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Adult ADHD: A Brief Review

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Case Report

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Abstract

In the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD), the psychiatrist may consider both stimulants and non-stimulant medications; in addition, there are some over the counter substances and adjunct medications that may be helpful in mitigation or resolution of symptoms. Behavioral, environmental and psychosocial approaches should be instituted in association with pharmacology and extra caution and conservatism should be used in patients under the age of 18 years and those diagnosed with Substance Use Disorders or Bipolar Disorder. When making clinical decisions, it is important to consider use of both immediate release and sustained release stimulant preparations, in addition to consideration of first line, second line and adjunct agents. It has been long recognized that the prominent central nervous system neurochemicals intimately involved with ADHD symptoms affect dopamine and/or norepinephrine receptor systems. Many consider ADHD to be largely a childhood condition, although there is evidence for two-thirds of patients to continue to experience symptoms into adulthood.

Keywords: Attention-Deficit/Hyperactivity Disorder; Adhd; Stimulants; Dopamine; Norepinephrine; Adult Adhd; Psychotherapy; Pharmacologic Treatment

Introduction

For treatment of ADHD, stimulants affect dopamine and should be considered first line agents proven to exhibit the highest efficacy in mitigation of symptoms in many patients. Agents that affect dopamine and/or norepinephrine appear to impact ADHD. The Food and Drug Administration approved Atomoxetine and long-acting alpha-2 adrenergic agents for the treatment of ADHD. Other medications such as bupropion and tricyclic antidepressants may be used as off label options for symptoms. In addition, other substances have been studied for their potential to mitigate symptoms.

ADHD has also historically been viewed largely as a childhood disorder; clear evidence exists that symptoms persist into adulthood (or fluctuate) in a majority of patient. The presentation of adult symptoms may vary from childhood, but the challenges in employment, academic, and interpersonal relationships are persistent for the majority of patients. This article serves as a brief review of evaluation and treatment of adult ADHD.

Review of Neurobiology, and Prevalence of ADHD

ADHD is a prevalent neurodevelopmental disorder that has been associated with structural and functional central nervous system aberrations. Neurobiological mechanisms in ADHD are not well understood; there is a clear genetic component in some families. Neurobiological research focused on catecholamine pathways are the main target of research and pharmacologic treatment. ADHD symptoms persist into adulthood in the majority of patients; however, the primary symptoms of concern and their presentation

may change over time.

ADHD is associated with functional impairment and increased risk of depression, substance use, and other psychiatric disorders. Three clear subtypes have been identified (inattentive, primarily hyperactive/impulsive, and combined subtype), and all have a chronic course. Catecholamines are the main targets of pharmacologic treatments; both stimulants and non-stimulants are considered efficacious and are approved by the Food and Drug Administration for treatment of ADHD. The neurobiology research continues to evolve.

Attention Deficit Hyperactivity Disorder is more prevalent in males versus females. Approximately 5.4 million children (~8.4%) have a current diagnosis of ADHD. This includes approximately 2.1% of children ages 2-5 years and 8.9% of school age children ages 6-11 years. Faraone, et al. conducted a global systematic review and meta-analysis and reported that the prevalence of persistent adult ADHD (diagnosed in childhood) and symptomatic adult ADHD (regardless of childhood onset) both decreased with advancing age. It was concluded that the prevalence of persistent adult ADHD from childhood and that of symptomatic adult ADHD were 2.58% and 6.76% in 2020. This represents more than 366 million affected adults globally; that said, ADHD clearly meets criteria to be considered a public health concern.

Clinical Case Vignette: Young Adult with Primary ADHD and Co-Occurring Anxiety

Dr. A welcomes his patient, B, into the office for his follow up appointment for ADHD. B reports that although his attention span, concentration and distractibility have all shown improvement with the stimulant regimen, he not only has residua ADHD symptoms, but also reports anxiety that affects his academic work as well as his relationships. B has recently been as asked to more social functions and began experiencing nervousness within social groups.

Dr. A discusses both first- and second-line ADHD medications and suggests that B continue the stimulant prescription but also add a serotonin norepinephrine reuptake inhibitor to target the residual ADHD symptoms as well as the recently identified anxiety. Dr. A also emphasized that B should continue his weekly psychotherapy to further develop coping strategies and focus on his relationships with new peers at school.

Stimulant Medications

Methylphenidate and amphetamine are common central nervous system stimulants, also known as sympathomimetic amines. These two are the medications of choice for the treatment of ADHD [1]. There are short acting and long-acting options, and issues such as adherence, potential for abuse, diversion, and various side effects should be carefully considered when prescribing. ADHD and the use of stimulants are the most widely published topics in child and adolescent psychiatry. The literature in the area clearly and consistently shows that stimulants are superior in efficacy versus placebo in improving attention span, decreasing impulsivity, and reducing hyperactivity [2,3]. There is solid scientific evidence for the benefit of both short and long-acting formulations. Stimulants undergo metabolism in both the liver and the gastro-intestinal tract, and subsequently excreted by the kidneys.

Clinical Case Vignette: Middle-Aged Adult with ADHD Symptoms, Coronary Artery Disease

C is a 33 y/o male patient diagnosed with ADHD, had searched the internet for information on the stimulant he was prescribed by his psychiatrist. He had a history of cardiac disease diagnosed several years ago. His father and two uncles also suffer with cardiac disease. His psychiatrist provided psychoeducation in the appointment, as well as a detailed informed consent discussion reviewing risks, benefits and alternative options. The psychiatrist explained that stimulants are considered a one first-line treatment option for ADHD. When stimulants are prescribed, they may initially cause a short-term spike in blood pressure; there is also evidence that some patients experience an increased risk of some cardiac-related medical conditions. For patients with documented cardiac illness or risk, a referral to a primary care physician, in addition to screening with ECG and laboratory values should be pursued prior to treatment with stimulants.

Side Effects

Serious cardiac conditions are a contraindication for the use of stimulants. Specifically, Adderall XR is documented to be associated with "serious cardiovascular adverse events and may cause sudden death in patients with pre-existing cardiac structural abnormalities" [4,5]. Children taking stimulants should always be monitored closely for chest pain, pre-syncope, syncope, and shortness of breath. Other contraindications to stimulants include known sensitivity to stimulants and glaucoma. Extra caution should be taken with patients who have history of tics, seizures, autism spectrum disorder, and psychosis. Care should be taken to identify a personal or family history of Bipolar Disorder; stimulants have the ability to induce hypomania and manic episodes in those who are vulnerable. Some patients with ADHD have baseline insomnia, so the medication trial may worsen this condition [4,5].

The most common adverse drug reactions and side effects associated with stimulants include insomnia, loss of appetite, nausea, abdominal pain or cramping, headaches, vomiting, mood lability, irritability, sadness, tearfulness, vital sign alterations such as tachycardia and blood pressure changes. Many of these may present during the initial stages of the trial or with dosage changes, and then may resolve.

Rebound effects may occur approximately five hours after the last dose of short acting agents. Symptoms of ADHD recur after the effects of the medication have worn off. In some patients, it is possible for the symptoms to be more exaggerated during these time periods. The presentation may include excitability, talkativeness, overactivity, insomnia, gastrointestinal upset and mild nausea. These symptoms are typically less pronounced with the use of long-acting agents, but still may occur approximately 8-12 hours following the last dose.

Alternate Treatments and over the Counter Options

- **Caffeine**

Caffeine is a mild stimulant with minimal evidence of treating frontal lobe function deficits. There is no evidence in the relevant literature that caffeine is therapeutically useful in the treatment of ADHD.

- **Amantadine Hydrochloride**

Amantadine has been known for its efficacy in the treatment of sequelae of brain injuries including disinhibition, behavioral dysregulation and agitation [6-12]. This may be the result of a direct or indirect effect on the central dopamine system. Amantadine is a water-soluble acid salt that is FDA-approved for the treatment of influenza A and for Parkinson's disease. It is also used for extrapyramidal side effects of antipsychotics, pseudo-parkinsonism, akathisia, and neuroleptic malignant syndrome.

It may be helpful for patients who are status/post traumatic brain injury and/or have moderate to severe intellectual disability and present with behavioral dysregulation and impulsivity. For patients with symptoms of agitation and aggression during coma-recovery treatment, amantadine may be helpful for disinhibition, behavioral instability, abulia, and hypo arousal, especially in the first several months of the recovery period. Amantadine should not be discontinued abruptly if neuroleptics are co-administered because patients are at high risk of catatonia and neuroleptic malignant syndrome.

- **Omega-3 Fatty Acids**

Liririnen (Vayarin) is a prescription medical food that contains phosphatidylserine omega-3 and can be used for dietary management of ADHD. (13) There is a possible connection between ADHD and low levels of omega-3 fatty acids. Omega-3 fatty acids are well tolerated, and no known serious side effects or adverse reactions have been identified. They have been studied in the treatment of many psychiatric disorders, including ADHD. Bozzatello, et al. [13] reviewed data from clinical trials, systematic reviews, and meta-analysis published between 1980 and 2015. They concluded that overall efficacy is lacking. Although it holds some promise, there is inconsistency among the existing literature regarding methods, dosing and formulation. More research is needed.

- **Vitamin D**

Vitamin D is a natural compound that has a relationship with ADHD that is unclear but requires further investigation. Khoshbakht, et al. [13] found in a meta-analysis that there is a possible connection between the disorder and Vitamin D levels. Children with ADHD had lower serum concentrations of 25-hydroxyvitamin D compared to their healthy child counterparts [14]. It is possible that perinatal suboptimal Vitamin D concentrations were significantly associated with a higher risk of ADHD in adult years. Although more research is required, some parents decide to add this over-the-counter option as the potential benefits outweigh the risks.

Substance Use Disorders and Co-Occurring ADHD

A meta-analysis found that ADHD was associated with a more than twofold greater odds of alcohol-use disorders (13 studies, over 20,000 participants) and nicotine-related disorder (14 studies, over 1,800 participants). A Swedish study of over half a million people found a more than threefold association between ADHD and subsequent Substance Use Disorders after adjusting for sex and parental education.

Extra caution must be used in patients diagnosed with ADHD and substance use disorders. Tolerance and physiological dependence are possible when stimulants are used chronically and in an abusive fashion. A thorough and systematic informed consent discussion reviewing the risks, benefits and potential side effects is necessary prior to and throughout the prescribing process. For patients with the diagnosis of ADHD, the appropriate prescription of stimulants may prevent patients from using illegal substances due to effective treatment of impulsivity, elimination of the need to self-medicate, the reduced risk of depression and anxiety symptoms. Some parents and guardians may ask about the risk of future substance use in children prescribed stimulants, but there is no scientific literature showing that this subgroup is at greater risk than controls [1,2].

Non-Stimulant Medications for the Treatment of ADHD

- **Selective Norepinephrine Reuptake Inhibitors (SNRIs)**

Atomoxetine Hydrochloride (Strattera) is an SNRI that selectively inhibits the presynaptic norepinephrine transporter [8]. It is thought that this is the mechanism that treats ADHD symptoms. Atomoxetine was approved by the FDA for the treatment of ADHD in 2002, and it remains one of the few non-stimulant medications approved for this specific diagnosis. By contrast to the rapid quieting of symptoms by stimulants, Strattera will take longer to achieve results.

Some patients do not tolerate stimulants, and others are not reasonable candidates due to abuse or risk of diversion (by either the patient, other family members, or alternate caregivers). Atomoxetine may be a good option for patients with co-occurring ADHD and tics or anxiety disorders. Another circumstance to consider an atomoxetine trial is when patients fail trials of stimulants. Atomoxetine carries a Black Box Warning from the FDA and therefore all patients being prescribed this agent should be carefully monitored for suicidal thoughts, suicidal behavior, clinical worsening, and any other unusual changes in behavior.

- **Alpha-Adrenergic Agonists**

The dopamine system is understood to be involved in executive functioning with regard to frontal lobe activity, but the norepinephrine system in some individuals diagnosed with ADHD appears to be related to behavioral and cognitive abnormalities [9,10]. Clonidine is a centrally acting antihypertensive agent. The only formulation with a pediatric indication for ADHD is clonidine hydrochloride extended release; this agent may be used as monotherapy and also as an adjunct to stimulants. IR Clonidine has been approved for use in the treatment of hypertension in older adolescents and adults. Studies are not available to prove the safety in children, but this agent is often prescribed off-label for the treatment of ADHD, anxiety, insomnia, tics, and aggression.

Clonidine is an alpha-2-adrenergic receptor agonist whose action is independent of norepinephrine levels. The three types of subtypes of alpha-2 receptors are 2A, 2B, and 2C. The 2A and 2C subtypes are both widely distributed throughout the central nervous system, including the prefrontal cortex. It is possible that alpha-2 agonists improve attention and behavior through direct stimulation of postsynaptic alpha-2A adrenoceptors. Alpha-2 agonists also bind to alpha-2B and alpha-2C receptors. All three subtypes are associated with sedation; hypotensive effects are related to subtype 2C. Clonidine binds to all three subtypes with some equanimity whereas guanfacine appears to be 15-20 times more selective for the alpha-2A-receptor subtype [10,11]. The most common side effects of clonidine include: sedation, irritability, sore throat, insomnia, nightmares, mood changes, constipation, stuffy nose, increased body temperature, dry mouth, hypotension and decreased pulse rate.

Other Non-Food and Drug Administration Approved Medications

Many non-medical treatments have been proposed for ADHD. Most of those offered on the Internet have not been tested or have been shown not to be effective. In this section, we distinguish between the effects of a treatment for ADHD symptoms and other benefits it may confer. Due to the way these therapies are implemented and recorded in the medical record; large scale naturalistic studies of longer-term outcomes are not possible.

- **Bupropion**

Bupropion (Wellbutrin, Wellbutrin SR, Wellbutrin XL) holds FDA approval for Major Depressive Disorder for adults, but it also used off label for this disorder and for ADHD in children and adolescents [11]. Bupropion is a norepinephrine-dopamine reuptake inhibitor and a nicotinic receptor antagonist. When prescribing for ADHD, it may be used as a sole agent or as an adjunct with other ADHD psychotropic medications. The decrease or resolution of ADHD symptoms may take weeks with the use of bupropion, and it also has a black box warning for suicidal ideation so this must be carefully discussed in the informed consent process. Of note, bupropion has several important contraindications, including anorexia, bulimia, and seizure disorders.

- **Tricyclic Antidepressants**

Tricyclic antidepressants (including amitriptyline, imipramine and nortriptyline) affect multiple receptor systems and therefore may improve conditions and disorders including but not limited to depression, anxiety, insomnia, ADHD, nocturnal enuresis, abdominal pain and headache prophylaxis [11,12]. Because TCAs affect many receptor systems, there is increased risk of side effects. Anticholinergic side effects are fairly common, and serious side effects include seizure activity, coma, and death (as in overdose). There is also a black box warning regarding suicidal ideas; this class of medications is rarely prescribed in the child and adolescent patient population.

- **Modafinil**

Narcolepsy medications include modafinil (Provigil), but Provigil may also be prescribed for shift-work sleep disorder and obstructive sleep apnea. It has also been used off label as an adjunct agent for ADHD symptoms.

Summary

Stimulants are considered first line agents in the treatment of Attention Deficit Hyperactivity Disorder. Non-stimulant medications are also another option for this symptom set. There are both immediate release and sustained release preparations, and these options should be carefully considered with regard to adherence, scheduling, tolerability, efficacy, among other factors. Agents that modulate dopamine and/or norepinephrine appear to improve or resolve the symptoms of ADHD. When only partial symptom relief is attained, second line agents and adjunct agents should be considered. Off-label, Over the counter and novel agents may be considered in treatment refractory patients. Under all circumstances, behavioral, environmental and psycho-social approaches should be instituted in association with pharmacology and extra caution and conservatism should be used in patients under the age of 18 years as well as those with co-occurring Substance Use Disorders and/or Bipolar Disorder. Because ADHD is still viewed by some as a condition of childhood, more attention is needed to study effective treatment of adult ADHD.

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