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General

Viloxazine for the Treatment of Attention Deficit Hyperactivity Disorder

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Purpose of Review

Attention deficit hyperactivity disorder (ADHD) is a widely diagnosed neurodevelopmental disorder giving rise to symptoms of hyperactivity, impulsivity, and inattentiveness that can impair daily functioning. Stimulants, such as methylphenidate and amphetamines, are the mainstay of treatment for ADHD. However, nonstimulant drugs such as viloxazine, atomoxetine, guanfacine, and clonidine are becoming more popular due to minimal adverse effects when compared to stimulants.

Recent Findings

Viloxazine is a selective norepinephrine reuptake inhibitor (NRI) originally used to treat depression in adults with activity in both the noradrenergic as well as serotonergic pathways. Studies have demonstrated its efficacy for its use in the treatment of ADHD. Unlike stimulants, viloxazine has a decreased chance of substance abuse, drug dependance, and withdrawal symptoms upon the cessation of therapy. Additionally, dopamine levels in the nucleus accumbens after treatment with viloxazine are elevated considerably less in comparison with traditional stimulant ADHD treatments. Viloxazine provides an alternative, nonstimulant approach to treating ADHD.

Summary

Viloxazine is a recently approved, non-stimulant medication functions by inhibiting the uptake of norepinephrine which has been seen to be decreased in patients with ADHD. When patients do not respond to first-line stimulants, cannot tolerate the side effects, or have contraindications to stimulants, viloxazine may be a nonstimulant option offering patients an increasing arsenal of medications to treat ADHD.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a persistent neurodevelopmental disorder that affects more than 5% of children and adolescents and 2.5% of adults worldwide.[1] ADHD is diagnosed clinically based on criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) that includes inattention and/or hyperactivity that is inconsistent with the individual's level of development for at least six months.[2] Additionally, symptoms must be present before the age of 12 and occur in multiple settings. Symptoms of ADHD present as a wide range depending on the individual but can impair functioning in many aspects of the individual's well-

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being including physical health, academic, social, and occupational functioning.[3] Individuals with ADHD, especially those that are diagnosed in adulthood, are often diagnosed with comorbidities such as mood disorders, anxiety disorders, substance use disorders, and conduct disorders.[4] The cause of ADHD is multifactorial due to genetic, social, economic, and environmental factors. However, it is important to note that the genetic component is very prominent with an estimated heritability of 60-80%.[2]

Currently, stimulants such as methylphenidate and dextroamphetamine-amphetamine are considered first-line therapy for ADHD. However, nonstimulant drugs such as viloxazine, atomoxetine, guanfacine, and clonidine are becoming more popular due to minimal adverse effects when compared to stimulants.[3] As prevalence of ADHD is increasing, different pharmacological therapies continue to be an opportunity for research to minimize the wide variety of symptoms that patients being treated for ADHD with stimulants may experience.

EPIDEMIOLOGY, PATHOPHYSIOLOGY, RISK FACTORS, AND PRESENTATION OF ADHD

EPIDEMIOLOGY

When initially determining prevalence in the 1970s and 1980s, the number of children being treated for ADHD was rapidly increasing. This led to concerns that ADHD was being overly diagnosed or possibly a cultural product of competitive developed societies.[3] However, more recent studies have determined that ADHD has a worldwide prevalence of about 7.2%, which is equivalent to 5.4 million children.[5] According to the 2011 National Health Interview Survey, prevalence in males was nearly double the prevalence in females, most likely because males present as disruptive while females are more inattentive.[2] The median age of diagnosis is 7 years old and usually persists into adulthood. Recent studies have estimated the prevalence of ADHD in adults above 18 years old to be 2.5%.[3]

RISK FACTORS

ADHD is considered a multifactorial disorder because numerous causes contribute to its development including genetics, lifestyle, and environment. However, genetics is currently considered the primary component due to an estimated 60-80% heritability as determined by multiple family-based studies.[2] Additional risk factors include birth complications, traumatic brain injury, maternal alcohol or tobacco consumption, maternal stress during pregnancy, prematurity, toxin exposure, family adversity, low income, and severe deprivation in childhood.[2]

PATHOPHYSIOLOGY

Although the pathophysiology of ADHD is not entirely clear, it is believed that a combination of neurotransmitter dysfunction, differing brain structures (though research has been inconsistent), and decreased cognitive functioning precipitate the development of symptoms in ADHD. Regarding neurotransmitter dysfunction, it has been hypothesized that a decrease in the catecholamines, dopamine and norepinephrine, lead to a delay in the communication between neurons. In children with ADHD, early neuroimaging has shown maturational abnormalities with a 2-3-year delay in reaching peak thickness of the cerebrum and prefrontal cortex.[3] Additionally, structural deficits in the frontal lobe, thalamus, and striatum (key components of the cortico-striato-thalamo-cortical loop for attention and cognitive processing) have been associated with the emergence of ADHD.[2] Imaging is similar in adults, which indicates smaller volumes in the frontal cortex, cerebellum, and subcortical structures.[6]

PRESENTATION OF ADHD

As previously stated, symptoms of ADHD come in a wide variety and can present differently in every patient. Diagnosis is made clinically via DSM-5 criteria that includes inattention and/or hyperactivity for at least six months, must be present before 12 years of age, and must be present in at least two settings.[3] In boys, ADHD predominantly presents as hyperactive behaviors such as restlessness, excessive talking, and difficulty waiting their turn.[5] However, girls exhibit inattentiveness via becoming easily distracted, not listening when spoken to, or working in a disorganized fashion. As they enter adolescence, hyperactivity and impulsivity decline and inattentive symptoms become more prominent. Moreover, adults present with deficient executive functions such as working memory, shifting tasks, initiation, and self-inhibition.[7]

CURRENT TREATMENT OPTIONS FOR ADHD

Over the years, much has been known about the pathophysiology of this disease entity and the ability to treat ADHD. Multiple centers of excellence including the American Academy of Pediatrics and Child and Adolescent Psychiatry have formulated guidelines in managing ADHD according to the age group.[8,9] Though the main stay of treatment for ADHD remains behavioral therapy techniques for pre-school children; medications are the first-line management for children ⩾ 6 years.[10–15] ADHD is a multifactorial disorder which incorporates neuropsychological, behavior-based, and emotional-based abnormalities, not just the symptoms; as a result, multiple management strategies are based on a combination of medications, behaviorial therapy, and combined interventions.[16–19]

For over eight decades, stimulant medications have been the mainstay of management in ADHD. Stimulants lead to an increase in release of catecholamines through dopaminergic and noradrenergic pathways, but the exact mechanism remains unknown.[13] In 1937, benzedrine sulfate, an amphetamine, became the first FDA medication approved for the treatment of ADHD. It was noticed that administration of benzedrine sulfate led to an increase in emotional responses and improvements in interactions, engagements, and school performances.[20] This eventually led to a formulation of methylphenidate - a stimulant medication, com-

Table 1a. Selected immediate-release stimulant preparations and dosing for children with ADHD.[13,23–25]

Medications	Medication Formulations	Dosages and Increments	Maximum Dosage/Day	Duration of Action
Methylphenidate	5, 10, 20 mg tablets 2.5, 5, 10 mg chewable tablets 5 mg/5 mL flavored oral solution 10 mg/5 mL flavored oral solution	5 mg once per day on Day 1, then 5 mg 2 times per day, increments of 5 mg/day can be made every 3 to 7 days Children ≤ 25 kg may be started with 2.5 mg per day and increased by 2.5 mg/day every 3 to 7 days	For children ≤ 25: 35 mg For children 25 kg or more: 60 mg	3-5 hrs
Dexmethylphenidate	2.5, 5, 10 mg tablets, non-scored	For patients not on methyphenidate use: 2.5 mg 2 times/day, increments of 2.5 to 5 mg/day every 3 to 7 days. For patients already on methyphenidate use: dose is one-half current daily dose up to 10 mg 2 times/day	20 mg	6-8 hrs
Amphetamine	5, 10 mg tablets, scored 2.5, 5, 10, 15, 20 mg orally disintegrating tablets	For 3-5 years: 2.5mg daily, increments of 2.5 mg/day every 7 days For ≥ 6 years: 5 mg 1 or 2 times/day, increments of 2.5 mg to 5 mg/day every 7 days depending on the formulation	40mg	4-6 hrs
Dextroamphetamine	2.5, 5, 7.5, 10 (scored), 15, 20, 30 mg tablets 5 mg/5 mL flavored oral solution	For 3 to 5 years: 2.5 mg once on Day 1, then 2.5 mg 2 times per day, increments of 2.5 mg/day every 3-7 days For ≥ 6 years: 5 mg once on Day 1, then 5 mg 2 times/day; increments of 5 mg/day every 3-7 days	For 3-5 years: 20 mg For ≥ 6 years and ≤ 50 kg: 40 mg For ≥ 6 years and ≤ 50 kg: 60 mg*	4-6 hrs

Doses of immediate-release preparations are given in the morning on rising and at lunch time 4 to 6 hours later. *Doses above 40 mg per day total are rarely needed and warrant close monitoring for adverse effects.

monly known as Ritalin – being approved by the FDA in 1955.[8] Now, stimulant medications such as methylphenidate (Ritalin, Methylin, Metadate, and Concentra) and amphetamines (Adderall, Dexedrine, and Dextrostat) are the first-line medications for ADHD.[16,19,21,22] Both methylphenidate and amphetamines are available in different forms (tablet, capsules, patch, oral suspension, or disintegrating tablets) and variety of formulations such as short, immediate or long-acting.[17–19] Response rate to dosing are highly variable. Guidelines to the dosage according to different formulations are represented in Tables 1A & B.

Growth should be continuously monitored as common side effects include poor growth, anorexia, weight loss, social withdrawal, jitteriness, and sleep disturbances. Other side effects such as increase in heart rate and blood pressure, headaches, dizziness, priapism, tics, and peripheral vasculopathy such as Raynaud's phenomenon have been noted; furthermore, symptomatic cardiovascular disease is a contraindication to stimulant use due to its increase in heart rate and blood pressure.[26–33] Moreover, stimulants have an addictive tendency with a potential of misuse to achieve euphoria in high-school and college-age students.[34,35]

To avoid the use of stimulants, the use of FDA-approved nonstimulants can be employed such as selective norepinephrine (NE) reuptake inhibitors (NRI), atomoxetine and viloxazine. They function by blocking the reuptake of NE in the nerve terminals, increasing the concentration of NE in the synapse.[15,36] The dose of atomoxetine (Strattera) depends on the child's weight; it is administered once or twice a day lasting 10-12 hours with a typical onset of action between 6-12 weeks.[15,23,37–39] The side effect profile of atomoxetine is similar to stimulants with the differences being that it can cause severe liver injury and an increase in suicidal ideations and behaviorial problems.

Metabolism is via the CYP450 system, and care should be taken when given with other medication that are metabolized by the same system as it can either increase or decrease serum concentrations.[15,27,40–47] For those who have contraindications, severe side effects, or poor response to

Table 1b. Commonly used intermediate and long-acting medications for children with ADHD.[13,23–25]

Medications	Medication Formulations	Dosages and Increments	Maximum Dosage/Day	Duration of Action
Methylphenidate	Methylphenidate ER 10 and 20 mg tablets	Initial dose of 10mg, increments of 10 mg/day every 3-7 days	≤ 50 kg: 60 mg > 50 kg: 100 mg *	Delayed onset with continuous release over 3 to 8 hours
	Methylphenidate ER chewable tablets 20 and 30 mg (scored), 40 mg (not scored)	Initial dose of 20 mg, increments of 10, 15, or 20 mg/day every 7 days	60 mg	Continuous release over 6 to 8 hours with duration of action up to 13 hours
	Methylphenidate ER 18, 27, 36, 54 mg tablets	Initial dose of 20 mg, increments of 9 to 18 mg/dose every 3-7 days	<13 years: 54 mg ≥13 years: 72 mg	20% immediate-release and 80% continuous-release over 10 to 12 hours by osmotic delivery
	Methylphenidate patch** 10, 15, 20, 30 mg patch	Initial dose of 10mg**, increments of 5 mg/dose every 3 to 7 days	30 mg	Onset 2 hours after application of patch and continuous release over 9 to 12 hours
	Methylphenidate LA (RITALIN) 10, 20, 30, 40 mg capsules	Initial dose of 10 or 20 mg, increments of 10 or 20 mg/dose every 3-7 days	≤ 50 kg: 60 mg > 50 kg: 100 mg *	50% immediate-release and 50% delayed-release over 8-12 hours
Dexmethylphenidate	Dexmethylphenidate XR 5, 10, 15, 20, 25, 30, 35, 40 mg capsules	Initial dose of 5 mg, increments of 5 mg/ dose every 3-7 days	40 mg	50% immediate-release and 50% delayed-release over 10-12 hours
Amphetamines	Dextroamphetamine-amphetamine ER **(**Adderall XR**)** 5, 10, 15, 20, 25, 30 mg capsules	Initial dose of 5 mg, increments of 5 mg/ dose every 3-7 days	≤ 50 kg: 40 mg > 50 kg: 60 mg ***	Combination of immediate- and continuous-release over 10 to 12 hours
	Dextroamphetamine SR *** 5, 10, 15 mg capsules	Initial dose of 5 mg, increments of 5 mg/ dose every 3-7 days	≤ 50 kg: 40 mg > 50 kg: 60 mg ***	Combination of immediate and continuous-release over 8-12 hours

*This maximum dose exceeds the FDA-approved maximum dose; careful monitoring for adverse effects is warranted. **Patch is applied 2 hours before needed effect and worn for a total of 9 hours. Doses for the methylphenidate patch are not equivalent to those for the oral preparations. ***Doses above 40 mg per day total are rarely necessary and warrant close monitoring.

stimulants or NRIs; alpha-2-adrenergic agonists such as extended-release clonidine and guanfacine can be prescribed for age groups 6-17. These drugs have been shown to improve ADHD symptoms but not to the same extent as stimulants alone and were not superior to stimulants; in fact, combination therapy has proven to be more beneficial in improving ADHD symptoms, tic disorders, and improving working memory.[13,48–58]

Due to their similar mechanism of action, tricyclic antidepressants (TCAs) such as imipramine, desipramine, nortriptyline; and dopaminergic re-uptake inhibitors (bupropion) have also been indicated for use in ADHD as reserve agents to those who respond poorly, have unacceptable side effects, or contraindications to stimulants.[59–61] Other investigational drugs for the treatment of ADHD, including cholinesterase inhibitors (tacrine and donepezil) and nicotinic analogues (ABT-418), are under investigation.[62]

VILOXAZINE DRUG INFO

Viloxazine (Qelbree by Supernus Pharmaceuticals) is a recently FDA approved non-stimulant drug for ADHD.[63] Previously used for its anti-depressive effects, viloxazine has been now shown to have effects on blocking the noradrenergic reuptake and has a low abuse potential; it now represents an alternative to stimulants for managing ADHD.[63–68]

Viloxazine is available as an extended-release capsule to be taken once daily (OD) with recommended dosing based on the age group. For ages 6-11, recommended starting dosage is 100 mg titrating upwards to a maximum dosage of 400mg.[69] For ages 12-17, recommended starting dosage is 200mg and titrating up to a maximum of 400 mg.[69] Patients receiving viloxazine should be very closely monitored for any evidence of suicidal behavior or thoughts as there is

an FDA black box warning.[69] Viloxazine can be associated with adverse effects such as increase in heart rate and blood pressure, exacerbation of manic or hypomanic episodes in patients with concomitant bipolar disorder, excessive somnolence, and fatigue.[69] The concomitant use of viloxazine and monoamine oxidase inhibitors (MAOIs), or initiation of viloxazine within 14 days of discontinuing MAOIs, should be avoided as there is an increased risk of hypertensive crisis.[69] The use of viloxazine in pregnancy is limited but is based on the animal representation model studies; thus, it is recommended to discontinue viloxazine once pregnancy is identified.[69]

MECHANISM OF ACTION OF VILOXAZINE

Viloxazine was originally used in Europe to treat depression in adults with activity in both the noradrenergic as well as serotonergic pathways. It initially garnered attention as a potential nonstimulant treatment for ADHD due to its different inhibitory potency for norepinephrine (NE) and 5-HT and reuptake of NE.[70–72] Viloxazine functions by increasing the availability of both NE and 5-HT in the prefrontal cortex of patients by inhibiting the neurotransmitter transporters specific to these chemicals, resulting in an improvement of ADHD related symptoms including impulsivity, hyperactivity, and attention deficit.[73] Viloxazine exhibited a moderate inhibitory activity on norepinephrine transporter (NET) with an IC_{50} (half maximal inhibitory concentration) around 0.3 μM; this relatively low IC_{50} on NET in relation to other drugs of this class is responsible for the marked decrease in cardiac related side effects traditionally seen in NRIs such as atomoxetine and reboxetine.[74–77] Increased extracellular concentrations of NE and 5-HT in the prefrontal cortex, nucleus accumbens, and amygdala have been shown as a result of viloxazine administration in rodent models.[77,78] Double-blind placebo controlled clinical trials in children revealed a significant alleviation of ADHD symptoms as determined by ADHD Rating Scale 5 (ADHD-RS-IV) rating scores in200mg, 300mg, and 400mg extended release dose ranges.[79,80]

Viloxazine has also demonstrated agonistic activity on 5-HT_{2C} receptors and antagonistic activity on 5-HT_{2B} receptors expressed in the central nervous system. These G-protein coupled receptors are expressed widely within areas of the central nervous system, including the prefrontal cortex, amygdala, nucleus accumbens, and hypothalamus. These serotonin receptors modulate neurotransmitter release in these areas of the brain and produce effects on mood, anxiety, behavior, and locomotion.[77,81–83] Pre-clinical animal trials have demonstrated increased levels of dopamine in the prefrontal cortex, nucleus accumbens, and amygdala as a result of viloxazine administration.[77] Elevated extracellular dopamine levels in the nucleus accumbens have been implicated in the pathophysiology of addiction and substance abuse.[84,85] Notably, dopamine levels in the nucleus accumbens after treatment with viloxazine are elevated considerably less in comparison with traditional stimulant ADHD treatments such as methylphenidate and amphetamine suggesting the potential for a lowered chance of substance abuse, drug dependance, and withdrawal symptoms upon the cessation of therapy in patients taking this medication.[77,86] High rates of substance abuse among adults with ADHD have been documented, and the potential for use of these non-stimulant treatments could make viloxazine beneficial to these patients.[87,88]

PHARMACOKINETICS/PHARMACODYNAMICS OF VILOXAZINE

Viloxazine was initially offered in an instant release formulation to be administered orally two to three times daily in adults for the treatment of depression. Current formulations to treat ADHD in pediatric patients and adults are now offered in once daily oral doses and were approved for its first use in the United States in April of 2021. These extended-release treatments are now offered in 100-600 mg dosages.[72,73]

Viloxazine is predominantly metabolized via the 5-hydroxylation by cytochrome P450 isoenzyme CYP2D6, with the majority of its metabolites excreted renally through urine; it has exhibited reversible inhibition of CYP1A2, 2B6, 2D6, and 3A4/5 with an IC_{50} of 0.269,184,141,221 μM respectively.[89] Volume of distribution of viloxazine following IV dosing is 0.73 ± 0.28 L/kg, and its absolute oral availability has been determined to be 85 ± 13%.[90] In a clinical trial examining the pharmacokinetics of viloxazine in healthy adults, the C_{max} (maximum measured plasma concentration of participants) of a 700 mg extended-release dose was determined as 4.73 ± 0.86 μg/mL and occurred 5 hours after dose administration. The half-life elimination for viloxazine ranges from 3 to 9 hours with a clearance rate of 6.29 ± 6.89 L/h in children and 7.88 ± 7.01 L/h in adolescents. Body weight has been identified as a prospective source for variability in the pharmacokinetics of viloxazine with a linear correlation between body mass index and drug exposure levels; however, further studies will be necessary to shed more light on this trend.[91,92]

Drug holidays are days or periods of time in which patients skip doses of medications and are often utilized by patients undergoing long-term ADHD therapy. These holidays as well as treatment adherence should be considered by physicians prior to beginning ADHD treatments, particularly in children and adolescents. The primary purpose of these holidays is to increase tolerability of the drug and to decrease the severity of adverse side effects such as insomnia and weight loss common in patients prescribed stimulants. Drug holidays typically coincide with school holidays or weekends and typically terminate with the resumption of school related activities.[92–94] The pharmacological effects of drug holidays consisting of 1-4 missed daily doses in patients taking viloxazine after steady state has been achieved have been analyzed. After cessation of therapy, drug levels dipped below the level of quantification (0.01μg/mL) and were achieved within three days, regardless of drug dose. Upon resuming therapy, steady state plasma concentrations were achieved on average within two doses. This suggests viloxazine plasma concentrations can quickly return to therapeutic levels in patients who have taken a drug

holiday or who have simply missed a dose, which is common in adolescents who self-administer medication making it a good option for patients that fall into this category.[92,95,96]

CLINICAL STUDIES: SAFETY AND EFFICACY OF VILOXAZINE

A phase III randomized control trial sought to measure the safety and efficacy of a viloxazine extended release (ER) formulation (SPN-812) in male and female children diagnosed with ADHD between the ages of 6-11 years old.[97] A double-blind method was utilized to randomize 477 individuals into a placebo, 100 mg, or 200 mg SPN-812. The effectiveness of the SPN-812 was measured through ADHD-RS-5, Clinical Global Impression-Improvement (CGI-I), Conners 3–Parent Short Form (Conners 3–PS), and Weiss Functional Impairment Rating Scale–Parent (WFIRS–P) by evaluating changes in scores obtained throughout the 6-week study.[97] The researchers reported a significant improvement in ADHD-RS-5 scores in impulsive, hyperactive, and inattentive behaviors in both the 100 mg/daily and 200 mg/daily groups versus placebo. Similar improvements were seen in the mean scores from the CGI-I, Conners 3-PS, and WFIRS–P assessment ($p = 0.0020$ and $p < 0.0001$), ($p = 0.0003$ and $p = 0.0002$), and ($p = 0.0019$ and $p = 0.0002$), respectively in comparison to the placebo.[97] When compared to the placebo, the frequent side effects were headaches, somnolence, and decreased appetite in ⩾5% of the participants indicating an overall safe drug profile.[97]

Another phase III randomized control trial assessed the safety and efficacy of SPN-812; however, the treatment groups received either 200 mg/daily, 400 mg/daily, or placebo over an 8 week period.[98] A total of 313 children between the ages 6-11 years were recruited and had their change from baseline (CFB) to end of study (EOS) scores from the ADHD-RS-5, CGI-I, Conners 3-PS, WFIRS-P analyzed to further assess the drug profile of SPN-812. Both 200 mg/daily and 400 mg/daily SPN-812 groups when compared to placebo revealed significant improvement in the ADHD-RS-5 scores ($p = 0.0038$, $p=0.0063$), CGI-I scale ($p = 0.0028$, $p = 0.0099$).[98] While there was a significant reduction in symptoms in all categories of the Conners 3-PS T-scores for the 200 mg/daily group, the 400 mg/daily treatment arm saw a reduction in hyperactivity ($p = 0.0030$) only. The frequent adverse events (AEs) were headaches, somnolence, decreased appetite in addition to fatigue (7.2%) and upper abdominal pain (4.8%) with only 1 participant in the 400 mg/daily group experiencing an increased heart rate and blood pressure.[97,98]

Similar results were obtained in a phase II randomized placebo-controlled trial which assessed the safety and efficacy of viloxazine ER in children diagnosed with ADHD between the ages of 6 to 12 years old.[99] ADHD-RS-5, CGI-S, and CGI-I scales were employed to analyze the different viloxazine groups 100 mg, 200 mg, 300 mg, or 400 mg/daily. A significant improvement in was seen in 200 mg, 300 mg, and 400 mg treatments with an effect size of 0.547, 0.596, and 0.623 respectively ($p < 0.5$). While the CGI-I scores only saw an improvement in the 300 mg treatment arm, the CGI-S scores did not result in significant ADHD symptom reductions in the 100 mg group.[99]

Two clinical trials were performed to examine the effects of dosing with one trial evaluating 200 and 400 mg/daily viloxazine ER in adolescents (12-17 years old) and the second trial evaluted 400 and 600 mg/daily.[100,101] When compared to placebo the 200 mg and 400 mg/daily saw an improvement in the ADHD-RS-5 ($p = 0.0232$, $p = 0.0091$), CBI-I ($p = 0.0042$, $p = 0.0003$) and no improvement in the Conners 3-PS and WFIRS-P scales.[100] The second trial demonstrated a significant change from baseline in the ADHD-RS-5 score for the 400 mg/daily ($p = 0.0082$) only when compared to placebo.[101] There was no significant improvement in the 600 mg/daily group, which the researchers attributed to an abnormally high response rate to the placebo. Both studies exhibited the same the adverse events in ⩾ 5% of the participants including somnolence, fatigue, headache, nausea, and decreased appetite.[100,101]

Additionally, the same group of researchers investigated the effects of a maximum dose viloxazine ER on cardiac repolarization in adults.[102] In a consecutive manner with appropriate 3-day washout periods, 22 participants received placebo, 400 mg moxifloxacin, and 1800 mg viloxazine ER. The corrected QT interval (ΔQTcI) was compared to viloxazine ER and 5-hydroxyviloxazine glucuronide (viloxazine metabolite) plasma concentrations resulting in a negative slope ($p = 0.0012$) and ($p = 0.0007$), respectively.[102] The supratherapeutic doses of SPN-812 did not elicit abnormal cardiovascular parameters and in some cases, a minor decrease in the QT interval was observed indicating the overall safety of the pharmacotherapy.[102]

Exploring the pharmacokinetics of viloxazine alone but also in combination with previously approved stimulant modalities is vital.[103,104] An open-label study assessed the bioavailability and safety of the stimulant used for ADHD methylphenidate (36 mg/daily) alone, viloxazine ER/SP-812 (700 mg/daily), and a combination of both drugs (36 mg + 700 mg/daily).[105] The three treatment arms were administered to 34 healthy adults aged between 18 to 55 years old over a 13-day period. Blood samples were drawn and analyzed using a mass spectrometer to measure bioavailability and possible drug interactions. The geometric low square mean (LSM) ratios (viloxazine ER + methylphenidate/drug alone) with a 90% confidence interval (CI) for the maximum concentrations of viloxazine and methylphenidate were C_{max} 100.98% (96.21–105.99), and 103.55% (97.42–110.07) respectively; which demonstrates no drug-drug interactions on bioavailability.[105] Common AEs that were reported in ⩾ 5% of participants included dizziness, nausea, somnolence, and a single patient displayed an abnormal ECG at EOS which was deemed to be an insignificant finding.[105]

A similar combination trial using lisdexamfetamine (psychostimulant) instead of methylphenidate was performed.[106] The open label trial administered viloxazine ER alone (700mg), lisdexamfetamine alone (50mg), and a combination of both therapies. The researchers reported geometric LSM ratios with a 90% CI for viloxazine maximum concentration, area under concentration-time curve from

time 0 to last measurable time and infinity; C_{max} = 95.96% (91.33–100.82), (AUC_{0-t}) = 99.19% (96.53–101.91), and (AUC_{inf}) = 99.23% (96.61–101.93) respectively. These data suggest viloxazine has no drug interactions with lisdexamfetamine or methylphenidate (as seen in the previous study).[105,106] The investigators reported one moderate AE where an individual experienced vomiting after receiving the combination therapy, and two participants were reported to have abnormal ECGs that were later deemed insignificant.[106] (All studies are summaried in Table 2)

CONCLUSION

ADHD is a widely diagnosed neurodevelopmental disorder giving rise to symptoms of hyperactivity, impulsivity, and inattentiveness that can impair daily functioning. On average, ADHD is diagnosed before the age of 7 and can progress into adulthood.[3] Since the 1930s, stimulant drugs including methylphenidate and amphetamines are considered first-line therapy for ADHD as they can block the transport of dopamine and norephinephrine.[1] However, the side effect profiles are not ideal and response rate is only 70%.[107] There have been reports of stunted height, increased likelihood of substance abuse, increased risk of cardiovascular events with long term use.[1] Moreover, second-line medications fall under the category of "non-stimulants" and can be used if stimulants are not adequate. Viloxazine is an example of a non-stimulant medication that has been recently approved for the treatment of ADHD by inhibiting the uptake of norepinephrine.[107] Adverse effects include decreased appetite, fatigue, insomnia, somnolence, nausea, vomiting, and irritability.[107] In children, viloxazine can be given 100 mg daily with a maximum daily dose of 400 mg. As age increases, initial doses are increased to 200 mg/day and while the maximum dose remains 400 mg/day.[107] Furthermore, patients on viloxazine should be closely monitored due to two significant adverse reactions: cardiovascular effects and suicidal ideation. Although there is need for more research for the safety and efficacy of viloxazine as a treatment for ADHD long-term, it has shown promise in patients who may not respond to first-line treatments.

AUTHOR CONTRIBUTIONS

All authors were involved in the writing and editing of the manuscript.

DISCLOSURES

There are no conflict of interests with the authors.

Table 2. Studies demonstrating th clinical efficacy and safety of viloxazine.

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Nasser et al. (2021)[97]	Four hundred seventy-seven children between ages of 6-11 were randomized to three treatment arms: SPN-812 100 mg/day, SPN-812 200 mg/day, or placebo. Primary outcomes measured by ADHD-RS-5 Total scores from CFB to EOS. Secondary outcomes measured by CGI-I, Conners 3-PS Composite T-score, and WFIRS-P Total average scores compared to placebo.	After 1 week of therapy the ADHD-RS-5 scores were improved in the 100 mg ($p = 0.0004$) and 200 mg/day ($p = 0.0244$) SPN-812 arms and present through EOS ($p = 0.0020$ and $p < 0.0001$, respectively). when compared to placebo. Somnolence, headache, decreased appetite were adverse events seen in ≥ 5% of participants related to treatment.	Viloxazine ER demonstrated a statistically significant reduction in ADHD symptoms in school aged children from both SPN-812 groups. Less than 5% of subjects discontinued the treatment due to AEs suggesting its tolerability and safety.
Nasser et al. (2021)[98]	Three hundred thirteen children ages 6-11 years old were enrolled in a phase III randomized control and administered 200 mg/day SPN-812, 400mg SPN-812, or placebo. The efficacy of the treatment arms were analyzed via ADHD-RS-5, CBI-I, Conners 3-PS, and WFIRS-P scales.	The CFB to EOS in the 200 mg/day and 400 mg/day showed significant improvements in ADHD-RS-5 ($p = 0.0038$, $p = 0.0063$, respectively) and CGI-I scores ($p = 0.0028$, $p = 0.0099$, respectively). Conners 3-PS scale only demonstrated an improvement in the 200 mg/day group, while the WFIRS-P observed no difference between either treatment arm.	Similar to the trial above, both doses of the SPN-812 were efficacious in reducing ADHD symptoms making it a promising novel therapy.
Johnson et al. (2020)[99]	Two hundred twenty-two children (ages 6-12) were administered placebo or 100, 200, 300, or 400 mg/day SPN-812 over an 8-week study period. The efficacy of the treatments were evaluated through ADHD-RS-4, CGI-S, CGI-I scales. Safety of the procedures were assessed through ECG, laboratory, and suicide severity rating scale.	All 4 treatment groups saw a significant reduction in the ADHD-RS-IV scale versus placebo. CGI-I scores were only improved in the 300 mg/day ($p = 0.009$). All SPN-812 treatment arms saw an improvement in CGI-S scores, while the 100 mg/day saw no statistically significant difference to placebo.	The 4 treatment arms demonstrated an overall safety and efficacy of SPN-812 on ADHD symptoms in children.
Nasser et al. (2021)[100]	Three hundred ten adolescents (aged 12-17) were randomized to three groups placebo or SPN-812 (200 mg/day or 400 mg/day). The trial was conducted over a 6-week period.	When compared to placebo, the 200 mg/day and 400 mg/day viloxazine groups had a significant reduction of ADHD symptoms in the ADHD-RS-5 scale ($p = 0.0232$, $p = 0.0091$). There were no statistically significant improvements in the Conners 3-PS and WFIRS-P scores versus placebo.	Viloxazine ER provided significantly improved clinical outcomes for adolescents diagnosed with ADHD.
Nasser et al. (2021)[101]	Two hundred ninety-seven adolescents (aged 12-17) were randomized to receive placebo or viloxazine ER (400 mg/daily or 600 mg/daily).	The ADHD-RS-5 total scores for the 400 mg/day ($p = 0.0082$) group had a statistically significant reduction in ADHD symptoms, whereas the 600 mg/day ($p = 0.0712$) did not.	Though the 400 mg/day SPN-812 resulted in ADHD symptom reductions, the 600 mg/day did not have the same statistical difference. This result was elaborated by the researchers as an abnormal placebo response.
Nasser et al. (2020)[102]	Fifty-six adults (aged 18-45) were randomized to receive placebo, 400 mg moxifloxacin, and 1800 mg SPN-812 in different sequences to observe effects on cardiac repolarization. The primary outcome measured was the relationship	The change in QTcI when compared to SPN-812 and metabolite concentrations demonstrated statistically negative correlations ($p = 0.0012$	There were no correlations between the supratherapeutic doses of SPN-812

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
	between the CFB in heart rate corrected QT interval (QTcI) versus SPN-812 and 5-hydroxyviloxazine glucuronide (SPN-812 metabolite) plasma concentrations. Secondary outcomes evaluated were heart rate, PR and QRS intervals, and ECG morphology.	and p = 0.0007, respectively).	and cardiac repolarization. No significant changes in heart rate and abnormal ECG morphologies observed were clinically relevant to the SPN-812 treatment.
Faison et al. (2021)[105]	Thirty-four healthy adults completed the open-label trial to receive single dose methylphenidate (36 mg), SPN-812 (700 mg), or combination of both drugs (36 mg and 700 mg). Blood samples were collected and measured using mass spectrometry to assess the pharmacokinetics of the two drugs in tandem.	The LSM ratios for the maximum plasma concentration for SPN-812 and methylphenidate with a 90% CI were 100.98% (96.21-105.99) and 103.55% (97.42- 110.07) respectively. The AUC concentration from time zero and infinity for both therapies fell within the 90% CI.	Administering SPN-812 in conjunction with methylphenidate did not negatively impact the pharmacokinetics of either drug.
Fasion et al. (2021)[106]	As above, thirty-four healthy adults completed the open-label trial to receive single dose lisdexamfetamine (50 mg), SPN-812 (700 mg), or combination of both drugs (50 mg and 700 mg). Blood samples were collected and measured using mass spectrometry to assess the pharmacokinetics of the two drugs in tandem.	The LSM ratios for the maximum plasma concentration for SPN-812 and lisdexamfetamine with a 90% CI were 95.96% (91.33–100.82) and 112.78% (109.93–115.71) respectively. The AUC concentration from time zero and infinity for both therapies fell within the 90% CI.	Administering SPN-812 in conjunction with lisdexamfetamine did not negatively impact the pharmacokinetics of either drug.

CFB: Change from Baseline; EOS: End of Study; AE: Adverse Event; ECG: Electrocardiogram; Viloxazine ER: Viloxazine Extended Release; LSM: Least Square Mean; CI: Confidence Interval; AUC: Area Under Curve

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