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Review Article

Attension Deficit/Hyperactivity Disorder (ADHD)- Signs and Symptoms, Diagnosis, Latest Management

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ABSTRACT

Background: Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by persistent inattention, hyperactivity and impulsivity. It affects millions of children, adults globally every year. ICD-11 guidelines state that ADHD onset begins before 12-years age and often persists in the adulthood. This is a review article which focuses mainly on ADHD symptoms and differentiates between child and adulthood symptoms. The 3 main symptoms of ADHD are inattentiveness, hyperactive-impulse symptoms and combined symptoms. Knowing the different symptoms in both the adults and children help in understanding the treatment options also. Managing ADHD is needed to improve the quality of life of effected patients, this article provides a brief therapeutic management and Simtriyo is the recently approved new drug for ADHD treatment in adults and pediatrics. This new drug approval helps to increase the treatment options. Although, not well-known , but the use of EndeavorRX, a video game for treating ADHD can also improve the symptoms. Managing ADHD: it includes both pharmacological and non-pharmacological treatments. Pharmacotherapy includes stimulants such as methylphenidate, amphetamines and non -stimulants such as atomoxetine, viloxazine, alpha-2 agonist (clonidine, guanfacine). Recently Centanafadine (Simtriyo) has been approved by FDA. Centanafadine is a norepinephrine, dopamine, serotonin reuptake inhibitors which helps in decreasing the symptoms. Non- pharmacological approaches are neurofeedback, dietary supplements, behavioral therapy.

INTRODUCTION

Attention deficit/hyperactivity Disorder (ADHD) is a neurodevelopmental disorder, characterized by impaired attention and or hyperactivity. This condition was also referred to as ‘minimal brain function’, since it was assumed to be related to brain. [1]. ADHD affects millions of children and adults worldwide [2]

ADHD affects the children in many areas, such as academics, mental health, disciplinary problems and adults

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may suffer with job related problems, attention disorder [2]. Approximately, 5.41% children and adolescents are being affected by ADHD globally every year. The symptoms usually begin at childhood and modify until adulthood affecting the social, academic and vocational outcomes [3].

International Classification of Diseases (ICD) classification system categorizes ADHD as "hyperkinetic disorder", ICD-10 says ADHD diagnosis requires the onset of symptoms before the age of 6 years. however, ICD -11 extends the age limit to 12 years [4].

Signs and symptoms

There are three main types of symptoms-

1. Hyperactive – impulsive symptoms- in which a person has impulsivity and hyperactivity (Hyperactivity means the condition of being restless and finding hard to sit still, moving very often, Impulsivity means acting without thinking, interruptions, finding hard to wait), other symptoms are fidgeting, talking nonstop and interrupting in between, reacting without thinking much, fight with parents or friends when they wish to do something.
2. Inattentive symptoms- in which a person is easily distracted and is not hyperactive (Inattentive means facing troubles, forgetfulness, disorganized). It also includes difficulty organizing things and self-activities; decreased attention, trouble in remembering things, easy distractions and day-dreaming, difficulty in findings things.
3. Combined symptoms- a mixture of both hyperactivity and inattentiveness [5].

Children are mainly diagnosed through noticing the following symptoms -

- high levels of depression, anxiety before the age of 12.
- Children with intellectual disabilities are identified with likely onset of ADHD symptoms at an early onset [6].
- Skipping the exam or test questions
- not understanding the test assignment
- difficulty in attending the lectures
- getting distracted easily during study hours
- forgetting the present tasks
- increased efforts in completing the tasks in the house
- staring at objects, leaving the present work
- struggling to follow multi-step process and instructions
- Unaware of their living surroundings and lost in their own world
- Increased daydreaming
- Struggle to remain seated for prolonged time i.e. "driven by a motor" like symptoms

Adults present with these symptoms-

- Hyperfocus i.e. Excessive overconcentration
- attention deficit,
- dysregulation.
- Increased outbursts of anger, irritation.
- Executive dysfunction
- Frequent changes in job areas
- Doing mistakes carelessly
- Mistakenly replacing the items such as keys, glasses etc
- Sometimes, superior self-care
- Difficulty in completing lengthy tasks both in home and in office
- Feeling of "driven by within like feeling"
- Persistent feeling of internal restlessness
- Difficulty managing the frustration signs
- Sleep disturbances due to restlessness [7,8,9,10]

Racing thoughts, that is, an increased overproduction of thoughts with increased speed is a sign of ADHD. Hyperactivity was found in relation with rumination and racing thoughts in both adults and children [11].

According to ICD-11 ADHD can be diagnosed by following criteria-

- Persistent pattern of inattention symptoms and/or combination of impulsivity-hyperactivity symptoms.

- Evidence of the symptoms before 12 years, although some individuals may present with clinical attention late in adolescence, in adults.
- Appearance of the symptoms across various multiple situations.
- The appearance of symptoms are not due to the effects of substance abuse (cocaine) or due to medication use (bronchodilators, drugs affecting CNS) and not because of any central nervous system disorders [7].

Risk factors

Increased inflammation during pregnancy was associated with increased risk of child to develop ADHD and only when there is less maternal sensitivity with the child [12]. Increased inflammation during mid- pregnancy with effects on maternal adiposity poses an increased effect on child's ADHD symptoms [13].

Use of social media for longer periods was associated with increased inattention symptoms. This social media includes the use of facebook, twitter and others for approximately 0.5hr/day at 9 years age to 2.5 hours/day at 13 years was associated with increased risk to develop ADHD. Even mere presence of a mobile phone nearby, without using it can cause increased inattention to current activities. IN contrast, playing video games for a shorter time can improve the cognitive function of the child [14].

Functional difficulties such as emotional dysregulation, executive functioning deficits, social or academic challenges among parents is indirectly causing parental stress which were related to development of ADHD symptoms in children. Children with their parents having ADHD are more likely to exhibit elevated symptoms than with children with no parental symptoms [15]. Disorganized and unpredictable parenting was associated with increased risk of developing ADHD in children [16].

Consumption of poor-quality carbohydrates such as sugary beverages, candies or sweet dietary patterns, junk foods, red meat processed meat, refined cereals, hydrogenated fats were positively associated with ADHD symptoms. Less adherence to healthy- dietary patterns, decreased exposure to vitamin-D can increase the risk of developing ADHD. High glycemic exposure could plausibly influence the attention and executive function and its regulation [17,18]. Higher craving for alcohol, greater willingness to drive after alcohol consumption were seen in adults and among college going students suffering with ADHD [19].

Management of ADHD

Drug therapy

The two types of drug classes are stimulants and non-stimulant drugs, which are as follows

Stimulant drugs-

All of the stimulant drugs belong to the class of sympathomimetic agents, with similar chemical and physiological properties. These drugs work by acting on the central nervous systemand increases the noradrenaline and dopamine levels in prefrontal cortex. These drugs also activate the adrenergic receptors in the cardiac system (heart and the blood vessel) and increases the blood pressure and also heart rate, increasing the risk of cardiovascular side effects and complications [20].

Methylphenidate

It works by inhibiting the presynaptic dopamine transporters of the central adrenergic neurons, and also inhibits the norepinephrine transporters to a lesser extent [21]. AAP recommends the use of methylphenidate, after the behavioral therapy in preschool children. Azstarys (brand name) capsules contain serdexmethylphenidate and dexmethylphenidate in a fixed 30/70 % molar ratio. This combination provides extended drug release for up-to 13 hours in which serdexmethylphenidate undergoes biotransformation in the lower GIT and allows conversion to dexmethylphenidate, owing to its extended action [22].

Amphetamine

It is a competitive inhibitor of dopamine, amplifies the dopaminergic neurotransmitters and also binds to norepinephrine transporter binding sites as pseudo-substrate. Side effects include decreased appetite, nausea, sleeping difficulties, increased blood pressure, psychosis [21,23].

NICE prescribes amphetamines as second- line agents, whereas AAP prefers it as first line drug. Xelstrym (brand name) with dexamphetamine as the primary drug was approved in March, 2022 by FDA. It was studied in children with ADHD of less than 6 years of age. Xelstym is available as transdermal patch, which should be applied before 2 hours of anticipated action and removed after 9 hours. Side effects of this Xelstrym included weight loss, decreased hunger, insomnia, headache [22].

Side effects of Stimulant drugs-

Majorly, these drugs cause cardiovascular complications due to their effects directly on the heart and the blood vessels.

Approximately, 1 in 600 patients develop new – onset of psychosis.

Gastrointestinal complications include- heartburn, indigestion, decreased appetite, delay in gastric emptying, constipation and bloating.

Ocular system side effects include- pupil dilation, changes in intraocular pressure, dry eyes.

Decreased growth was also seen in patients taking these drugs [20].

Non-stimulant drugs

Atomoxetine

A non- stimulant drug for ADHD. It selectively inhibits norepinephrine reuptake at the presynaptic region. Dose is 60mg/day for 4 weeks and is discontinued due to gastrointestinal symptoms, irritability [24]. Adverse events included sleep disturbances, irritability [25].

Viloxazine

It is a selective norepinephrine reuptake inhibitor approved by FDA in April 2021 for use in kids and adolescents [26]. By unknown mechanism, Viloxazine helps in increasing 5- Hydroxy tryptamine (5-HT) levels, act as antidepressant and thereby decreases ADHD symptoms [27]. Side effects observed during the clinical trials were headache, decreased appetite, somnolence, increased psychiatric adverse events[28].

Alpha-2 agonists

Alpha agonists such as guanfacine and clonidine are used to improve the symptoms of ADHD, mainly in children [29]. These agents were used to decrease the aggressiveness, outbursts of temper, and other features [30]. These agonists work by stimulating alpha-2-adrenergic receptors at the post synaptic region. Guanfacine, a potent alpha-2A receptor agonist, mimics the nor-epinephrine action [31]. Monitor for hypotension, syncope, sedation, dry mouth and others as side-effects [22]. The drugs can be used in combination with stimulant drugs for enhanced efficacy [26].

Cholinergic agents and nicotine showed a short-term effect on decreasing the symptoms [30]. Dysregulation of cholinergic system has some evidence in the development of ADHD. Therefore, Pharmacological enhancement of the cholinergic system can improve the cognitive functions of ADHD [31].

General side effects of non-stimulant drugs

Headache, sleep disorders, decreased appetite, psychosis, dry mouth, increased irritation and other effects.

Centanafadine [recently approved drug]

In a Phase 3 randomized, placebo-controlled studies conducted to evaluate the safety and efficacy of Centanafadine in adults, 200 and 400mg/day showed a significant statistical improvement in inattentiveness and hyperactivity-impulsivity symptoms of ADHD [32].

Centanafadine with brand name as Simtriyo is the first norepinephrine dopamine and serotonin reuptake inhibitor (NDSRI) and also a central nervous system stimulant drug which has received USFDA approval for treating ADHD in adults and pediatric patients of age 6 years and older patients [33]. Simtriyo works by increasing the bioavailability of norepinephrine, dopamine, serotonin neurotransmitter pathways which are involved in attention and behavioral regulation [34]. During the trials, centanafadine was well tolerated, with common adverse events such as headache, insomnia, dry mouth, fatigue, rashes, irritability [35].

Non pharmacological approach for ADHD

Neurofeedback

It helps in improving ADHD symptoms by training the people to self-regulate the neural activity through real time feedback, mostly by assessing EEG [24]. Neurofeedback is used as a tool to normalize the brain activity and treat ADHD. It also helps in developing the relations between the oscillatory and cognitive functions of brain [36].

Physical exercise

Mild to moderate exercises can be beneficial in improving the symptoms [24]. Moderate-intensity aerobic exercise can help in improving executive function in ADHD. Exercise can help in promoting increased secretion of Dopamine, norepinephrine, thereby improving the executive functions in children [37]. Martial arts, team sports can promote behavioral control. Physical activity can be helpful in improving sleep quality, self-esteem [38].

Diet and supplements

Omega-3-fatty acids, vitamin supplements and a balanced diet can improve the symptoms [24]. Micronutrients such as iron and zinc as supplements can be helpful, which can improve the efficacy of stimulant drugs [26]. Consuming vegetables, fruits, fishes, foods rich in poly unsaturated fatty acids (PUFA) can decrease the risk of developing ADHD by 37% [18].

Behavioral therapy

Behavioral therapy is one such approach which helps in managing ADHD, along-side with the drug use. Educating the children in the classroom, providing rehabilitation plan during classroom hours has improved the symptoms in children [22]. Caregivers should identify the problematic behavior in children and delimit the child from doing unwanted things. Encourage quality friendships in schools and in the neighborhood. Biofeedback which uses sensors to detect biological activities such as heart rate, breathing and sends the real-time information to the computer systems. It can help in managing the symptoms by evaluating the symptoms on real time basis [39]. The study results published in an article, states that meta cognitive therapy can provide significant benefit to patients (mainly adults), with respect to inattentive symptoms [40].

Digital therapeutics that is the use of video games to manage the symptoms and improve cognitive functions has found to be helpful, these games improved the attention, memory, motor ability and increased cognitive flexibility. EndeavorRx was approved by FDA in 2020, which was the first game- based model receiving FDA approval for symptomatic treatment in children under 12 years of age, but only up-to a limit [22].

CONCLUSION

ADHD is a complex, neurodevelopmental disease requiring proper diagnosis, treatment. Understanding about the recognizable signs and symptoms, risk factors can help in early detection and diagnosis of ADHD. Individuals with ADHD need understanding, support and the right pathway to survive, continuing the education about ADHD is needed in this process. Although, males and females are both affected, males experience ADHD at an early age than females because of differences in maturity levels in both genders. Being cautious right from the pregnancy till the child-birth and also during the growth of child can help prevent the ADHD. Neglecting the behavior patterns during early childhood can delay the proper diagnosis, and there is a significant role played by the care-givers in a child who develops ADHD. Use of digital media for a prolonged time can also increase the risk, with direct effects in the brain by abnormal release of neurotransmitters such as noradrenaline and dopamine. In this modern era with a complex-dietary habits, increased carbohydrate intake of poor quality is changing the behavioral patterns among children and adults, so there is a need to change these dietary habits and include iron and other supplements in individuals with ADHD.

Managing ADHD with medications is necessary to prevent the further complications, if left untreated. While traditional medications such as methylphenidate, amphetamines, atomoxetine and others remain as standard drugs, recently approved Centanafadine (Simtriyo) expands the medication options for patients who cannot tolerate or in patients experiencing adverse events with

conventional therapies. Although, every drug has its side-effects, considering the benefit-risk ratio, using these drugs is necessary.Besides pharmacological therapy, there is an availability of non-pharmacological approaches to manage ADHD, which includes neurofeedback, physical activity, behavioral therapy.

For an overall well-being of the patient suffering from ADHD, knowing the early symptoms, diagnosis, management- both pharmacological and non- pharmacological treatment is needed.

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