General

Viloxazine, a Non-stimulant Norepinephrine Reuptake Inhibitor, for the Treatment of Attention Deficit Hyperactivity Disorder: A 3 Year Update

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Attention deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in childhood. Current treatment options for ADHD include pharmacological treatment (stimulants, non-stimulants, anti-depressants, anti-psychotics), psychological treatment (behavioral therapy with or without parent training, cognitive training, neurofeedback), and complementary and alternative therapies (vitamin supplementation, exercise). Central nervous system (CNS) stimulants are the primary pharmacological therapy used in treatment; however, these stimulant drugs carry a high potential for abuse and severe psychological/physical dependence. Viloxazine, a non-stimulant medication without evidence of drug dependence, is a selective norepinephrine reuptake inhibitor that has historically been prescribed as an anti-depressant medication. The extended-release (ER) form was approved by the US Food and Drug Administration (FDA) in April 2021 for the treatment of ADHD in pediatric patients aged 6-17 years. Phase 2 and 3 randomized control trials have demonstrated significant efficacy of viloxazine in improving ADHD symptoms versus placebo. Related to its long-standing use as an antidepressant, the safety profile and pharmacokinetics of viloxazine are well understood. Viloxazine appears to be a suitable alternative to current standard-of-care pharmacotherapy for ADHD, but the further investigation remains to be done in comparing its efficacy to that of current treatments.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that is defined by the presence of hyperactivity-impulsivity, inattention, or a combination of both symptoms and is now recognized to be the most common neurodevelopmental disorder of childhood.[1] Since it was initially characterized by a German physician in 1775, our understanding of the disorder has advanced significantly, and with rates of diagnosis and intervention skyrocketing in recent years, there has been controversy regarding its proper management.[2,3]

While ADHD was originally identified in children, it is now understood that it persists through adulthood in up to 65% of cases.[4] However, despite this recognition, there remains a gap in both diagnosis and treatment between childhood and adult ADHD.[5] As children with ADHD age, their symptoms change along with their environments, and the pathological behaviors that initially resulted in poor academic and social development manifest in different, but equally harmful ways.[6] The classic symptom of hyperactivity often decreases, while deficits in executive function lead to poor professional performance and increased risky behavior.

Since its initial characterization, ADHD has been treated with both pharmacologic and non-pharmacologic interven-

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tions. Pharmacologic treatment has classically been divided between psychostimulants, such as amphetamines, and non-stimulant-types, such as atomoxetine.[7] While pharmacologic therapies have been shown to improve academic performance and patient symptomology, many of these medications are not without risks or side effects. As such, controversy still exists regarding their appropriate use, especially in younger children.[8] Stimulant medications act as powerful sympathomimetic agents. As a result, these medications may result in alterations in mood, sleep, appetite, and blood pressure. Some patients may even display hallucinations or an increased level of aggression or anxiety. Accordingly, the use of non-stimulant medications may be preferred in some patients. Non-pharmacologic interventions, such as cognitive behavior therapy and exercise, have not been shown to improve symptoms to the same degree as their pharmacologic counterparts, and are thus, generally prescribed as adjunctive therapies.[9]

Recently, the FDA approved the non-stimulant selective norepinephrine reuptake inhibitor (NRI) viloxazine (Qelbree™) for the treatment of ADHD in pediatric and adolescent patients. Formerly, this medication had long been used in the treatment of depression. As a new therapy for ADHD, continual review of viloxazine and its use in the treatment of ADHD are necessary. In this paper, we will review the current literature regarding the safety and efficacy of viloxazine.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

In the US, both diagnosis and pharmacological intervention for ADHD have rose rapidly in recent years. A study by Visser et al.[10] found that 11% of children age 4–17 had received a diagnosis of ADHD in 2011, and 69% were receiving pharmacologic treatment — around 3.5 million children nationwide.

The pathophysiology of ADHD involves a cerebral imbalance in neurotransmitters, particularly dopamine (DA) and norepinephrine (NE). These catecholamines are theorized to play a central role in certain cerebral functions, specifically those pertaining to functions of the pre-frontal cortex. Functional magnetic resonance imaging (fMRI) studies have demonstrated that patients with ADHD may also have reduced frontal lobe activity.[11,12] As a result, clinical features of ADHD characteristically reflect the dysfunction of these brain regions.[13] Most current pharmacotherapies used in the treatment of ADHD improve activity within these brain regions by acting as neuromodulating agents to increase catecholamine signaling. Increased dopaminergic or norepinephrinergic activity in the prefrontal cortex and basal ganglia nuclei has shown to reduce the symptoms of inattention and hyperactivity associated with ADHD.[14]

CURRENT TREATMENT OF ADHD

Current treatment options for ADHD include pharmacological treatment with stimulants, non-stimulants, anti-depressants, and anti-psychotics.[15] Psychological treatments can include behavioral therapy with or without parent training, cognitive training, and neurofeedback.[15] In most patients, the preferred first-line treatment includes pharmacologic therapy with psychostimulants such as amphetamine or methylphenidate. However, recommendations for specific ADHD treatments can vary based on subtypes, patient age, and the presence of certain comorbid conditions.[16]

Although as many as 60-75% of children with ADHD will respond to stimulant pharmacotherapy, some remaining patients may have a limited response or may be considered non-responders.[17,18] As many as 20-50% of adults with ADHD are non-responders to stimulant therapy, either as a result of inadequate symptom reduction or an inability to tolerate associated adverse effects.[19,20] Patients treated with stimulants often experience adverse effects including reduced appetite, weight loss, headache, dry mouth, abdominal discomfort, and sleep disturbances. Others adverse effects include hypertension, serotonin syndrome, mood liability, dysphoria, and growth retardation.[21,22] Severe side effects include increased risk of myocardial infarction, stroke, pulmonary hypertension, drug abuse/addiction, and psychosis.[22] Stimulants may also cause withdrawal symptoms upon discontinuation including fatigue, increased appetite, irritability, headaches, anxiety, lack of concentration, depression, and paranoia.[22] In some instances, the adverse effects of these medications may result in stimulant discontinuation and the initiation of non-stimulant therapies.

Alternative treatments may also be preferred in patients with certain comorbid mental conditions. Examples of comorbid mental conditions associated with ADHD include emotional dysregulation, depression, anxiety disorder, bipolar disorder, and personality disorders.[23,24] In some circumstances, the use of stimulants may result in new or worsening comorbid mental conditions. For example, the use of stimulants in patients with comorbid bipolar disorder may result in mood instability or stimulant-associated mania/hypomania.[25] Those with anxiety disorders or tic disorders may also experience an exacerbation of comorbid symptoms and further subsequent social impairment with the use of stimulants.[26,27]

The preferred pharmacologic second-line therapy for the treatment of ADHD is non-stimulants such as atomoxetine, guanfacine, and clonidine.[28] In some patients who cannot tolerate stimulants or who have certain contraindications to their use, these medications offer a safe and effective means to reduce symptoms of ADHD.[29] Like other non-stimulants, viloxazine offers alternative therapy for the treatment of patients with ADHD who cannot tolerate typical stimulant medications.

VILOXAZINE DRUG INFO

Viloxazine is a selective NRI that has historically been prescribed for use as an anti-depressant. The extended-release (ER) form was approved by the US Food and Drug Administration (FDA) in April 2021 for the treatment of ADHD in pediatric patients ages 6–17 years.[30,31] Viloxazine is a non-stimulant medication with no evidence of drug dependence; still, it creates a CNS stimulant-like effect.[32] Phase 2 and 3 double-blind, placebo randomized controlled trials (RCTs) have demonstrated significant efficacy of viloxazine

in improving ADHD symptoms versus placebo.[33] Viloxazine ER reduced executive function deficits, reduced school and learning problems, and improved ADHD symptoms in children and adolescents.[34,35]

This prescription is available as 100 mg, 150 mg, or 200 mg ER capsules for once-daily oral administration in pediatric patients aged 6–17 years old.[30,36] Dosing can be titrated up in increments of 100 mg weekly in pediatric patients aged 6–11 and in increments of 200 mg in pediatric patients, aged 12–17 to the maximum recommended dosage of 400 mg once daily.[30]

In patients with severe renal impairment (eGFR<30 ml/min/1.73m^2), the maximum recommended dosage is 200 mg once daily.[30] Per FDA prescribing information, viloxazine is contraindicated in patients being actively treated with, or within 14 days following discontinuation of, a monoamine oxidase inhibitor (MAOI), due to the increased risk of hypertensive crisis. Viloxazine is a strong cytochrome P450 (CYP)-1A2 inhibitor and is contraindicated in patients receiving substrates sensitive to CYP1A2 or CYP1A2 substrates with a narrow therapeutic range.[30] Viloxazine also weakly inhibits CYP2D6 and CYP3A4, increasing the risk for adverse reactions and prompting dosage adjustments of CYP2D6 and CYP3A4 substrates during coadministration as clinically indicated.[30,37] The most common side effects of viloxazine include sleepiness, tiredness, nausea, vomiting, decreased appetite, irritability, and trouble sleeping.[30,38]

VILOXAZINE MECHANISM OF ACTION

Viloxazine targets the monoaminergic system within the CNS, specifically by increasing extracellular norepinephrine concentrations via reuptake transporter inhibition.[31] Viloxazine moderately inhibits the norepinephrine transporter (NET) both in vitro and in vivo and results in increased activity in the noradrenergic systems.[39] Viloxazine expresses weak antagonistic effects on β-2 adrenergic and α-1b adrenergic norepinephrine receptors.[31,38] With negligible binding to serotonin transporters (SERT), viloxazine does not significantly inhibit the reuptake of serotonin into human blood platelets or CNS tissue.

Viloxazine exhibits potentiation of 5-HT without inhibiting SERT.[31] It expresses some agonistic activity on serotonin receptor 5-HT$_{2C}$, antagonistic activity on 5-HT$_{2B}$, and weak antagonistic activity on 5-HT$_7$.[36,39] In vivo, viloxazine increases norepinephrine, dopamine, and 5-HT activity in the prefrontal cortex, which is a brain area that is implicated in ADHD.[38,39] In the clinical setting, patients being administered viloxazine, even at supratherapeutic doses, were observed to experience low rates of cardiac-related effects, which is a common feature seen in drugs whose primary mechanism of action is via norepinephrine reuptake inhibition.[31,36,39,40] Therefore, the therapeutic effects of viloxazine are likely the result of its binding to a variety of receptors and transporters mostly related to serotonin and norepinephrine.[39]

PHARMACOKINETICS/PHARMACODYNAMICS OF VILOXAZINE

Orally administered viloxazine immediate-release (IR) has a plasma half-life of 2.5 hours after being absorbed through the small intestinal walls.[31] Maximal plasma concentrations for IR formulation are reached 1-4 hours after ingestion, with an average bioavailability of 85%.[31] Clearance rate of intravenous (IV) dosing was found to be 124 +/- 11 mL/hour/kg, and V_D was 0.73 +/- 0.28 L/kg.[31]

During capsular administration of viloxazine ER, once-daily dosing resulted in a steady state being reached after approximately 2 days.[36] Bioavailability of ER formulation is about 88% to an IR formulation, and peak plasma concentration of viloxazine ER was reached approximately 5 hours following a single 200mg dose.[30,36] Viloxazine is 76%-82% bound to human plasma proteins over blood concentrations of 0.5-10μg/mL.[30,36] Viloxazine ER has a C_{max} and area under the curve (AUC) that increase proportionally over the dosage range from 100 mg to 400 mg once daily.[30]

Viloxazine is highly metabolized as only 12–15% of viloxazine is excreted from the kidneys unchanged, and renal clearance for orally administered viloxazine is 90% within 24 hours post-dose (urine excretion half-life of 4–5 hours) with < 1% of the dose being excreted through the feces.[30,31] Viloxazine is primarily metabolized by CYP2D6, UGT1A9, and UGT2B15 into its major metabolite 5-hydroxy-viloxazine glucuronide.[30,36,41] The overall mean half-life of elimination of viloxazine was 7.02 +/- 4.74 hours.[30] In a pediatric population, the estimated steady-state C_{max} and AUC of viloxazine and its metabolites were approximately 40-50% higher in patients aged 6–11 compared to those aged 12–17.[30,36]

Although the volume of distribution and clearance of viloxazine seems to be inversely related to age, the effect of age is not statistically significant when controlling for body weight.[42] In phase 3 clinical trials of viloxazine ER for ADHD, no dose-related increase in safety or tolerability issues were established in the effective 100-400 mg/day range suggesting that viloxazine has a wide therapeutic window with no indication to a dose based on milligrams per kilogram.[42]

Medication interruptions resulting in missed doses after already establishing a steady-state will decrease plasma concentrations of viloxazine rapidly to unquantifiable levels after 3 days of drug holiday.[42] Resuming daily administration after a drug holiday also rapidly increased plasma concentrations to reach steady-state within 2 days at all dose levels and regardless of the duration of the interruption. Suggesting that an occasional missed dose is unlikely to carry a significant clinical impact.[42] Pharmacokinetic drug-drug interactions can often predict changes in clinically significant outcomes and are useful to consider when deciding to co-prescribed medications. In the treatment of ADHD, single-dose coadministration of viloxazine ER with methylphenidate, and viloxazine ER with lisdexamfetamine, did not impact the pharmacokinetics of either drug relative to their administration alone.[40,43]

CLINICAL STUDIES: SAFETY AND EFFICACY OF VILOXAZINER

Viloxazine is a novel, bicyclic NRI which also exhibits selective serotonergic activity. It is taken once daily for the treatment of ADHD. The IR formulation has been proven to be safe and effective.[44] SPN-812 is the extended-release formulation of viloxazine which was developed with the goal of improving patient tolerance as well as improving the plasma concentration profile.[44] It is an investigational medication for ADHD.[45]

A randomized, double-blind, placebo-controlled, phase II study was conducted over the course of 8 weeks to assess the safety and efficacy of SPN-812 in healthy children, between the ages 6–12, diagnosed with ADHD as per the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV).[44] Additionally, participants must have discontinued ADHD medications at least one week prior to treatment. Efficacy was assessed as a measure of the change in the participant's baseline scores on the ADHD Rating Scale-IV (ADHD-RS-IV), Clinical Global Impression-Severity (CGI-S), and Clinical Global Impression-Improvement (CGI-I) tests when compared with placebos. Participants (n = 222) were screened and randomized to the placebo or treatment groups (100, 200, 300, 400 mg/day SPN-812). Patients receiving doses higher than 100 mg were titrated up by 100 mg per week until the desired dosage was reached.[44] The change in scores on the ADHD-RS-IV from baseline to the end of the study was the main measure of efficacy. The baseline score was assessed at visit 2 (the visit preceding the experimental phase) and the ADHD-RS-IV was administered each week during the study (the child's primary caregivers were respondents). Other measures of efficacy used included changes in scores from baseline on the CGI-S and CGI-I. Both were administered weekly like the ADHD-RS-IV. Safety was assessed by monitoring treatment-emergent adverse events (TEAEs) defined as per the Medical Dictionary for Regulatory Activities (MedDRA version 18.1), physical examinations, clinical laboratory tests, vital signs, and electrocardiograms (ECG), and suicidality per the Columbia-Suicide Severity Rating Scale (C-SSRS). Results showed that the average ADHD-RS-IV scores decreased from baseline compared to at the end of the study across all treatment groups and the placebo group. The least-squares average change was statistically significantly higher for the SPN-812 treatment groups at 200 mg ($p = 0.031$), 300 mg ($p = 0.027$), and 400 mg ($p = 0.021$) compared to the placebo. The average change from baseline over time in the ADHD-RS-IV total score (assessed at each visit) was determined to be statistically significant compared to placebo. This difference was statistically significant at week 4 in the 100 mg group, weeks 4–6 in the 200 mg group, and weeks 4–8 in the 300 mg and 400 mg groups. ADHD-RS-IV subscales of hyperactivity and impulsivity showed an average decrease in scores from baseline across all groups including the placebo. Least squares average changes were statistically significant in the 200 mg ($p = 0.025$), 300 mg ($p = 0.012$), and 400 mg ($p = 0.009$) groups. The average inattention subscale also showed an improvement across all groups including the placebo group; however, the least-squares average change was not statistically significant between placebo and treatment groups of any dosage (100 mg, $p = 0.101$; 200 mg, $p = 0.091$; 300 mg, $p = 0.055$; 400 mg, $p = 0.053$).[1] CGI-I analysis showed a decrease in scores during the first 5 weeks of treatment, after which they stayed consistent in all groups. The change noted in the least-squares average shows a statistically significant improvement in the 300 mg group when compared to the placebo ($p = 0.009$). CGI-S analyses showed decreased scores in all groups and the change in the least-squares average from baseline was statistically significant compared to the placebo for all SPN-812 dosage groups apart from the 100 mg group. The adverse effects (AEs) most common among participants ($\geq$ 15% participants) included decreased appetite, irritability, headaches, and somnolence; headaches and somnolence were dose-dependent. Thirteen participants (6.7%) left the study due to AEs. The incidence of AEs was greater for the treatment group (52.8%) compared to the placebo group (37.5%) during the titration period. During the maintenance period, AEs were 41.2% for the treatment group compared to 16.7% for the placebo group. There were no clinically significant changes in labs, vitals, or ECGs, however, 8 patients did experience tachycardia.[44]

A randomized, double-blind, placebo-controlled, 3-arm, parallel-group study was conducted over 6 weeks to determine the safety and efficacy of SPN-812 in children, between the age of 6–11, diagnosed with ADHD as per the DSM, 5th edition (DSM-V).[46] Participants must have scored 28 or greater on the ADHD Rating Scale-V (ADHD-RS-V), 4 or greater on the CGI-S, and discontinued ADHD medication at least one week prior to randomization. Efficacy was assessed as a measure of the change in the participant's baseline scores and total score on the ADHD-RS-V, CGI-S, and Conners 3-Parent Short Form (Conners 3-PS) Composite T-score, and the Weiss Functional Impairment Rating Scale-Parent (WFIRS-P) Total average score. Safety was assessed by AEs, physical examinations, laboratory tests, vital signs, ECGs, and suicidality per the C-SSRS. Participants (n = 477) were randomized into placebo, 100 mg of SPN-812 daily, and 200 mg of SPN-812 daily groups. At 1 week of treatment, statistically significant improvements in ADHD-RS-V total scores were seen in both treatment groups (100 mg group, $p = 0.0004$; 200 mg group, $p = 0.0244$) when compared to the placebo; this improvement was seen throughout the entire treatment period. At the end of the study, statistically significant improvement was also seen on the CGI-I scale (100 mg group, $p = 0.002$, 200 mg group, $p < 0.0001$), Conners 3-PS Composite T-score (100 mg group, $p = 0.0003$; 200 mg group, 0.0002), and the WFIRS-P total average score (100 mg group, $p = 0.0019$, 200 mg group, $p = 0.0002$). AEs were seen in greater than 5% of patients and included decreased appetite, headaches, and somnolence.[46]

A phase 3 randomized, double-blind, placebo-controlled, three-arm, parallel-group trial was conducted in 27 clinical sites across the country over 7 weeks.[47] The goal of this study was to evaluate the safety and efficacy of once-daily 400 mg and 600 mg SPN-812 in adolescents age 12–17 diagnosed with ADHD. Participants (n = 297) were randomized to one of three groups: the placebo group, 400 mg treatment group, and 600 mg treatment group. The efficacy of SPN-812 was measured as a difference between baseline

scores and end-of-study scores, termed the "change from baseline (CFB)", on multiple scales, using the ADHD-RS-5 as the primary measurement. Like the other studies, the CGI-I, Conners 3-PS composite T-Score, and WFIRS-P were utilized as secondary forms of measurement. The CFB on the ADHD-RS-5 at the end of the study for all 3 groups were −18.3 ± 1.36 (400 mg/day group), −16.7 ± 1.39 (600 mg/day group), and −13.2 ± 1.38 (placebo group). There was a statistically significant difference between the 400 mg group of SPN-812 and the placebo group ($p = 0.0082$), however, there was no statistically significant difference for the 600 mg group when compared to the placebo ($p = 0.0712$). At the end of the study, the average CGI-I scores for both treatment groups at were lower compared to the placebo. There was a statistically significant difference in the 400 mg group compared to the placebo ($p = 0.0051$), however, there was not a statistically significant difference for the 600 mg group when compared to the placebo. On the Conners 3-PS scale at the end of the study, there was a statistically significant difference in the CFB composite T-Score of the 400 mg group ($p = 0.0434$) when compared to the placebo. Both doses of SPN-812 were well tolerated and there was a discontinuation rate of 4.5% due to AEs which occurred in 9 subjects. The AEs are similar in nature in occurrence to those in the other studies: somnolence occurred in 15.1% of subjects, fatigue in 10.6%, headache in 8.0%, nausea in 6.5%, and decreased appetite in 6.0%.[47]

A phase 3, randomized, placebo-controlled, double-blind, 3-arm, parallel-group trial was conducted in 33 clinical sites across the country over 6 weeks.[48] The goal of this study was to evaluate the safety and efficacy for once daily 200 mg and 400 mg viloxazine extended-release capsules (VLX-ER) as a monotherapy in adolescents aged 12–17 diagnosed with ADHD. 310 subjects were randomized to one of three groups: the placebo group, 200 mg treatment group, and 400 mg treatment group. The efficacy of VLX-ER was measured as the CFB on multiple scales, using ADHD-RS-5 as the primary measurement. Like the other studies, the CGI-I, Conners 3-PS composite T-Score, and WFIRS-P were utilized as secondary forms of measurement. Statistically significant differences were shown in the CFB at the end of the study in the 200 mg and 400 mg VLX-ER groups on the ADHD-RS-5 scale total score for the 200 mg group ($p = 0.0232$) and the 400 mg group ($p = 0.0091$) when compared to the placebo. Additionally, there was a statistically significant difference on the ADHD-RS-5 sub-scores for inattention (200 mg, $p = 0.0424$; 400 mg, $p = 0.0390$) and hyperactivity/impulsivity (200 mg, $p = 0.0069$; 400 mg, $p = 0.0005$) when compared to the placebo. At the end of the study, the CGI-I scores for both treatment groups showed a statistically significant improvement in the 200 mg ($p = 0.0042$) and the 400 mg ($p = 0.0003$) when compared to the placebo. Both the Conners 3-PS composite T-Score and the WFIRS-P demonstrated an average score improvement in both treatment groups, however, the difference was not statistically significant when compared to the placebo. Both doses of VLX-ER were well tolerated and there was a discontinuation rate of 2.9% due to AEs which occurred in 6 subjects. The AEs are similar in nature in occurrence to those in the other studies: somnolence occurred in 13.7% of subjects, fatigue in 4.9%, nausea in 4.9%, and decreased appetite in 6.9%.[48]

A phase 3, randomized, placebo-controlled, double-blind, 3-arm, parallel-group trial was conducted in 28 clinical sites across the country over 8 weeks.[49] The goal of this study was to evaluate the safety and efficacy of once-daily 200 mg and 400 mg SPN-812 in children aged 6–11 diagnosed with ADHD. 313 subjects were randomized to one of three groups: the placebo group, 200 mg treatment group, and 400 mg treatment group. The efficacy of SPN-812 was measured as the CFB on multiple scales, using ADHD-RS-5 as the primary measurement. Like the other studies, the CGI-I, Conners 3-PS composite T-Score, and WFIRS-P were utilized as secondary forms of measurement. Statistically significant differences were shown in the CFB at the end of the study in the 200 mg and 400 mg SPN-812 groups on the ADHD-RS-5 scale total score for the 200 mg group ($p = 0.0038$) and the 400 mg group ($p = 0.0063$) when compared to the placebo. At the end of the study, the CGI-I scores for both treatment groups showed a statistically significant improvement in the 200 mg ($p = 0.0028$) and the 400 mg ($p = 0.0099$) when compared to the placebo. On the Conners 3-PS scale at the end of the study, there was a statistically significant improvement in the CFB composite T-Score of the 200 mg group ($p = 0.0064$) when compared to the placebo. The 400 mg group did not show a statistically significant difference ($p = 0.0917$) when compared to the placebo. There were no statistically significant differences between the 3 groups in the WFIRS-P total average score. Both doses of SPN-812 were well tolerated and there was a discontinuation rate of less than 5%. The AEs are similar in nature in occurrence to those in the other studies: somnolence occurred in 14% of subjects, fatigue in 7.2%, headache in 6.8%, upper abdominal pain in 4.8%, and decreased appetite in 7.7%.[49]

CONCLUSION

As it is the most common neurodevelopmental disorder of childhood, the development of more efficacious and tolerable pharmacotherapies for ADHD is of utmost importance.[50] Due to its long-standing use as an antidepressant, the safety profile, and pharmacokinetics of viloxazine, a selective norepinephrine reuptake inhibitor with weak antagonistic effects at serotonin receptors, are well understood. Several clinical trials have shown significant efficacy in the improvement of ADHD symptoms among children taking the SPN-812 extended-release form (Qelbree™) over placebo, which is now approved for the treatment of ADHD in pediatric and adolescent patients. As such, viloxazine appears to be a suitable alternative to current standard-of-care pharmacotherapy, but the further investigation remains to be done in comparing its efficacy to that of current treatments, especially in different subgroups of the patient population it is approved for.

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Table 1. Clinical Efficacy and Safety

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Johnson JK, Liranso T, Saylor K, et al.[44] (2020)	Randomized, double-blind, placebo-controlled, phase II study on the efficacy of SPN-812 in children with ADHD between ages 6-12 with 222 participants. The study took place over 8 weeks and participants were split into placebo and 4 treatment groups (100 mg, 200 mg, 300 mg, 400 mg)	Decreased scores on the ADHD-RS-IV, CGI-I, and CGI-S tests across all group, including the placebo group. SS differences present in least squares average difference from baseline to tend of study in treatment group when compared to placebo group. SPN-812 is safe with only minor TEAEs reported.	SPN-812 is statistically significant in terms of effectiveness and is a safe treatment for ADHD in children between the ages of 6-12. It is well tolerated.
Nasser A, Liranso T, Adewole T, et al.[46] (2020)	Randomized, double-blind, placebo-controlled, phase III study on the efficacy of SPN-812 in children with ADHD (ages 6-11) with 477 participants. The study took place over 6 weeks and participants were split into placebo and 2 treatment groups (100 mg and 200 mg).	Decreased scores on the ADHD-RS-V, CGI-S, Conners 3-PS, WFIRS-P across all groups. A SS improvement was seen the least squares average difference from baseline to tend of study in treatment group when compared to placebo group.	SPN-812 was statistically significant in reducing the symptoms of ADHD in children between ages 6 and 11. It was also well tolerated with few, minor TEAEs.
Nasser A, Liranso T, Adewole T, et al.[47] (2021)	Randomized, double-blind, placebo-controlled, three-arm, parallel-group, phase 3 trial was conducted to study the effect on once-daily 400 mg and 600 mg SPN-812 in adolescents with ADHD (ages 12-17) with 297 subjects over 7 weeks. There were 3 groups: the placebo group, 400 mg treatment group, 600 mg treatment group.	SS decreased scores from baseline versus end of study were seen in the ADHD-RS-V, CGI-I, and Conners 3-PS composite T-Score only in the 400 mg group (not the 600 mg group) when compared to the placebo.	SPN-812 was statistically significant in reducing the symptoms of ADHD. SPN-812 was well tolerated at both doses, with minor AEs. There was a discontinuation rate of 4.5% due to AEs which occurred in 9 subjects.
Nasser A, Liranso T, Adewole T, et al.[48] (2021)	Randomized, double-blind, placebo-controlled, three-arm, parallel-group, phase 3 trial was conducted to study the effect on once-daily 200 mg and 400 mg VLX-ER in adolescents with ADHD (ages 12-17) with 310 subjects over 6 weeks. There were 3 groups: the placebo group, 200 mg treatment group, 400 mg treatment group.	SS decreased scores from baseline versus end of study were seen in the ADHD-RS-V total score and both sub score categories for both 200 mg and 400 mg treatment groups. SS decreased scores were also seen in the CGI-I scale score for both treatment groups. The Conners 3-PS composite T-Score and the WFIRS-P showed an average score improvement in the treatment groups, but it was not SS compared to the placebo.	VLX-ER was statistically significant in reducing the symptoms of ADHD and was well tolerated at both doses, with minor AEs. There was a discontinuation rate of 2.9% due to AEs which occurred in 6 subjects.
Nasser A, Liranso T, Adewole T, et al.[49] (2021)	A randomized, double-blind, placebo-controlled, three-arm, parallel-group, phase 3 trial was conducted to study the effect of once-daily 200 mg and 400 mg VLX-ER in children with ADHD (ages 6-11) with 313 subjects over 8 weeks. There were 3 groups: the placebo group, 200 mg treatment group, and 400 mg treatment group.	SS decreased scores from baseline versus the end of the study were seen in the ADHD-RS-V total score and both sub-score categories for both 200 mg and 400 mg treatment groups. SS improvement in scores was seen in the CGI-I scale score for both treatment groups. The Conners 3-PS composite T-Score showed a SS improvement in scores for the 200 mg group, so SS improvement in the 400 mg group. The WFIRS-P didn't show a statistically significant differences between the 3 groups.	SPN-812 was statistically significant in reducing the symptoms of ADHD and was well tolerated at both doses, with minor AEs. There was a discontinuation rate of less than 5% due to AEs.

Key: Viloxazine extended-release capsule (SPN-812); Attention deficit hyperactivity disorder (ADHD); ADHD-Rating Scale (ADHD-RS); Clinical Global Impressions-Improvement (CGI-I); Clinical Global Impressions-Severity (CGI-S); Statistically significant (SS); treatment emergent adverse events (TEAEs); Connors 3-Parent short form(Connors 3-PS); Weiss Functional Impairment Rating Scale-Parent (WFIRS-P); adverse events (AEs); Viloxazine extended release capsules (VLX-ER)

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This study has been performed in accordance with the ethical standards in the 1964 Declaration of Helsinki.

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