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Treatment Options for ADHD in Adults - a Literature Review

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***Abstract*—** Attention-Deficit/Hyperactivity Disorder (ADHD) is a common neurodevelopmental condition that significantly impacts various aspects of daily life. This literature review examines current treatment options for adults with ADHD. Psychostimulants, including methylphenidate and amphetamines are recommended as first-line therapies. Atomoxetine and bupropion are discussed as effective alternatives, especially in patients with comorbid conditions or with contraindications to stimulants. When considering non-pharmacological approaches, cognitive-behavioral therapy (CBT) is supported by strong evidence. A multimodal, individualized treatment strategy that combines pharmacological and psychological interventions is the most beneficial for adult patients with ADHD.

***Keywords*— ADHD, methylphenidate, amphetamines, stimulants, atomoxetine, bupropion, CBT**

1. Introduction

ADHD (Attention Deficit-Hyperactivity Disorder) is a common neurodevelopmental disorder defined by persistent levels of inattention, disorganization, hyperactivity and impulsivity that interfere with functioning and/or development[1]. ADHD affects approximately 5-8% of children worldwide [2] and was historically a focus of developmental age psychiatry, however, currently is believed to persist in adult life in 15-50% of cases[16]. It is also increasingly recognized in adults that were not diagnosed in childhood and the estimated percentage of affected adult population in 2,5%[3]. The impact of untreated ADHD affects different areas of life, and includes academic difficulties[4], impaired interpersonal relationships, occupational challenges, obesity, diabetes mellitus, increased risk of legal issues, and even premature death due to accidents and suicide [5]. Comorbidity of ADHD with other psychiatric disorders is high (23%), and includes anxiety, affective disorders or substance abuse[6]. As children with ADHD grow older, their quality of life is worse in physical, emotional, and school/work domains to typically developing peers [8]. Taking these factors into account, it is important for the medical professionals to accurately diagnose and treat individuals affected by the disorder, not only children but also adults.

ADHD has been a topic of extensive research in past decades, resulting in a wide choice of treatment options available currently. Pharmacologic treatment options of ADHD include psychostimulants (methylphenidate and amphetamine-based products) and non-stimulant options (such as atomoxetine, modafinil, guanfacine and bupropion). Moreover, there is more and more interest in non-pharmacological approaches. In this literature review, we aim to summarize current treatment modalities for ADHD and their potential in adults.

2. Psychostimulants

Psychostimulants used for treatment of ADHD include methylphenidate and amphetamines (dexamphetamine and lisdexamfetamine).

Methylphenidate acts as a dopamine and noradrenaline re-uptake transporters' inhibitor, therefore increasing the concentrations of these neurotransmitters in the synaptic cleft[10]. Currently, clinicians focus mainly on long-acting, dual-release methylphenidate formulas, with capsules combining immediate-release and extended-release components in varying proportions[9]. The main benefit of these long-acting formulas is the possibility of once-a-day administration, therefore improving compliance, as patients with ADHD may likely forget to take their medication a few times a day. The long-acting methylphenidate is also believed to have smaller potential for misuse, due to non-rapid onset, stable plasma concentration and longer duration [14].

The mechanism of action of amphetamines is similar to methylphenidate, as they also increase dopamine and noradrenaline concentrations at the synapse, however, in addition to the re-uptake inhibition, they are also believed to inhibit the metabolism of these neurotransmitters and increase the release of dopamine in pre-synaptic neurons. Available types are lisdexamphetamine, dexamphetamine (or dextroamphetamine), that can also be mixed in one capsule (so called MAS, mixed amphetamine salts). Lisdexamphetamine is a prodrug, metabolized to dexamphetamine and can be administered once daily. Dexamphetamine and MAS are administered two times a day, or once a day, depending on a formula [16]. Similar to methylphenidate, the long acting formulas offer better compliance and smaller potential for misuse.

Long-lasting stimulants are recommended as a first line treatment in adults in many professional health care association guidelines [6][12][13]. Both methylphenidate and amphetamines have been found effective in reduction of symptoms of ADHD in meta-analyses [11][26][33].

Authors of a large-scale network meta-analysis by Cortese at al. [11] have found amphetamines to have the best efficacy compared to other medications, including methylphenidate, in all populations, in terms of assessment by clinicians and self-reports. Authors of this meta-analysis recommend amphetamines as a first line treatment in adults, as, in this population, amphetamines had the best efficacy among all types of treatment. In adults, amphetamines also had better acceptability than methylphenidate and equal tolerability. Some meta-analyses [16][33] provide evidence that favors lisdexamfetamine over other amphetamines, British guidelines also recommend lisdexamphetamine or methylphenidate as a first line treatment in adults[11]. Taking these things into concern, there is evidence that lisdexamfetamine is the most effective stimulant in treatment of ADHD in adults, however methylphenidate, dexamphetamine and MAS also remain a solid, science-backed up choice.

The most common concern regarding treatment with stimulants is its effect on the cardiovascular system. Both methylphenidate and amphetamines increase blood pressure and heart rate in adults[11][23]. The importance of monitoring hemodynamic values during treatment must be stressed. Stimulants also can contribute to weight loss[11], therefore weight should be monitored in patents. Another common concern of clinicians and the general public is the abuse potential of stimulants. The non-medical use of stimulants is indeed a public health problem [27], especially in patients with dual diagnosis (history of substance abuse, personality disorders, mood and anxiety disorders) [18]. Good practices of caregivers to avoid the misuse of psychostimulants are careful assessment of risk, patient's psychoeducation, coordination between psychiatrist and other specialists (to ensure that the patient does not receive prescriptions from multiple doctors) and secure prescribing practices, such us avoiding prescribing of large quantities and choosing extended release formulation[18]. However, there is evidence that in people with ADHD, treatment leads to less substance abuse. For example, patients taking ADHD medication (stimulant or atomoxetine) prescribed by a physician were less likely to visit an emergency department due to substance intoxication [25].

3. Atomoxetine

Atomoxetine is a non-stimulant, selective norepinephrine reuptake inhibitor (NRI) that is recommended as a second-line treatment for adults with ADHD, particularly for individuals who do not tolerate or respond adequately to stimulant medications [12][13][22]. While some studies have demonstrated that the efficacy of atomoxetine in adults is comparable to methylphenidate [11][19], others have reported it to be less effective than stimulant therapies [26]. In contrast to stimulants, which exhibit therapeutic effects shortly after the initial dose, atomoxetine may require six to eight weeks of continuous treatment to achieve maximal clinical benefit [12]. Additionally, evidence from several studies indicates that atomoxetine may have lower tolerability compared to stimulants [21][11]. However, it has shown potential benefits in patients with comorbid social anxiety disorder [24]. Despite the evidence that suggests that stimulant medications can be used safely in this population when appropriately monitored, some clinicians may prefer atomoxetine for patients with a history of substance use disorders, due to its low potential for abuse. Atomoxetine has also been associated with increases in blood pressure comparable to those observed with stimulant use [11][23], therefore it is important to regularly monitor a patient's haemodynamic parameters during treatment.

4. Other pharmacological treatments

There is not enough data to support the use of guanfacine and clonidine in adults with ADHD, though these substances are used in treatment of children in some countries [11]. Modafinil does not exert a better effect than placebo in mitigating the symptoms of ADHD in adults [33][11]. There is data that suggests bupropion might be an option for some patients with ADHD. Bupropion has been found effective as an antidepressant and as a pharmacological support in smoking cessation. Its mechanism of action is very similar to psychostimulants, involving the re-uptake inhibition of the catecholamines, dopamine and noradrenaline, although strength of this mechanism is much weaker for bupropion [34]. Meta-analyses [11][34] show evidence that bupropion is effective and well tolerated in patients with ADHD, however, it is less effective than stimulants [11]. As bupropion is an antidepressant and the comorbidity of ADHD and depression is high, it is possible that the alleviation of ADHD symptoms observed in studies was actually due to the improvement in affective symptoms [34]. Canadian (CADDRA) guidelines offer this medication as a third-line treatment [13]. Therefore, bupropion is an option for patients that did not respond well to stimulants nor atomoxetine. It can also be considered as a choice in patients struggling primarily with depression.

5. Non-pharmacological interventions

While pharmacological interventions are generally effective, some patients may continue to experience residual symptoms, poorly tolerate the prescribed medications, or prefer to avoid pharmacotherapy. Among many therapeutic modalities, cognitive-behavioral therapy (CBT) has been found effective in reducing symptoms of ADHD [30][31]. Across studies, CBT interventions for ADHD exhibit several consistent characteristics in structure and content. The studied approaches are highly structured and typically begin with psychoeducation, focus on organization and time management, emotional regulation, problem-solving, prosocial behavior, and strategies to enhance attention and manage impulsivity. Patients are also encouraged to practice and apply learned skills in daily life. Moreover, strategies such as the identification of negative automatic thoughts, correction of cognitive distortions, and the application of cognitive restructuring methods are introduced[6]. Studies show that while pharmacotherapy is effective in reducing core symptoms of ADHD (deficits in attention and hyperactivity), they provide only small to moderate results on emotional dysregulation. Emotional dysregulation is defined as an impaired ability to modulate emotional responses in an adaptive way[18] and although it is not currently included in the diagnostic criteria, evidence from clinical, neuroimaging, and genetic research suggests that it constitutes a core feature of ADHD, affecting up to 70% of diagnosed adults[18]. CBT may be especially helpful for patients struggling with this aspect.

There is also data that meditation-based therapies (mindfulness-based cognitive therapy, mindfulness-based stress reduction strategies and yoga) may offer benefits for adults with ADHD, especially in the domain of inattention [32]. However, the evidence quality is limited, therefore, researchers suggest this type of therapy as complement to other interventions.

Neurofeedback does not show meaningful benefits for patients with ADHD and is not recommended. Neurofeedback provided only slight improvement in the processing speed [35].

Studies show that psychological interventions alone are not sufficient enough and the combination of pharmacological and non-pharmacological treatment is most consistently associated with improved long-term outcomes[28][29]. Positive effects of combined treatment was most visible in the domains of self-esteem, social function, academics and driving [28]. Group therapy, often recommended by clinicians, does not outperform individual psychological intervention[29].

6. Conclusion

ADHD is a common condition that can affect many parts of a person’s life, such as work, relationships, and emotional well-being. Stimulant medications, namely methylphenidate and amphetamines are usually the first choice and are effective for many patients. There is evidence suggesting the advantage of amphetamines over methylphenidate for adult patients, however, the choice of medication should always be tailored to the individual. Although the efficacy of other medications is less backed up in evidence, for some patients other medications such as atomoxetine or bupropion may be a good option. However, medication alone is often not enough. The best results usually come from combining pharmacological treatment with psychological therapy, especially cognitive-behavioral therapy (CBT). CBT can help people with ADHD build better habits, manage emotions, and reduce impulsive behavior. This is especially helpful for adults who struggle with emotional dysregulation which is very common in ADHD.

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