

**Review on recent challenges of Diagnosis and treatment of Attention Deficit
Hyperactivity disorder (ADHD)**

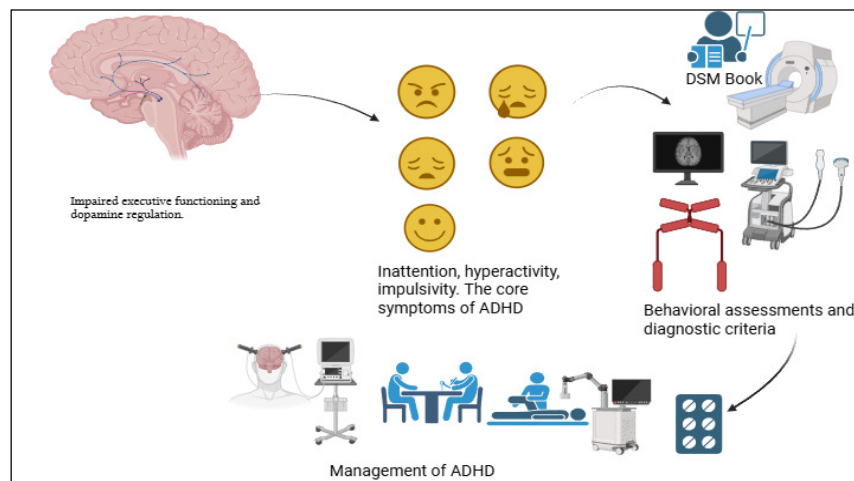
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Abstract

Attention Deficit Hyperactivity Disorder (ADHD) is a psychiatric condition marked by hyperness, impulsive and inattention. Being caused by a deficiency of the neurotransmitter dopamine. Although it can be challenging to diagnose and treat, new diagnostic tools, such as objective behavioral assessments and sophisticated neuroimaging methods, are being investigated to improve the accuracy of ADHD diagnoses. Furthermore, the development of more focused and individualized diagnostic techniques is being aided by an increasing comprehension of the genetic and neurological foundations of ADHD. The purpose of this review is to examine current issues and developments in the identification and treatment of ADHD to overcome problems faced during diagnosis. Understanding the heterogeneity of ADHD better could result in more individualized treatment plans that incorporate lifestyle, pharmacological, and therapeutic interventions. In terms of treatment, current research is producing novel pharmacological interventions, such as the introduction of new drugs and formulations with enhanced potency and reduced adverse effects. The profession is also observing a persistent focus on customized therapy regimens that acknowledge the distinct requirements and reactions of every patient. Additionally, the integration of digital technology is improving remote monitoring and support for individuals with ADHD and increasing access to care through the use of telehealth and mobile applications. These developments could lead to more accurate diagnoses of ADHD, more individualized treatment plans, and the creation of a more accepting and encouraging atmosphere for people with ADHD.

Keywords: ADHD, Diagnostic tools, Dopamine, Tele-health, Formulations



The Graphical Abstract

1. Introduction

As the second most frequent chronic illness in children, attention-deficit/hyperactivity disorder (ADHD) is the most common behavioral problem. It is still one of the most well-researched, contentious, and chronic disorders. It is now acknowledged as a lifetime disorder. Understanding the background and current standards of care with ADHD is crucial for reading and using the updated guidelines [1]. Over the past few decades, the prevalence of Attention-Deficit/Hyperactivity Disorder (ADHD), one of the widespread neurobehavioral dysfunction in children, has been steadily rising worldwide [2]. Regarding the prevalence rate of ADHD in kids and teenagers, there is currently no consensus. A comprehensive meta-analysis revealed that the best-estimated prevalence rate of studies utilizing case definitions was 1.4% (range: 1.1–3.1), despite meta-regression analyses placing the rate at 5.29% [3] and 7.1% [4] worldwide [5]. Children's and their families' general quality of life and functioning could be greatly enhanced by early identification and efficient management. Child psychologists and other medical specialists, such as the American Academy of Pediatrics, recommend screening for the disease as early as preschool [6] to allow affected children to receive prompt treatment and reach their full potential both at home and in school [7]. Furthermore, several characteristics unique to childhood or adolescence, such as gender, age, race, socioeconomic situation, and the severity of symptoms, may influence the diagnosis of ADHD [8,9]. Parents are crucial in identifying behavioral issues in their children at an early age, as well as in their view, knowledge, and acceptance of the disease as well as their decision to bring the child to a specialist [10].

Parents must have access to expert care when they choose to ask for help.

Parents must have access to expert care when they choose to ask for an accurate diagnosis as soon as possible and the best possible treatment plans. Despite the existence of an operationalized psychodynamic diagnostic method, there is currently no objective test and much debate surrounds the difficulty of accurately diagnosing patients [11,12,13]. The primary goals of this review paper were to examine current issues and the early identification and treatment of ADHD.

2. Symptoms

ADHD is a chronic, early-emerging condition typified by impulsivity and hyperactivity/inattention can cause significant impairment in a variety of contexts. Inattention and hyperactivity/impulsivity are often strong at this early developmental stage, but there is also significant variation in children's trajectories [14]. Especially before the age of seven years old, there are signs of impulsivity/hyperactivity and inattention, which greatly hinder functioning both at home and at school (American Psychiatric Association 2000). The same criteria must be met for an adult ADHD diagnosis made using the DSM-IV-TR (American Psychiatric Association 2000). However, adult ADHD symptoms can take many other forms. While attention impairments can appear as a lack of focus on specifics, forgetting appointments, and an inability to plan and organize work and activities, adult ADHD symptoms can show as restlessness, difficulties relaxing, and dysphoria. Disorganization, which is defined by incomplete tasks and ineffective time management, may exacerbate this. Depression and irritability are prominent examples of mood symptoms (Wender 1995; Asherson et al. 2007).

Boys and females experience ADHD symptoms in different ways. ADHD-Inattentive (ADHD-I), which manifests as distraction, disorganization, and forgetfulness, is more commonly diagnosed in girls [15]. ADHD-Hyperactivity/Impulsivity (ADHD-HI), a medical condition that involves increased levels of aggression, impulsivity, and irritability, is more common in boys than in girls [16]. Due to these symptoms, which are often more disruptive in the classroom, boys have been reported to be more susceptible than girls to be referred for examination. Seventy-two percent of the children in the research who had a clinical diagnosis of ADHD were boys. 12.9% more people who did not have an official diagnosis of ADHD reported symptoms that were consistent with the disorder. There were differences in diagnostic rates and criteria by gender, with 36% of these extra undiagnosed participants being girls and 64% being boys [17]. In girls compared to boys, externalizing behaviors are a better indicator of diagnosis. females who exhibit notable externalizing behaviors are more likely than those

who exhibit internalizing symptoms to be diagnosed, indicating that females may be more prone to go overlooked during the diagnostic process if they do not demonstrate noticeable externalizing behaviors [18].

Consequently, it is currently thought that ADHD is a neurodevelopmental condition. decreases in frontal, temporal, and parietal areas' gray matter, surface area, and cortical thickness; limbic areas like the amygdala and hippocampus; and reduced Gray matter in subcortical regions, most notably the basal ganglia, and insula, have all been found in meta- and mega-analyses of structural volumetric studies in ADHD. Moreover, there is proof that the frontal, temporal, and parietal regions exhibit a delayed peak of cortical thickness and surface area maturation. The condition has also been shown to damage white matter tracts, including the Fronto-striatal, Fronto-cerebellar, interhemispheric, and long-distance front-occipital tracts [19].

3. Epidemiology of ADHD

All age groups combined (children, adolescents, and adults) did not have a single nationwide prevalence estimate supplied by any of the included studies. One study, however, offered an aggregate estimate of 2.9% for all provinces, spanning a broad age range of 20 to 64 years of age and gender [20].

3.1 Age group

According to the one study that gave an estimate for children alone (ages 3 to 9), the incidence of ADHD varies by province, with preschoolers having an approximate frequency of 1.1% and school-aged children having an approximate prevalence of 4.1% [21]. The estimated prevalence of ADHD in children and adolescents as a whole varied from 2.6% [22] to 8.6% according to the research that offered such data. Of these studies, only one offered an overall estimate of 8.6% for the provinces of Alberta, Manitoba, Newfoundland, Ontario, and Quebec [23]. Estimates of the prevalence of ADHD in adults in Canada [24,25,26,27] were found in research, with results varying from 2.7% or 2.9% (across all provinces) to 7.3% (across five provinces). According to one study, the prevalence of ADHD was estimated differently for young adults (18–34 years old, or 7.3%) and older adults (35–64 years old, or 5.5%) [23]. Table1 below provides a typical percentage breakdown of the prevalence of ADHD by age group.

Table 1 Prevalence of ADHD [Age Group]

Age	Percentage Case found	Age group
3-9yrs	1.1 %	Preschoolers
3-9yrs	4.1 %	School-aged children
14-18yrs	2.6% - 8.6%	Adolescents
18-65	2.9% - 7.3%	Adults
18-34	7.3%	Young Adults

3.2 Gender

It is estimated that males are roughly twice as likely as females to have ADHD [28]. The range of estimates for men is 3.7% to 13.3% [29]. Female estimates vary from 1.5% to 7.0%. According to three studies, the gender disparity continues throughout adulthood. Elderly male estimates range between 5.8% and 10.3%, whereas adult female estimates range between 2.6% and 6.5% [30]. The average incidence of ADHD by gender group is often described in percentage form in Table 2 below.

Table 2 Gender group prevalence

Gender	Case found
Male	3.7%- 13.3%
Female	1.5% - 7.0%
Adult	5.8%- 10.3%
Adult Female	2.6%- 6.5%

According to data released by the National Centre for Health Statistics (NCHS) in 2015, 15% of children in the United States between the ages of 3 and 17 are thought to be impacted by neurodevelopmental disorders (NDDs) [31].

4. Related factors of ADHD in the environment

Factors that occur before, during, and after pregnancy, such as low birth weight and preterm, stressful events experienced by the mother, or other maternal health concerns [32] are the most commonly linked environmental variables that have been hypothesized as risk factors predisposing to ADHD. Pregnancy-related and early childhood exposure to alcohol [33],

tobacco [34], drugs [35,36,37], and other materials like manganese and lead [38] has been shown to have a significant impact on the risk of ADHD. Dietary habits and nutritional factors have also been identified as potential determinants of susceptibility to ADHD across the lifetime [39, 40, 41]. Psychosocial circumstances like inadequate income, unfriendly parental care, and life traumas are additional risk factors for ADHD. It's crucial to keep in mind, nevertheless, that these variables may have a greater impact on prognostic course modifications than on the disorder's underlying etiology [42].

For instance, genetic or familial variables may complicate maternal-related risk factors. However, other biological alterations brought on by environmental exposures can also occur, like DNA methylation, which has been connected to ADHD and is a reversible change in genomic activity independent of DNA sequence [43,44].

5. Variations in neurotransmission in ADHD

Dysregulation of monoaminergic neurotransmission systems, primarily dopaminergic and noradrenergic, has long been considered a potential pathophysiological mechanism associated with ADHD. These neurotransmitters operate by a process that resembles a "inverted U" curve; that is, both extremely high activity (such as in stressful situations) and extremely low activity (such as in sleepy states) hinder the operation of these systems [45].

Dopamine and norepinephrine binding to their respective receptors causes physiological changes that include the regulation of certain cognitive and executive functions that are typically compromised in ADHD, supporting the pathophysiology of the disorder as being primarily monoaminergic [46]. For instance, the brain regions primarily involved in signaling. There are many dopamine receptors of subtypes D1 and D2 in reward circuits, learning and memory, and locomotor activity. Also responsible for reabsorbing dopamine into presynaptic neurons is the dopamine transporter (DAT), is more densely expressed in ADHD individuals [47]. This could change the amount of dopamine in the synaptic cleft. Working memory processes have been demonstrated to be influenced by norepinephrine's binding to adrenergic receptors. There are variations in the binding affinities to each kind of receptor depending on the concentration of norepinephrine, which results in different physiological effects on working memory [48]. Furthermore, methylphenidate treatment appears to depend on $\alpha 2$ noradrenergic receptors for its effects on working memory, while the $\alpha 1$ subtype is involved in the improvement of sustained attention [49].

6. Role of ADHD Inheritance and its causing syndrome

The heredity of ADHD can be investigated in several ways. Twin studies are used in a classical technique because they allow for the evaluation of the disorder's genetic impact, or heritability. A recent meta-analysis of twin studies suggested that 77–88% of cases of ADHD are heritable [50]. Thousands of people are screened for hundreds of thousands of single-nucleotide polymorphisms (SNPs) using genome-wide complex trait analysis (GCTA), which yields a measure of heredity known as SNP-based heritability. SNP-based heritability ($h^2_{\text{snp}} = 22\%$) is estimated in a recent meta-analysis within a range that is comparable to earlier estimates of h^2_{snp} for ADHD in smaller sample sizes (h^2_{snp} , 10–28%). The heritability percentage responsible for the discrepancy between roughly 74% in twin studies and 22% in SNP Regarding the astronomical search for dark matter, based heritability is also known as “hidden heritability” [51].

6.1 Syndrome associated with ADHD

Fragile X syndrome (FXS)- FXS is one of the genetic disorders most commonly associated with ADHD. 59% of boys with FXS meet the diagnostic behavioural criteria for ADHD mixed type (14.8%), ADHD inattentive type only (31.5%), or ADHD hyperactive type only (7.4%), according to reports from parents or teachers [52]. The FMR1 gene encodes the RNA-binding protein called fragile X mental retardation protein (FMRP), which is lost of function and causes FXS. The primary mechanisms of FXS have been proposed to be diminished GABA-Signalling and increased glutamatergic excitement.

Neurofibromin 1 (NF1)- Neurofibromin 1(NF1) symptoms include various skin malignancies, central nervous system, and eyes. The location of the NF1 locus is on chromosome 17q11.2. ADHD symptoms are present in roughly one-third of cases during childhood [53]. The association between NF1 and ADHD may have a neurological foundation that arises from lesions in the basal ganglia.

Tuberous sclerosis complex (TSC)- The autosomal dominant genetic disease known as tuberous sclerosis complex (TSC) is linked to skin lesions, brain tumors, and mainly benign tumors in other organ systems. It is frequently accompanied by epileptic seizures and cognitive impairment. The prevalence of ADHD has varied from roughly 30% to 60% among TSC patients [54].

Williams-Beuren syndrome (WBS)- A microdeletion on chromosome 7 causes Williams-Beuren syndrome (WBS), which is characterized by a common collection of symptoms that include abnormalities of the heart and lungs as well as unique facial traits that make a person appear "elf-like." They are labeled as "hypersocial" due of their behavior. Approximately two thirds of WBS exhibit signs of ADHD [55]. In mice lacking *Limk1*, there is a decrease in spatial learning and an increase in hyperactivity.

Velo-cardio-facial/DiGeorge syndrome- Velo-cardio-facial/DiGeorge syndrome (22q11 deletion syndrome) is linked to several psychological conditions as well as problems in the cardiovascular system. Prior research frequently concentrated on schizophrenia. Still, a far higher percentage of patients (about 40%) have ADHD, with the majority having the inattentive form. The *COMT* gene, a bottleneck for catecholamine neurotransmission, is included in the hemizygous 22q11 deletion [56].

7. Diagnosis

The primary symptoms of ADHD have been linked to deficiencies in the dopaminergic and noradrenergic neurotransmitter systems; however, dopaminergic neurotransmitter systems have received the majority of attention in genetic research.

7.1 Relevant Dopamine-Related Biomarkers in ADHD- Dopamine Transporter Gene (*DAT1*, *SLC6A3*): *DAT1* is important in the genetics of ADHD for at least the following four reasons:

- 7.1.1** The *DAT1* protein controls dopaminergic neurotransmission.
- 7.1.2** Methylphenidate (MPH) and amphetamine (AMP) are two ADHD drugs that primarily target the *DAT1* protein.
- 7.1.3** *DAT1* knockout animals exhibit hyperactivity and deficiencies in inhibitory behavior [57].
- 7.1.4** *DAT1* has been implicated in several neurological disorders located close to the 5p13 ADHD susceptibility gene [58].

The most researched *DAT1* variant is a variable number of tandem repeats (VNTR) at the 3'-untranslated region (3'-UTR) of the gene, which consists of 40 base pairs. The most prevalent alleles are the ten repeat (10R) and nine repeat (9R) variants. It has been shown that children with ADHD who have homozygosity for the 10R in the basal ganglia—a region of the brain

involved in inhibitory behaviors—had a considerably greater DAT density when evaluated in vivo using neuroimaging. This implies that the 10R allele has a functional impact. Although a reverse connection has been observed for individuals with ADHD, a recent meta-analysis showed a correlation between the 10R allele and ADHD [59].

7.2 Dopamine D4 Receptor (DRD4)

considering its strong expression in brain areas related to attention and inhibition, such as the anterior cingulate cortex [60], the DRD4 gene is an appealing option for ADHD. The first to be correlated with novelty-seeking, a personality trait common to ADHD, was DRD4. The mRNA expression levels of DRD4 (which is found on chromosome 11p15.5) are lower in ADHD. In association studies, a highly polymorphic functional VNTR in the third exon has been thoroughly examined. It consists of 11 copies of a 48-bp repeat sequence, with the most common repeat alleles being 4, 7, and 2R. A meta-analysis revealed a connection between ADHD and the 7R allele.

7.3 Dopamine D5 Receptor (DRD5)

At chromosome 4p15.3, DRD5 is located. Studies using in situ hybridization revealed that the hippocampus, a part of the brain implicated in the pathophysiology of ADHD, has greater gene expression levels. Additionally, functional research revealed that DRD5 is related to synaptic strength during the creation of hippocampus memories. This variant consists of 12 alleles with lengths ranging from 134 to 156 bps, the most prevalent of which are 148 bps and 136 bps. Meta-analyses showed that the 148 bp allele was associated with an increased risk of ADHD, but the 136 bp allele was associated with a lower risk of the disorder [61].

7.4 Molecular Biomarker

It is generally accepted as an acceptable process for molecular research to collect blood samples and/or buccal swabs from participants in order to evaluate their gene alterations. Two research combined with imaging analysis while twenty-one papers looked only at molecular markers. Seven research reported the results using Polymerase chain reaction (PCR) or real-time quantitative reverse transcription PCR (qRT-PCR), the most popular technique for gene-related investigations. Higher DAT autoantibody levels were seen in ADHD patients; these levels can return to normal following methylphenidate treatment.

7.5 Physiological Biomarker

Physiological biomarkers may be included in the diagnostic criteria set, in addition to the DSM-5. Twenty publications either employed imagining analysis alone or in conjunction with physiological parameters. Many research have exploited the principles of eye physiology. One method of measuring pupil size was pupillometry. Pupillometry is a technique that quantifies the dilation of pupils in response to a stimulus, with particular emphasis on small variations. These studies relate pupil size dynamics to ADHD. Interestingly, when doing spatial working memory tasks, ADHD patients' pupil diameters were larger and their temporal complexity and symmetry were lower than that of the controls.

7.6 Detection of ADHD by estimating neurotransmitter levels in the Brain

In high-risk groups, biomarkers found in bodily fluids and the brain may also be utilized to screen for ADHD. Using MRI imaging, it was discovered that the right prefrontal cortex of ADHD brains had lower levels of various neurotransmitters, including glutamate, N-acetyl aspartate, and choline. In a saliva study, higher levels of the inflammatory markers IL-6 and C-reactive protein, lower levels of cortisol at bedtime and upon awakening, and lower levels of TNF- α and brain-derived neurotrophic factor (BDNF) were linked to ADHD [62].

7.7 ADHD detected by Counselling Patients

Several standardized diagnostic interview instruments for adult ADHD have been developed so that doctors can utilize them to help establish the diagnosis of ADHD in the first place. The key diagnostic criteria of the disorder, are as follows:

- (I) onset of the disorder before age 12,
- (II) At least five of nine significant symptoms of inattention or hyperactivity,
- (III) Meaningful impairments in at least two settings; and
- (IV) Symptoms that ADHD best explains and not another disorder, can be established with the help of a structured interview instrument used to assess for adult ADHD based on DSM-5 criteria. The Adult ADHD Clinical Diagnostic Scale (ACDS v1.2), Conner's Adult ADHD Diagnostic Interview for DSM-IV (CAADID), and the Diagnostic Interview for ADHD in Adults (DIVA-5) are often used diagnostic tools that may help in making the diagnosis of ADHD [63]. The behavior of ADHD patients as observed through counseling is shown in the graphic below.
- (V)

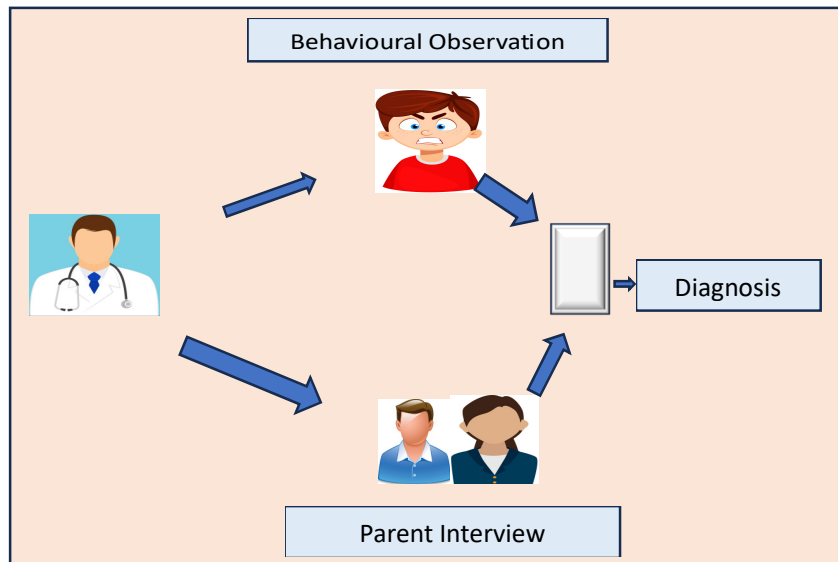


Fig. 6.7.1 Illustrates Adult ADHD Diagnostic Interview

8. Therapeutics-

8.1 Pharmacological treatment

In children and adolescents with ADHD, both stimulant and non-stimulant pharmacological treatments are beneficial in reducing symptoms, while stimulant medicine appears to be more successful. We'll talk about one commonly used stimulant (methylphenidate) and one commonly used non-stimulant (atomoxetine) in this article.

8.1.1 Methylphenidate

Among the medications most frequently used to treat ADHD is methylphenidate. For more than half a century, this product has been on the market, helping children and adolescents with ADHD who exhibit excessive hyperactivity, impulsivity, and inattention. Approximately 3% to 5% of the same population in Europe and 8% of children and adolescents under the age of 15 in the United States are prescribed it. Methylphenidate increases dopamine and norepinephrine transmission in the prefrontal cortex by blocking. The synaptic cleft's supply of dopamine and norepinephrine is increased by DAT and NET, which reduce reuptake.

Atomoxetine

Treatment for ADHD with atomoxetine has been reported to be successful, however more so in adults than in children. Because atomoxetine inhibits norepinephrine absorption, there is a greater concentration of dopamine and norepinephrine in the prefrontal cortex. Atomoxetine

has no addiction potential because it doesn't raise dopamine or norepinephrine levels in the nucleus.

8.2 Non- Pharmacological Therapies-

8.2.1 Neurofeedback Therapies

With neurofeedback (NFB), patients can train operant conditioning to change their EEG patterns. A theory explaining how NFB impacts different brain disorders by inducing synaptic plasticity, which ultimately leads to a homeostatic set point, is supported by articles detailing the induction of plastic changes after NFB training. Additionally, other than a few rare cases of headache, this method has not been linked to any documented adverse effects. The potential of NFB to cause plastic changes in the brain under physiologically normal circumstances without the requirement for outside inputs, such as transcranial stimulation or medication, to alter brain activity is one of its most fascinating characteristics. Consequently, there is extremely little chance of adverse effects.

8.2.2 Attention Training Techniques

Attention-training strategies are widely used to improve quality of life and well-being. Studies are currently being conducted on the use of these techniques to improve life quality and lessen symptoms of ADHD in patients because of their impact on brain activity, attention, and self-regulation. Following an 8-week mindfulness awareness practice period, adult ADHD patients showed reduced symptoms of anxiety, depression, and ADHD. Similarly, a study conducted on children found that an 8-week mindfulness-oriented meditation period improved both the symptoms of ADHD and the children's performance on neuropsychological tests [64].

8.2.3 Cognitive Behavioural Therapy (CBT)

Cognitive behavioural therapy (CBT), a type of behavioural intervention, aims to lessen ADHD behaviours or related challenges in two ways: by enhancing positive behaviours and creating situations where desired behaviours may occur. In the case of preschoolers and early school-age children, CBT focuses on parents and educators, providing them with guidance and training to act in accordance with CBT principles, while older children and teenagers may receive direct training in more appropriate behavioral strategies. CBT and its more specialized forms, like social skills training, planning and organizational skills training, and self-management

techniques, have positive effects on behaviour, parenting skills, child-parent relationships, and some aspects of daily life, but when blinded assessments are the only ones considered, the effects on the core symptoms of ADHD are patchy and negligible.

8.2.4 Additional Nonpharmacological Strategies to Treatment

As of right now, there is little empirical proof linking mindfulness training, exercise, and yoga to improved behavior in people with ADHD; at best, these interventions are meant to be used in conjunction with other therapies. A clinical validity test is still needed to determine the efficacy that are currently support applications or digital home treatment programs being created for parents or children with ADHD Youth with ADHD are more likely to exhibit problematic internet use and gaming (estimated at 37% in ADHD vs. 12% in TD). This may lead to increased compliance, however, children and adolescents with ADHD frequently demonstrate a strong liking for digital media, which may improve compliance [65].

8.2.5 Robotic Treatment

Robotics' development has made it possible to develop activities that humans are incapable of performing, or at least cannot do so precisely. Robotics has been essential in the eHealth sector in aiding and treating patients with a range of neurological diseases, including trauma, dementia, cerebral palsy, and ADHD. Even though there has been a lot of research done recently on the use of robots to treat and assist adhd, it is still significantly less effective than therapies for dementia, autism, and cerebral palsy. According to the Scopus and WoS databases, the use of robotics in the treatment and support of ADHD began in the 2000s, but it has peaked in the recent five years, indicating that therapists are finding this technology to be an appealing alternative to traditional treatments.

Humanoid multifunctional robots, tiny multipurpose robots, and bespoke robots are the robots utilized to treat ADHD. Additionally, a variety of therapies are administered using robots-

8.2.6 Ethno-pathy development

In particular for young infants, language is essential for socialization and communication. There may be phonological and pragmatic issues if language and communication abilities are not developed as quickly. Children took part in individual sessions with the NAO robot as part of this study. Children's interest and involvement increased when NAO was introduced into the program, which was centered on writing and attention. The findings demonstrate that children's

confidence has increased as a result of improvements in their phrase formation, structure, and vocalization.

8.2.7 Therapy for the improvement of motor skills

The complicated perceptual-motor skill of handwriting requires the use of language, concentration, perception, and fine motor abilities. Dysgraphia, which is described as an impairment in quality or speed to generate adequately smooth and automatic handwriting, can result from handwriting abilities that become difficult to write. Numerous advancements in robotics are aimed at improving the care that individuals with motor disorders receive to enhance their fine motor skills [66].

9. Future Perspective

Examining current problems and advancements in the diagnosis and management of attention deficit hyperactivity disorder is the goal of this review. Nevertheless, it was evident from reading through and analyzing several publications that there were still several issues that needed to be resolved, such as early diagnosis, long-term care, limiting side effects, various nano-based formulations, alternative medications, and interventions. As of now, ADHD lacks conclusive biomarkers. Self-reports and behavioral assessments play a major role in diagnosis, but they can be unreliable. The goal of current research is to find neurobiological indicators for ADHD by using genetic and sophisticated imaging studies. This could lead to more objective diagnostic criteria. Understanding the heterogeneity of ADHD better could result in more individualized treatment plans that incorporate lifestyle, pharmacological, and therapeutic interventions. One important area of research is the development of novel medications with fewer side effects and non-stimulant options. Addressing these challenges requires a multifaceted approach involving advances in medical research, technology, public health policy, and education.

10. Conclusion

Deficit in Attention Diagnosing and treating hyperactivity disorder (ADHD) can be challenging due to its neurological nature, which is evidenced by impulsivity and hyperactivity. Many studies produced distinct detection methods that are currently being used, and other cutting-edge treatments—such as the creation of speech therapy and robotics—are employed. The current review's conclusions can point to the need for more studies on adult ADHD early diagnosis, long-term care, and other related issues.

11. Reference

1. Wolraich ML, Chan E, Froehlich T, Lynch RL, Bax A, Redwine ST, Ihyembe D, Hagan JF, ADHD diagnosis and treatment guidelines: a historical perspective, *Pediatrics*, 2019, **144**, doi- <https://doi.org/10.1542/peds.2019-1682>.
2. Boyle CA, Boulet S, Schieve LA, Cohen RA, Blumberg SJ, Yeargin-Allsopp M, et al. Trends in the prevalence of developmental disabilities in US children, 1997–2008. *Pediatrics*. 2011;127:1034–42.
3. Polanczyk G, de Lima MS, Horta BL, et al. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *Am J Psychiatry*. 2007;164(6):942–8. <https://doi.org/10.1176/ajp.2007.164.6.942>.

4. Willcutt EG. The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. *Neurotherapeutics*. 2012;9(3):490–9. <https://doi.org/10.1007/s13311-012-0135-8>.
5. Reale L, Bonati M. ADHD prevalence estimates in Italian children and adolescents: a methodological issue. *Italian journal of pediatrics*. 2018 Dec;44:1-9.
6. Brown RT, Amler RW, Freeman WS, Perrin JM, Stein MT, Feldman HM, Pierce K, Wolraich ML, Committee on Quality Improvement, Subcommittee on Attention-Deficit/Hyperactivity Disorder. Treatment of attention-deficit/hyperactivity disorder: overview of the evidence. *Pediatrics*. 2005 Jun 1;115(6):e749-57.
7. Faraone SV, Sergeant J, Gillberg C, Biederman J. The worldwide prevalence of ADHD: is it an American condition?. *World psychiatry*. 2003 Jun;2(2):104.
8. Bussing R, Gary FA, Mills TL, Garvan CW. Parental explanatory models of ADHD: gender and cultural variations. *Soc Psychiatry Psychiatr Epidemiol*. 2003;38(10):563–75. <https://doi.org/10.1007/s00127-003-0674-8>.
9. Able SL, Johnston JA, Adler LA, Swindle RW. Functional and psychosocial impairment in adults with undiagnosed ADHD. *Psychol Med*. 2007;37(1):97–107. <https://doi.org/10.1017/S0033291706008713>.
10. Hamed AM, Kauer AJ, Stevens HE. Why the diagnosis of Attention Deficit Hyperactivity disorder matters. *Front Psychiatry*. 2015;6. <https://doi.org/10.3389/fpsy.2015.00168>.
11. Ford-Jones P. Misdiagnosis of attention deficit hyperactivity disorder: ‘Normal behaviour’ and relative maturity. *Paediatr Child Health*. 2015;20(4): 200–2. <https://doi.org/10.1093/pch/20.4.200>.
12. Taylor E. Attention deficit hyperactivity disorder: overdiagnosed or diagnoses missed? *Arch Dis Child*. 2016;102(4):376–9. <https://doi.org/10.1136/archdischild-2016-310487>.
13. Ilaria Rocco, Barbara Corso, Maurizio Bonati and Nadia Minicuci, Time of onset and/or diagnosis of ADHD in European children: a systematic review, *BMC Psychiatry*, 2021, **21**, doi- <https://doi.org/10.1186/s12888-021-03547-x>.
14. O’Neill, S., Rajendran, K., Mahubani, S.M. *et al*, Preschool Predictors of ADHD Symptoms and Impairment During Childhood and Adolescence, *Current Psychiatry Report* 19, 2017, **95**, doi- <https://doi.org/10.1007/s11920-017-0853-z>.

15. Nussbaum, N. L. (2011). ADHD and Female Specific Concerns: A Review of the Literature and Clinical Implications. *Journal of Attention Disorders*, 16(2), 87-100. <https://doi.org/10.1177/1087054711416909> (Original work published 2012)
16. Waite R. Women with ADHD: It is an explanation, not the excuse du jour. *Perspectives in Psychiatric Care*. 2010 Jul;46(3):182-96.
17. Mowlem FD, Rosenqvist MA, Martin J, Lichtenstein P, Asherson P, Larsson H. Sex differences in predicting ADHD clinical diagnosis and pharmacological treatment. *European child & adolescent psychiatry*. 2019 Apr 1;28:481-9.
18. Attoe DE, Climie EA. Miss. Diagnosis: a systematic review of ADHD in adult women. *Journal of attention disorders*. 2023 May;27(7):645-57.
19. Rubia K, Westwood S, Aggensteiner PM, Brandeis D. Neurotherapeutics for attention-deficit/hyperactivity disorder (ADHD): a review. *Cells*. 2021 Aug 21;10(8):2156.
20. Hesson J, Fowler K. Prevalence and correlates of self-reported ADD/ADHD in a large national sample of Canadian adults. *Journal of Attention Disorders*. 2018 Jan;22(2):191-200.
21. Brault MC, Lacourse É. Prevalence of prescribed attention-deficit hyperactivity disorder medications and diagnosis among Canadian preschoolers and school-age children: 1994–2007. *The Canadian Journal of Psychiatry*. 2012 Feb;57(2):93-101.
22. Leung BM, Kellett P, Youngson E, Hathaway J, Santana M. Trends in psychiatric disorders prevalence and prescription patterns of children in Alberta, Canada. *Social psychiatry and psychiatric epidemiology*. 2019 Dec;54:1565-74.
23. Morkem R, Handelman K, Queenan JA, Birtwhistle R, Barber D. Validation of an EMR algorithm to measure the prevalence of ADHD in the Canadian Primary Care Sentinel Surveillance Network (CPCSSN). *BMC medical informatics and decision making*. 2020 Dec;20:1-8.
24. Connolly RD, Speed D, Hesson J. Probabilities of ADD/ADHD and related substance use among Canadian adults. *Journal of attention disorders*. 2019 Oct;23(12):1454-63.
25. Vasiliadis HM, Diallo FB, Rochette L, Smith M, Langille D, Lin E, Kisely S, Fombonne E, Thompson AH, Renaud J, Lesage A. Temporal trends in the prevalence and incidence of diagnosed ADHD in children and young adults between 1999 and 2012 in Canada: a data linkage study. *The Canadian Journal of Psychiatry*. 2017 Dec;62(12):818-26.
26. Yallop L, Brownell M, Chateau D, Walker J, Warren M, Bailis D, LeBow M. Lifetime prevalence of attention-deficit hyperactivity disorder in young adults: examining

- variations in the socioeconomic gradient. *The Canadian Journal of Psychiatry*. 2015 Oct;60(10):432-40.
27. Sareen, J., Bolton, S.L., Mota, N., Afifi, T.O., Enns, M.W., Taillieu, T., Stewart-Tufescu, A., El-Gabalawy, R., Marrie, R.A., Richardson, J.D. and Stein, M.B., 2021. Lifetime prevalence and comorbidity of mental disorders in the two-wave 2002–2018 Canadian Armed Forces Members and Veterans Mental Health follow-up survey (CAFVMHS): Prévalence et Comorbidité de Durée de vie Des troubles Mentaux Dans l'Enquête de Suivi Sur la Santé Mentale Auprès des Membres des Forces Armées Canadiennes et Des ex-Militaires (ESSMFACM) en deux cycles de 2002 à 2018. *The Canadian Journal of Psychiatry*, 66(11), pp.951-960.
 28. Hauck TS, Lau C, Wing LL, Kurdyak P, Tu K. ADHD treatment in primary care: demographic factors, medication trends, and treatment predictors. *The Canadian Journal of Psychiatry*. 2017 Jun;62(6):393-402.
 29. Gadermann AM, Petteni MG, Janus M, Puyat JH, Guhn M, Georgiades K. Prevalence of mental health disorders among immigrant, refugee, and nonimmigrant children and youth in British Columbia, Canada. *JAMA network open*. 2022 Feb 1;5(2):e2144934-.
 30. Espinet SD, Graziosi G, Toplak ME, Hesson J, Minhas P, A review of Canadian diagnosed ADHD prevalence and incidence estimates published in the past decade, *Brain sciences*, 2022, 12, doi- <https://doi.org/10.3390/brainsci12081051>.
 31. Francés L, Quiñero J, Fernández A, Ruiz A, Caules J, Fillon G, Hervás A, Soler CV, current state of knowledge on the prevalence of neurodevelopmental disorders in childhood according to the DSM-5: a systematic review in accordance with the PRISMA criteria, *Child and adolescent psychiatry and mental health*, 2022, 16, doi- <https://doi.org/10.1186/s13034-022-00462-1>.
 32. Anderson PJ, de Miranda DM, Albuquerque MR, et al. Psychiatric disorders in individuals born very preterm / very low-birth weight: an individual participant data (IPD) meta-analysis. *EClinicalMedicine*. 2021. <https://doi.org/10.1016/j.eclinm.2021.101216>.
 33. Wetherill L, Foroud T, Goodlett C. Meta-analyses of externalizing disorders: genetics or prenatal alcohol exposure? *Alcohol Clin Exp Res*. 2018;42:162–72. <https://doi.org/10.1111/acer.13535>.
 34. Huang L, Wang Y, Zhang L, et al. Maternal smoking and attention-deficit/hyperactivity disorder in offspring: a meta-analysis. *Pediatrics*. 2018. <https://doi.org/10.1542/peds.2017-2465>.

35. Masarwa R, Platt RW, Filion KB. Acetaminophen use during pregnancy and the risk of attention deficit hyperactivity disorder: a causal association or bias? *Paediatr Perinat Epidemiol.* 2020;34:309–17. <https://doi.org/10.1111/ppe.12615>.
36. Leshem R, Bar-Oz B, Diav-Citrin O, et al. Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) during pregnancy and the risk for autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) in the offspring: a true effect or a bias? a systematic review & meta-analysis. *Curr Neuropharmacol.* 2021;19:896–906. <https://doi.org/10.2174/1570159X19666210303121059>.
37. Ai Y, Zhao J, Shi J, Zhu TT. Antibiotic exposure and childhood attention-deficit/hyperactivity disorder: systematic review and meta-analysis. *Psychopharmacology.* 2021;238:3055–62. <https://doi.org/10.1007/s00213-021-05989-3>.
38. Nilsen FM, Tulve NS. A systematic review and meta-analysis examining the interrelationships between chemical and non-chemical stressors and inherent characteristics in children with ADHD. *Environ Res.* 2020. <https://doi.org/10.1016/j.envres.2019.108884>.
39. Shareghfarid E, Sangsefidi ZS, Salehi-Abargouei A, Hosseinzadeh M. Empirically derived dietary patterns and food groups intake in relation with attention deficit/hyperactivity disorder (ADHD): a systematic review and meta-analysis. *Clin Nutr ESPEN.* 2020;36:28–35. <https://doi.org/10.1016/j.clnesp.2019.10.013>.
40. Prades N, Varela E, Flamarique I, et al. Water-soluble vitamin insufficiency, deficiency and supplementation in children and adolescents with a psychiatric disorder: a systematic review and meta-analysis. *Nutr Neurosci.* 2022. <https://doi.org/10.1080/1028415X.2021.2020402>.
41. Kotsi E, Kotsi E, Perrea DN. Vitamin D levels in children and adolescents with attention-deficit hyperactivity disorder (ADHD): a meta analysis. *Atten Defic Hyperact Disord.* 2019;11:221–32. <https://doi.org/10.1007/s12402-018-0276-7>.
42. Thapar A, Cooper M, Eyre O, Langley K. What have we learnt about the causes of ADHD? *J Child Psychol Psychiatry.* 2013;54:3–16. <https://doi.org/10.1111/j.1469-7610.2012.02611.x>.
43. Dall’Aglio L, Muka T, Cecil CAM, et al. The role of epigenetic modifications in neurodevelopmental disorders: a systematic review. *Neurosci Biobehav Rev.* 2018;94:17–30. <https://doi.org/10.1016/j.neubiorev.2018.07.011>.

44. Müller D, Grevet EH, da Silva BS, et al. The neuroendocrine modulation of global DNA methylation in neuropsychiatric disorders. *Mol Psychiatry*. 2021;26:66–9. <https://doi.org/10.1038/s41380-020-00924-y>.
45. Beaulieu J-M, Gainetdinov RR. The physiology, signaling, and pharmacology of dopamine receptors. *Pharmacol Rev*. 2011;63:182–217. <https://doi.org/10.1124/pr.110.002642>.
46. Del Campo N, Chamberlain SR, Sahakian BJ, Robbins TW. The roles of dopamine and noradrenaline in the pathophysiology and treatment of attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2011;69:e145–157. <https://doi.org/10.1016/j.biopsych.2011.02.036>.
47. Fusar-Poli P, Rubia K, Rossi G, et al. Striatal dopamine transporter alterations in ADHD: pathophysiology or adaptation to psychostimulants? A meta-analysis. *Am J Psychiatry*. 2012;169:264–72. <https://doi.org/10.1176/appi.ajp.2011.11060940>.
48. Berridge CW, Spencer RC. Differential cognitive actions of norepinephrine α_2 and α_1 receptor signaling in the prefrontal cortex. *Brain Res*. 2016;1641:189–96. <https://doi.org/10.1016/j.brainres.2015.11.024>.
49. Da Silva BS, Grevet EH, Silva LC, Ramos JK, Rovaris DL, Bau CH, An overview on neurobiology and therapeutics of attention-deficit/hyperactivity disorder, *Discover Mental Health*, 2023, 1, doi- <https://doi.org/10.1007/s44192-022-00030-1>.
50. Faraone SV, Larsson H. Genetics of attention deficit hyperactivity disorder. *Mol Psychiatry*. 2019;24(4):562–75.
51. Demontis D, Walters RK, Martin J, Mattheisen M, AlsTD, Agerbo E, et al. Discovery of the first genome-wide significant risk loci for ADHD. *Nat Genet*. 2018. Available from: <https://doi.org/10.1101/145581>.
52. Lo-Castro A, D'Agati E, Curatolo P. ADHD and genetic syndromes. *Brain Dev*. 2011;33(6):456–61.
53. Kayl AE, Moore BD. Behavioral phenotype of neurofibromatosis, type 1. *Ment Retard Dev Disabil Res Rev*. 2000;6(2):117–24.
54. deVries PJ, Hunt A, Bolton PF. The psychopathologies of children and adolescents with tuberous sclerosis complex (TSC). *Eur Child Adolesc Psychiatry*. 2007;16(1):16–24
55. Leyfer OT, Woodruff-Borden J, Klein-Tasman BP, Fricke JS, Mervis CB. Prevalence of psychiatric disorders in 4 to 16-year olds with Williams syndrome. *Am J Med Genet Part B Neuropsychiatr Genet*. 2006;41B(6):615–22.

56. Grimm O, Kranz TM, Reif A, Genetics of ADHD: what should the clinician know?, *Current Psychiatry Reports*, 2020, 22, doi- <https://doi.org/10.1007/s11920-020-1141-x>
57. Cortese S. The neurobiology and genetics of attention-deficit/ hyperactivity disorder (ADHD): what every clinician should know. *Eur J Paediatr Neurol*. 2012;16(5):422–33.
58. Friedel S, Saar K, Sauer S, Dempfle A, Walitza S, Renner T, et al. Association and linkage of allelic variants of the dopamine transporter gene in ADHD. *Mol Psychiatry*. 2007;12(10):923–33.
59. Cheon KA, Ryu YH, Kim JW, Cho DY. The homozygosity for 10 repeat allele at dopamine transporter gene and dopamine transporter density in Korean children with attention deficit hyperactivity disorder: relating to treatment response to methylphenidate. *Eur Neuropsychopharmacol*. 2005;15(1):95–101.
60. Noaín D, Avale ME, Wedemeyer C, Calvo D, Peper M, Rubinstein M. Identification of brain neurons expressing the dopamine D4 receptor gene using BAC transgenic mice. *Eur J Neurosci*. 2006;24(9):2429–38.
61. Faraone SV, Bonvicini C, Scassellati C, Biomarkers in the diagnosis of ADHD—promising directions, *Current psychiatry reports*, 2014, 16, 1-20, doi- <https://doi.org/10.1007/s11920-014-0497-1>.
62. Chen H, Yang Y, Odisho D, Wu S, Yi C, Oliver BG, Can biomarkers be used to diagnose attention deficit hyperactivity disorder, *Frontiers in Psychiatry*, 2023, 14, doi- <https://doi.org/10.3389/fpsy.2023.1026616>.
63. Anbarasan D, Kitchin M, Adler LA. Screening for adult ADHD, *Current psychiatry reports*, 2020, 22, 1-5, doi- <https://doi.org/10.1007/s11920-020-01194-9>.
64. Núñez-Jaramillo L, Herrera-Solís A, Herrera-Morales WV, ADHD: Reviewing the causes and evaluating solutions, *Journal of personalized medicine*, 2021, 11, doi- <https://doi.org/10.3390/jpm11030166>.
65. Drechsler R, Brem S, Brandeis D, Grünblatt E, Berger G, Walitza S, ADHD: Current concepts and treatments in children and adolescents, *Neuropediatrics*, 2020, 51, 315-35, doi- [10.1055/s-0040-1701658](https://doi.org/10.1055/s-0040-1701658).
66. Berrezueta-Guzman J, Robles-Bykbaev VE, Pau I, Pesántez-Avilés F, Martín-Ruiz ML, Robotic technologies in ADHD care: Literature review, *IEEE Access*, 2021, 10, 608-25, doi- [10.1109/ACCESS.2021.3137082](https://doi.org/10.1109/ACCESS.2021.3137082).