomoxetine, a selective norepinephrine reuptake inhibitor, facilitates improved executive functioning and impulse regulation without inducing substance dependence. Guanfacine and clonidine, acting as α2-adrenergic receptor agonists, contribute to symptom management by modulating noradrenergic pathways and attenuating sympathetic nervous system activity. These agents have demonstrated particular utility in addressing comorbid issues, including sleep disturbances and emotional dysregulation. However, their therapeutic onset is generally delayed compared to stimulants, necessitating prolonged administration for optimal clinical benefit.The selection of an appropriate ADHD pharmacotherapy should be guided by individualized patient needs, considering drug tolerability, safety profile, and potential coexisting disorders such as anxiety or sleep disturbances. Neuroimaging studies have provided insights into the neurobiological underpinnings of ADHD, revealing hypoactivation of prefrontal cortical regions implicated in cognitive control. Stimulants have been shown to enhance functional activity in key brain areas, such as the inferior frontal gyrus and insula, which may explain their efficacy in symptom reduction. Nonetheless, in cases where stimulant use is contraindicated or associated with intolerable side effects, non-stimulants offer a valuable alternative for sustained management of ADHD symptoms. Optimizing pharmacological treatment necessitates a comprehensive approach, incorporating continuous monitoring of therapeutic outcomes and individualized adjustments to ensure maximal clinical efficacy and improved patient quality of life.

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