Review

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# Adult attention deficit hyperactivity disorder: a comprehensive review

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**Abstract**

Attention deficit hyperactivity disorder (ADHD) is a common childhood disorder, with only 2–3% prevalence into adulthood. The epidemiology and proposed causes of ADHD are multifactorial, including genetic, prenatal and environmental influences. The diagnosis of ADHD is often complicated by masking coping mechanisms, an overlap of symptoms with other, more commonly diagnosed disorders. Traditionally, it has been treated with stimulant medications. Non-stimulant options often target norepinephrine and dopamine regulation and are preferred in cases of comorbid substance use disorder, anxiety and other complicating factors, due to an improved side-effect profile and patient preference. They include atomoxetine and viloxazine. The latter, Viloxazine, in the form of extended-release capsules, is the first novel, non-stimulant option approved for adults with ADHD, in the past two decades. Its therapeutic effects are predominantly produced by its action as a norepinephrine reuptake inhibitor and may also modulate the serotonergic system. Viloxazine is relatively safe and effective in treating other disorders such as depression, anxiety, epilepsy and substance use disorder. Its pharmacokinetics includes metabolization by CYP enzymes. As antiepileptics inhibit CYP1A2, therefore, a special consideration would be needed, when co-administering with anti-epileptic drugs. Similarly, individuals with liver or cardiovascular disease and a personal or family history of bipolar disorder require close monitoring, while on this medication. A thorough review of the history, mechanism of action, pharmacokinetics and drug–drug interactions has been presented here, with special attention on treatment in adults with comorbid conditions. This study conducted an all-language literature search on Medline, Cochrane, Embase, and Google Scholar until December 2022. The following search strings and Medical Subject Headings (MeSH) terms were used: "Viloxazine," "ADHD," "Stimulants," and "adult ADHD." We explored the literature on the growing knowledge of Viloxazine. A thorough review of the history, mechanism of action, pharmacokinetics, and drug–drug interactions are reviewed here with special attention on treatment in adults with comorbid conditions.

**Keywords:** ADHD, amphetamines, attention deficit hyperactivity disorder, Qelbree, review, viloxazine

## Introduction

ADHD is a neurological and neurodevelopmental disorder that begins in childhood and is characterized by persistent patterns of inattention, impulsivity, restlessness and hyperactivity[1]. ADHD is well recognized in the paediatric population, first described as a clinical diagnosis in the 1930s, but the focus has shifted to recognition and treatment of the disorder in adults[2]. ADHD has an estimated adult prevalence of ~2–3%[3]. In addition, ADHD has been shown to be significantly correlated with a wide range of psychiatric disorders, including mood disorders, oppositional and antisocial personality disorders, self-harm and substance abuse, which impose a significant social and family burden increase[4]. Compared with ADHD in childhood, ADHD in adults has been relatively neglected in epidemiological studies, mainly due to the lack of established valid diagnostic criteria[4]. The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM) is a widely used approach for diagnosing ADHD in adults and requires childhood onset[4]. The purpose of this review is to describe the

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characteristics and the associated comorbidities of Adult ADHD and to depict the scope of available treatment. In this review, treatment options are summarized with a special emphasis on non-stimulants.

## Aetiology

Several factors contribute to ADHD symptoms, including genetics, neurodevelopmental disorders, abnormal neuronal maturation, brain injury, environmental exposure and consanguinity. A recent study by Posner and colleagues reported that environmental risk factors contribute to ADHD symptoms at prenatal, perinatal, and postnatal stages. Prenatal and perinatal risk factors such as prematurity, low birth weight, maternal smoking history, stress, trauma and obesity are substantially associated with ADHD. Postnatal risk factors such as trauma, parenting style, artificial colours and fragrances, pollutants, and pesticides can exacerbate ADHD symptoms[1]. Medication-based treatment strategies have proven effective and inexpensive in the short term, and many compounds are available, recommended and widely used. The long-term efficacy of these treatments on clinical, occupational and social outcomes remains unknown. It is clear that better long-term treatments for ADHD are urgently needed[5].

## Gender differences

Studies in children and adolescents have shown that the disorder is at least three times more common in men, but that the adult male/female ratio here tends to decrease to 2:1[5]. The prevalence of ADHD is estimated at 7.1% in children and adolescents, 2.5–5% in adults, and ~2.8% in the elderly. Sex differences in the prevalence of ADHD are well documented. Male clinical referrals typically outnumber females, with ratios ranging from 3:1 to 16:1[6].

The observed sex difference could be explained by the higher frequency of hyperactivity and behavioural problems in boys and their greater likelihood of referral to a clinician. Conversely, girls with ADHD may exhibit more attentional symptoms and fewer hyperactivity/impulsivity symptoms, coupled with better coping skills, making them less likely to be referred. Sex differences also appear to influence the prevalence of comorbidities. In particular, women who suffer from ADHD are more likely to have depression and eating disorders, and men are more likely to have substance use disorders[7]. This increase in awareness of ADHD among women is partly due to the growing awareness of gender differences in ADHD symptoms. ADHD men are more likely than women to exhibit the core symptoms of her ADHD-I (inattentiveness), HI (hyperactivity/impulsiveness) and C (combined) symptoms. ADHD-I is more common in women and ADHD-HI is more common in men. HI presentation is associated with impulsive and hyperactive behaviours, and I presentation is associated with hypo arousal, inattentiveness and withdrawal. Her ADHD-I symptoms, characteristic of women, are often reflected in mood and emotional dysregulation, making differential diagnosis very difficult and interfering with internalizing disorders such as mood disorders, anxiety disorders and depression and lead to misdiagnosis[8].

### HIGHLIGHTS

- Attention deficit hyperactivity disorder (ADHD) is a common disorder of childhood, with only 2–3% prevalence into adulthood.
- The epidemiology and proposed causes of ADHD are multifactorial.
- ADHD has an estimated adult prevalence of ~2–3%.
- ADHD has been shown to be significantly correlated with a wide range of psychiatric disorders.
- Compared with ADHD in childhood, ADHD in adults has been relatively neglected in epidemiological studies, mainly due to the lack of established valid diagnostic criteria.

## Clinical presentation and comorbidities

ADHD in adults is characterized by the following behavioural criteria: inattentiveness, impulsivity, hyperactivity and restlessness[6].

ADHD is recognized by the DSM- IV to fit into three different subtypes-hyperactive or impulsive, inattentive and combined[9]. According to Wilens, 90% of individuals suffering with ADHD show inattentive symptoms, who recognized it as the most prevalent symptom domain[10]. Literature shows that females present with far higher levels of inattentiveness leading to infrequent access to care[11–13]. In contrast, the least represented domain is the hyperactive subtype[9].

Lahey and colleagues found 66% of adolescents displaying the combined subtype[14] which has been linked to a greater incidence of comorbid conditions, neuroticism and substance abuse disorders[15–17].

Adults usually present with difficulties in organizing, planning and make impulsive decisions which result in unstable employment and relationships[18]. ADHD is associated with poor academic and professional performance because it presents with reading disabilities which lead to repeating grades and attending special educational facilities hindering higher educational opportunities[19]. As these adults have recurrent employment changes and exhibit poor performance in their jobs , they are unable to maintain stability in their profession[20]. While they are able to manage inter-personal relationships, it is reported that they have difficulty in forming and keeping close friends. ADHD adults hold a negative impression of marriage leading to separation and divorces[21]. It has also been associated with driving accidents and jail time[22,23].

Recently, focus has shifted to symptoms arising from emotional dysregulation like irritability, emotional fluctuations, low frustration tolerance and daydreaming, which increase the risk of misdiagnosing patients as having mood disorders resulting in many adults not receiving the required intervention[22,24,25].

ADHD adults often feel different from others due to their inability to comprehend social cues and because they lack propriety. But there are positive aspects of ADHD.

The patients are creative and thus usually prosper in the art industry. Accomplishing tasks is rewarding when it is in their interest. They develop coping strategies to overcome their deficits by keeping track of to-do lists, setting alarms. Diagnosis is essential as it helps them to come to term with their shortcomings[26].

Two-thirds of ADHD adults present with one comorbid psychiatric disorder[27]. Studies also show that ADHD is found in

15% of psychiatric patients[28]. These comorbidities are responsible for masking ADHD which reduces the frequency of correct diagnosis[29]. Comorbidity rates of 57–92% have been shown in various studies[15]. Bipolar disorder, Personality disorders, depression, anxiety disorders, Substance abuse disorders are the common comorbidities that occur with ADHD[2].

### Stimulants

For many years, psychostimulant medications have been regarded as the mainstay of ADHD therapy. As per evidence, they have shown to enhance the presence of dopamine as well as norepinephrine in the frontal lobes. This ensures increased effectiveness of processing information in the brain, especially at the site of pyramidal cells. This in turn helps to alleviate manifestations of ADHD[30].

Stimulants are considered to be the primary pharmacologic therapy for ADHD. A study review article conducted by Steingard *et al.*[31] in 2013 showed that amphetamine have a success rate of 70% to treat the patient with Adult onset ADHD

Some of the popular treatments for ADHD include psychostimulant drugs like methylphenidate, dextroamphetamine, and combined isomers of amphetamine[32].

ADHD manifestations include inattentiveness, hyperactivity, impulsiveness and poor concentration. Additionally, stimulants enhance alertness, comprehension, response inhibition and immediate memory[33].

### Amphetamine salts

Dexamphetamine, lisdexamfetamine, and mixed amphetamine salts are a few of the various formulations of amphetamine available and effective for ADHD therapy[34]. There are three key modes of action that amphetamines exhibit[31].

Firstly, it inhibits the reuptake of neurotransmitters after adhering to transporters of monoamine, norepinephrine and dopamine.

It also enables the phosphorylation of the dopamine transporter by trace-amine-associated receptor 1. This leads to decreased transportation of dopamine. It may also cause outflow of the neurotransmitters in the direction of the synapse as a result of its entry into presynaptic vesicles[31].

A study conducted in 2018 by Castells and colleagues ($n=2521$) explored the effects of three forms of amphetamine. This included: dexamphetamine, lisdexamfetamine and mixed amphetamine salts. The study showed that the magnitude of ADHD-associated complaints was successfully reduced with the use of any of all the 3 forms of amphetamine. The effectiveness of amphetamines did not seem to fluctuate while varying the dose. The study looked into the effects of both immediate- and sustained-release formulations, but there were no variations in the results[35].

A study conducted in 2017 by Lenard A Adler and colleagues ($N=40$) analyzes the efficacy ,validity and reliability of lisdex amphetamine Dimesylate by measuring the ADHD Rating scale , Adult ADHD Medication Smoothness of Effect Scale and Adult ADHD Medication Rebound Scale concluded that effectiveness of LDX is good by showing the untroubled effect whole day with less rebound symptoms with reliable measure of Adult ADHD Medication Smoothness of Effect Scale and Adult ADHD Medication Rebound Scale[36].

### Side effects

When amphetamines are used to treat ADHD, anorexia, and a decrease in body weight are some of the anticipated side effects. Other negative effects brought on by amphetamine use include vomiting, nausea, aches in the abdomen, hypertension and tachycardia.[37] Administration of an additional in the noon may be beneficial if side effects, such as agitation, start to manifest subsequently in the day and when patients exhibit rebound phenomena. A relatively frequent side effect of stimulants is initial sleeplessness. It is crucial to determine whether insomnia is a side effect of the drug or in fact, preexists this treatment modality. By limiting doses in the latter part of the day and adopting healthy sleep schedules, insomnia as a side effect can be avoided[33].

### Methylphenidate salts

Methylphenidate was first developed in 1944 and was initially employed as an analeptic to treat barbiturate-induced coma. However, these days, it is most commonly utilized to treat ADHD[38].

Methylphenidate amplifies neuronal dopamine efflux and inhibits dopamine reuptake from the synapse. The drug adheres to the dopamine transporter of the presynaptic cell. This prevents dopamine reuptake and leads to an increased amount of extracellular dopamine[33,38].

Methylphenidate is present in the form of four stereoisomers: dextro- / levo-threo , dextro- /levo-erythro. The majority of MPH preparations present in the market contain a racemic combination of both d-MPH and l-MPH. According to studies, d- Methylphenidate is found to be the most potent among these. The alkaline characteristic of Methylphenidate hydrochloride makes it extremely soluble in the gastrointestinal tract, allowing for its oral administration. It is suggested that due to the acidic nature of the stomach, minimal degradation of the drug occurs there. When taken orally, immediate-release MPH is quickly and entirely absorbed. One to three hours may pass before the maximum plasma concentration is reached, taking into account its variability in different individuals[39].

Methylphenidate hydrochloride has been developed to be effective in individuals who require management of their ADHD symptoms from morning to evening. Multilayer-release methylphenidate has shown to have safe and positive efficacy[40]. A randomized controlled trial (RCT) conducted in 2021 by Margaret D Weiss and colleagues to evaluate safety and efficacy of the 16 h multilayer-release methylphenidate(PRC-063) in a community based adult ADHD population ($n=375$) concludes PRC-063 led to a greater symptoms relief in the ADHD-RS-5 total score from baseline compared with Placebo.Headache, decrease in sleep deprivation and loss of appetite were the most commonly seen adverse effect[41].

When compared with a placebo, immediate-release methylphenidate was successful in treating the three main symptoms of ADHD: hyperactivity, impulsiveness and inattentiveness. The general clinical status was found to be improved with the use of immediate-release methylphenidate. However, results were inconsistent, making it unclear if immediate-release methylphenidate therapy is beneficial for accompanying anxiety or depression[42].

In 2017, Childress and colleagues conducted a clinical trial to investigate the effects of HLD200 in children and adults. It is a delayed-release/extended-release MPH composition given during

the evening. It was found to be efficacious and the pharmacokinetic properties met its objectives in the tested age groups. Between children, and healthy adults with ADHD, there were no discernible variations in the pharmacokinetic results when body weight was taken into consideration[43].

#### *Side effects*

Methylphenidate is linked to a higher risk of mild side effects including sleep issues and reduced appetite, however, it is not associated with major adverse effects.[33] Additional side effects include increased heart rate, blood pressure, anxiety and sleeplessness. Its use can rarely be linked with arrhythmias, rash, and urticaria. Methylphenidate may produce a sense of euphoria when administered intravenously[39].

## Non-stimulants

Even though stimulants are incredibly effective in short-term RCTs, not all patients react to or tolerate them adequately[40]. Various innovative non-stimulant approaches for treating ADHD are presently under development[40]. The FDA has only recently approved the non-stimulants atomoxetine (ATX), guanfacine (guanfacine-XR), and clonidine (clonidine-XR) for the treatment of ADHD. Adult usage has only been approved for ATX. Due to the many drugs now undergoing clinical investigations and having completed Phase 2 and Phase 3 trials, there will likely be a growth in the number of non-stimulant choices available in the following years. Each candidate differs chemically and may have different molecular targets. Based on their pharmacologic characteristics, non-stimulants may be divided into three groups:

(1) Monoamine reuptake (transporter) inhibitors (like ATX)
(2) Receptor modulators (like guanfacine-XR and clonidine-XR)
(3) Multimodal drugs

In this section, we examine the clinical characteristics of both approved and licensed CII stimulant substitutes that have shown effectiveness in double-blind, placebo-controlled Phase 2 or Phase 3 studies. In addition to a multimodal stimulant with a lower abuse potential (mazindol controlled release), several monoamine reuptake inhibitors (dasotraline, OPC-64005) and multimodal non-stimulants (vortioxetine, viloxazine extended-release) are being developed as substitutes for CII stimulants.

#### *Monoamine reuptake (Transporter) inhibitors*

##### Atomoxetine

With a strong affinity for presynaptic norepinephrine transporters (NET), atomoxetine inhibits noradrenergic reuptake[41,42]. Even though ATX was initially researched as a potential treatment for major depressive disorder in adults in the 1980s, depression research was discontinued due to its ineffectiveness[43]. Atomoxetine was the first non-stimulant medication authorized by the FDA for the treatment of ADHD, and it was based on a series of double-blind, RCTs in children under 6 years of age, adolescents, and adults. In a thorough, in-depth meta-analysis that included information from 24 RCTs in paediatric ADHD, the effect size for overall ADHD symptom improvement with ATX was 0.64[44]. It was often 4 weeks after the commencement of therapy before significant changes in ADHD symptoms versus placebo were seen[44]. Atomoxetine was linked to a bimodal response, meaning that 40% of patients were classified as non-responders at the end of the study while 45% of patients fared noticeably better[44].

##### Dasotraline

Since dasotraline primarily inhibits dopamine transporters (DAT) and NET while inhibiting serotonin transporters (SERT) less, it is categorized as a dual reuptake inhibitor[45]. Similar to ATX, dasotraline development in adults was stopped due to inefficiency[46,47]. The effects of dasotraline on adults and kids with ADHD were then studied in a series of RCTs, starting with a Phase 2 proof-of-concept study in adults given either 4 mg or 8 mg (estimated DAT receptor occupancy, 56% and 71%, respectively)[48]. In this exploratory investigation, just 8 mg of dasotraline was more effective than a placebo in reducing all-around ADHD symptoms (effect size, 0.41), although it was poorly tolerated (discontinuation owing to AEs, 28%). Dasotraline dosages between 2 and 6 mg were tested in later Phase 3 RCTs for ADHD[49–51].

##### OPC-64005

OPC-64005 (SERT, NET and DAT) is a triple reuptake inhibitor[52]. OPC-64005 (titrated up to 30 mg/day) was contrasted with placebo and ATX (titrated up to 80 mg/day) in a Phase 2 flexible-dose study in patients with ADHD[53]. The study's findings were kept confidential.

#### *Receptor modulators - clonidine and guanfacin*

The two extended-release forms of the α2 adrenoreceptor agonists, guanfacine and clonidine, are the only FDA-approved ADHD medicines with pharmacologic actions presumably restricted to receptor modification. Clonidine appears to be more selective for presynaptic α2A, α2B and α2C receptors than postsynaptic 2A receptors, whereas guanfacine appears to be more selective for postsynaptic α2A receptors[54]. Contradictory results have been found in clinical studies on a number of receptor modulators, including nicotinic acid, histamine, gamma-aminobutyric acid (GABA), 5-HT, and adenosine A2A, despite the fact that these compounds have attracted a lot of interest for their potential to treat ADHD[55]. None have advanced to Phase 3 studies in people with ADHD; as a result, it is doubtful that they will ever be clinically accessible[56].

#### *Multimodal agents*

Pharmaceuticals known as "multimodal" drugs combine receptor modulation (agonist and/or antagonist) action with transporter modulation or inhibition (e.g. NET, SERT and DAT). Many of these substances are being studied as possible therapies for ADHD[55].

#### *Viloxazine*

The United States Food and Drug Administration (FDA) approved a novel stimulant viloxazine extended-release (ER), also called SPN-812, after nearly 10 years[49]. It was marketed under the trade name QELBREE™, targeted to treat ADHD in paediatric and adult patients[50]. In several open-labelled randomized controlled studies, Viloxazine has been proven effective in

various kinds of mood disorders (depression, anxiety) and associated comorbid conditions like alcohol dependence, obesity, and substance abuse[51,56]. A recent case report by Naguy and colleagues also reported that add-on Viloxazine to Clozapine-Responsive Schizophrenia successfully mitigated metabolic parameters and addressed clozapine-sialorrhea[57].

Further studies by Yu and colleagues suggest a powerful mechanism for increased serotonin is the inhibition of the inhibitory 5-HT-2B-GABA interneurons, which generally decrease the release of serotonin at the synapse. By modulating the interneuron, there is an increased release of serotonin, especially in the prefrontal cortex area. It is likely that the therapeutic effect of ADHD is due in significant part to these serotonergic effects with some enhancement by norepinephrine and dopamine[58].

Viloxazine blocks the reuptake of norepinephrine in the amygdala, nucleus accumbens, and prefrontal cortex of the brain[58]. On a stereochemical level, the S isomer of Viloxazine resembles the R-isomer of norepinephrine[58]. Additionally, this results in increased dopamine via the inhibition of the norepinephrine transporter, which also is responsible for the uptake of dopamine in some areas of the cortex. The increased dopamine effects from reuptake inhibition are seen primarily on the prefrontal cortex and amygdala but notably not in the nucleus accumbens, which is one of the brain's reward centres. It is possible the lack of dopamine modulation in the nucleus accumbens reduces the potential for addiction, which differentiates Viloxazine in an essential way from stimulant medications currently used to treat ADHD[49].

Many patients under psychiatric care are taking drugs that are substrates or inhibitors of CYP enzymes. Because Viloxazine is majorly metabolized by CYP2D6, special care must be taken to monitor possible side effects. One single sequence study on the pharmacokinetics of Viloxazine showed only a modest increase in Viloxazine and its metabolites when taken with paroxetine, a potent CYP inhibitor, and no adverse toxicities or side effects were noted[59]. Because Viloxazine is also minorly metabolized by other CYP enzymes, the effects of an inhibitor, in this case, were not clinically significant. Based on this data, interaction with multiple CYP inhibitors or substrates is theoretically possible and should be monitored in patients treated for depression and other psychiatric comorbidities (Figure 1).

In patients treated for co-occurring anxiety and ADHD, first-line treatment with stimulants can exacerbate anxious feelings[60]. In this case, non-stimulant options such as atomoxetine along with non-pharmacological therapies are used. Viloxazine is a non-stimulant drug that may be helpful for patients whose anxiety is worsened with first-line medications. Viloxazine is another drug in the toolbox of practitioners co-treating ADHD and substance use disorder. It is hypothesized that because Viloxazine does not antagonize dopamine reuptake in the reward centre of the brain, it lacks the addictive effects of methylphenidate and dexamphetamine[50].

One study, a bayesian meta-analysis of the use of anti-depressants, disulfiram and anti-epileptic medications in subjects with alcohol use disorder, found Viloxazine to be highly effective in reducing depressive symptoms when compared to SSRIs and venlafaxine. There were no additional adverse effects of viloxazine use in the alcohol use disorder cohort[61,62].

In comparison to medications used for depression, the drug viloxazine seems to have anti-epileptic properties at low doses[63]. However, patients concurrently being treated with phenytoin and carbamazepine run the risk of increased serum concentrations and toxicity, which remit when viloxazine therapy is withdrawn[64]. This seems to be due to viloxazine inhibitory effects on CYP1A2, as several anti-epileptic medications are substrates. Levels of anti-epileptic medications or other CYP1A2 substrates should be carefully monitored when co-administering Viloxazine and doses adjusted as needed to avoid adverse effects.

Viloxazine is generally metabolized by the liver before being excreted in the urine. There have been modest elevations in serum liver aminotransferases without a report of jaundice or liver injury in paediatric patients taking Viloxazine for ADHD[65]. Patients with significant liver disease should not use Viloxazine, or if needed, levels need to be monitored and doses adjusted accordingly. Adults with liver disease needing viloxazine therapy should be monitored closely (Tables 1, 2).

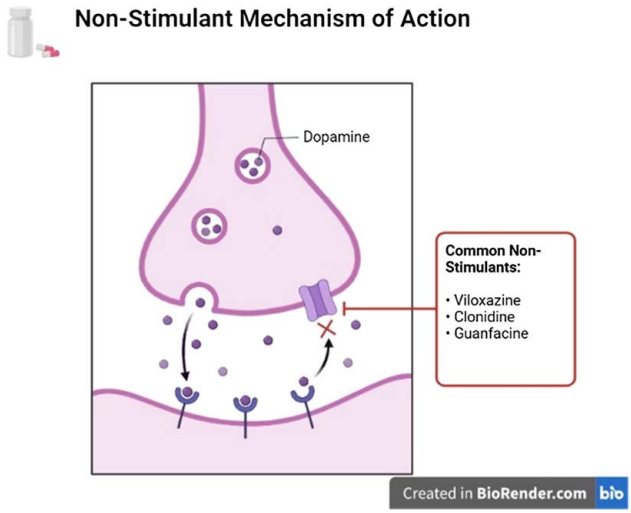


**Figure 1.** Mechanism of action of non-stimulant drugs.

## Prognosis ADHD

For individuals with ADHD, a meta-analysis of follow-up studies depicted that at 25 years of age:

**Table 1**

**Aetiological factors associated with ADHD.**

| | |
|---|---|
| Genetics | People who have a parent or sibling with ADHD are more likely to have ADHD themselves, and twins are more likely to both have ADHD. |
| Birth factors | Born very early or very low birth weight. |
| Factors for the expectant mother include: | Smoking |
| | Drug use or alcohol use |
| | Use of certain drugs, such as corticosteroids and antidepressants |
| | Mental problems |
| | High blood pressure |
| | Hyperthyroidism |
| | Exposure to certain environmental toxins, such as lead. |
| TOXINS | Exposure to toxins such as lead increases her risk of ADHD. |

ADHD, attention deficit hyperactivity disorder.

**Table 2**

**Comorbidities associated with ADHD.**

| Comorbidity | Principal disease | Incidence | Comments |
|---|---|---|---|
| (1) Bipolar disorder | Bipolar I | Lies between 5.1 and 47.1%. | Comorbid ADHD hastens earlier onset of bipolar symptoms and worsens the disease with frequent manic and depressive episodes. A longitudinal study, conducted to assess whether ADHD in children would result in manic episodes in adulthood was conducted over 11 years, showed that these children had higher rates of developing bipolar disorder by the age of 22 years. Several symptoms of ADHD and Bipolar disorder overlap, making diagnosis difficult for physicians[66–68]. |
| (2) Personality disorders | Cluster B [more common] and Cluster C disorders | 50% of adults with ADHD are seen to have cluster B and C disorders. | These patients show marginal response to methylphenidate therapy. ADHD presenting with emotional dysregulation has a higher prevalence of these personality disorders[29]. There is found to be troubling less response to ADHD therapy in patients with high personality disorders[66]. |
| (3) Depression | | 18.6–53.3%[67]. | There is a greater burden of both depression and ADHD. This might be due to the low hedonic tone of ADHD manifesting as depression[68]. Undetected ADHD in these patients is mostly due to serotonergic drugs which lower the dopamine and noradrenaline levels[69]. To diagnose depression in these adults, there must be suicidal ideation and a static depressed affect. |
| (4) Anxiety disorders | Social phobia | There is a 50% risk for anxiety disorders in ADHD patients[70]. | In the presence of ADHD; these individuals have severe anxiety and an earlier onset of symptoms. As the presence of anxiety inhibits impulsivity, a major symptom of ADHD, it is diagnosed later in life[71]. This correlation can be attributed to poor dorsolateral prefrontal activity. A study showing ADHD children with delayed maturation in their prefrontal cortex supports this theory[72]. There is no difference in response to ADHD treatment in high vs. low anxiety patients[73]. |
| (5) SUD | Alcohol, nicotine, cocaine and cannabis use[74]. | 15–25% of adults with an substance use disorder have a comorbid ADHD[75]. | ADHD adults who use cigarettes have significant physical dependence to nicotine[76]. As impulsivity is a key symptom of ADHD, it leads to increased alcohol consumption[77]. SUDs occur due to neurobiological characteristics, behavioural symptoms and self-medicating on ADHD treatment. Adults with ADHD and SUDs have shown more suicidal attempts, increased hospital admissions and lesser rates of adherence to treatment[75]. Screening must therefore be performed in ADHD individuals for SUDs[78]. |

ADHD, attention deficit hyperactivity disorder, SUD, Substance use disorder.

Approximately 15% retained the full ADHD diagnosis (Persistent ADHD).
Approximately 65% were in partial remission; (with persistence of some symptoms and continuing significant functional impairment, such as psychological, social or educational difficulties)[32].

While symptoms of hyperactivity tend to remit over time, impairments in attention persist. In fact, due to the lack of hyperactivity and impulsivity in patients with predominantly inattentive presentation of ADHD, they are usually less disruptive in primary school than children with combined ADHD and often present later (e.g. middle school, high school)[62].

Adolescents and adults with ADHD symptoms are more likely to struggle in school and at work, have maladaptive relationships, increased injuries and car accidents, and teen pregnancies[79–81]. ADHD is associated with increased risks of psychiatric disorders, including oppositional defiant disorder, conduct disorder, substance abuse, and possibly mood disorders, such as depression and mania. Autism spectrum disorder, dyslexia, dyscalculia and dyspraxia are also over-represented. Therefore, the overall prognosis of the individual depends on the severity and management of any comorbid disorders[32].

However, the adult prognosis for the ADHD child is not fully revealed by these relative impairments. In fact, majority of these individuals were gainfully employed. In addition, two-thirds of these children showed no signs of any mental illness in adulthood. In conclusion, although ADHD children, as a group, fare poorly compared with their non-ADHD counterparts, the childhood syndrome does not preclude achieving high educational and vocational goals, and most children no longer exhibit clinically significant emotional or behavioural difficulties once they reach their mid-twenties[19].

Thus, it is crucial that these individuals get medical attention as early as possible. In the long run, these recommended therapies and medications will aid the affected individuals in coming to terms with their condition and coping with their situation. Timely diagnosis, appropriate medications and supportive therapies along with an empathetic environment will help patients with ADHD lead fulfilling lives.

## Future challenges

Many national and international guidelines recommend a multimodal approach to ADHD treatment[82,83]. The American Academy of Pediatrics (AAP) suggests that children with academic or behavioural problems and difficulty with attention, hyperactivity or impulsivity should be evaluated for ADHD. The guidelines encourage medical professionals to gain reports and statements regarding the child's symptoms from parents, teachers, caregivers and, importantly, the child. The DSM-5 criteria must be met, as well as the exclusion of other medical conditions that may present similarly. The recommendations also suggest screening for comorbid conditions that commonly occur with ADHD to ensure comprehensive management.

Parent training in behaviour management is recommended as first-line therapy in children ages 4–18. If the child/adolescent's school programme offers behavioural classroom interventions, it is considered a necessary aspect of the treatment plan. For children ages 4–6 years, methylphenidate is used after the first-line treatments of behavioural therapy and interventions have been exhausted. Children and adolescents ages 6–18 years are recommended to utilize approved medications, behavioural

classroom interventions or parent training in behaviour management. Schools often offer Individualized Education Programs (IEP) or a 504 plan for extra support. Lastly, the AAP guidelines encourage adjusting medication dosages to optimize treatment while minimizing side effects. Once the child reaches adolescence, the patient should begin to partake in their treatment plan and ultimately approve their care[82,83].

Due to the newness of Viloxazine for use in ADHD, it has not yet been proven efficacious to other pharmaceuticals. Although many studies, including a meta-analysis of 1605 participants across five RCTs, concluded Viloxazine ER to be more productive than placebo[84], additional studies are needed to conclude comparative efficacy. Whether Viloxazine's usefulness will outweigh others is still to be determined; its recent widened approval should allow more studies to reveal its potential advantage in ADHD treatment. An article from the Carlat Child Psychiatry Report compared Viloxazine with Strattera (Atomoxetine), noting the newly approved ADHD medication could have an advantage due to its more significant rapid onset[85].

Diagnostic materials such as the DSM-V, vision and hearing tests, and neurologic assessments are used throughout a patient's care to aid in correctly diagnosing the condition. Many reviews are used during the diagnosis, treatment, and follow-up of patients of various age groups with ADHD. Once other psychiatric disorders and learning disabilities have been ruled out, the appropriate scales may be utilized. It is important to note that the various ADHD scales are only a contribution to the overall assessment and treatment and are recommended to be used in conjunction with other modalities of ADHD treatment. Focusing on a child's symptoms or treatment progression may be difficult due to the various people and places the patient encounters daily. The scales are a valuable set of tools that allow the child, parents, teachers, coaches, etc., to collect and evaluate information in an organized manner[86].

Clinicians can utilize a variety of tools depending on the age of a patient, as well as which stage of ADHD they are managing. The use of the tools can be beneficial before and after treatment with an ADHD pharmaceutical agent(s), such as Viloxazine. Children and adolescent scales primarily consist of questionnaires that are targeted at the patient's parents, teachers, or caregivers. It is recommended that multiple people who regularly interact with the patient complete the same forms to gain a more comprehensive picture of the child and how they interact in various environments[87]. For instance, the Child Behaviour Checklist (CBCL/6–18) is a 120-question form that assesses a child based on questions that use a scale from 0 to 2, with 0 being "not true" to 2 being "very true/often true"[88]. Other ADHD assessment scales, such as Conners' and Vanderbilt, are utilized similarly[89,90].

The following scales could be used before and during treatment with Viloxazine to enhance the patient's overall treatment plans. Adult Rating Scales are also used during diagnosis, treatment, and follow-up of patients with ADHD symptoms or diagnosed with ADHD[91]. The Adult ADHD Self-Report Scale is constructed for individuals to self-report, as stated in its title. This short, 18-item tool is beneficial as a first-line assessment for adults who may be experiencing ADHD symptoms[92]. To follow patients who have ADHD symptoms, the ADHD Rating Scale-IV is an 18-item assessment that has patients score the frequency and severity of their symptoms on a 4-point scale ranging from 0 (never) to 3 (very often)[93].

## Conclusion

In conclusion, adult ADHD is a complex condition that has a significant impact on the quality of life of people who have it. It is a relatively new area of study that has garnered a lot of interest recently. The considerable research has provided fresh perspectives on the causes, symptoms and therapies of adult ADHD. There are effective medications available that could aid people with ADHD in improving their symptoms and functioning, despite the challenges associated with diagnosis and therapy. To ensure that individuals with ADHD receive the required assistance and treatment, it is imperative to increase awareness of ADHD among medical professionals and the general public. Further research is needed to develop more effective treatments for this population and to better understand the complex nature of adult ADHD.

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## Availability of data and material

The data supporting this review are from previously reported studies and datasets, which have been cited. Please refer to the manuscript for this data.

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