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THERAPY IN PRACTICE

Viloxazine for attention-deficit hyperactivity disorder: a new formulation for a new indication

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Abstract

Viloxazine (SPN-812), an age-old antidepressant, has recently been approved by the US FDA for the treatment of attention-deficit hyperactivity disorder (ADHD) in children aged 6–17 years, at a dose range of 100–400 mg/day. Viloxazine acts primarily by norepinephrine reuptake inhibition and may also modulate the serotonergic system. The efficacy of viloxazine for the treatment of ADHD in children aged 6–17 years has been demonstrated in a series of short-term clinical trials. The most common adverse events include somnolence and gastrointestinal upset, while the FDA has issued a black-box warning regarding suicidal ideation or behavior. This article summarizes the information regarding viloxazine based on previously published narrative reviews, preclinical studies, and blinded controlled clinical trials.

Key Messages

- Viloxazine (SPN-812) has recently been approved by the US FDA for the treatment of attention-deficit hyperactivity disorder (ADHD) in children aged 6–17 years, at a dose range of 100–400 mg/day.
- Viloxazine acts primarily by norepinephrine reuptake inhibition and may also modulate the serotoninergic system.
- In several clinical trials, viloxazine has shown efficacy relative to placebo for the treatment of ADHD in children.
- The drug is generally well tolerated and the most common adverse events include somnolence and gastrointestinal upset.

Introduction

Attention-deficit hyperactivity disorder (ADHD) is a common childhood disorder with poorly understood etiology, defined as persistent inattention and hyperactivity impulsivity that interferes with normal functioning or development [1]. ADHD leads to numerous psychosocial problems in children and adolescents, such as substandard school performance, poor relationships with parents and peers, school dropout, substance abuse, and more risk of accidental injuries. Adults with ADHD often have less education achievement, poor job performance, and emotional instability [2]. The treatment of ADHD involves both behavioral and pharmacological interventions. Behavioral therapy focuses on decreasing distractions and improving time management and organization skills, while pharmacological management encompasses two drug categories—stimulants (methylphenidate, amphetamine) and non-stimulants (guanfacine, clonidine, atomoxetine) [3].

When treated with stimulants as monotherapy, the response rate in ADHD is usually 70%, and the response rate increases up to 90% when two stimulants are concomitantly used [4]; however, the most common adverse effects of stimulant drugs include loss of appetite, altered sleep, blood pressure and heart rate, suicidal ideation, and emotional liability [4, 5]. In children with ADHD, early morning functional activities, such as brushing teeth, bathing, dressing up, and eating, which require time management, task memory, and cooperation with their parents, can be

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impaired [6]. In an online survey, 77% of parents/caregivers reported that these activities are impaired among children with ADHD despite taking stimulant medications [6]. Another problem with using stimulants is that about one in five children and adolescents sell or trade their drugs [7].

The alternative treatment approach is the use of a non-stimulant, however this is usually less effective than stimulant medication [8, 9]. The most common adverse events (AEs) associated with the non-stimulants, such as atomoxetine, include sleep disturbances, gastrointestinal discomfort, and loss of appetite [10]. A novel drug with efficacy, tolerability, and least abuse potential is still sought after for the treatment of ADHD.

Viloxazine was first introduced during the 1970s in several European countries; however, during the early 2000s, due to its limited commercial success and low profitability, the manufacturer withdrew viloxazine from the market. Due to its stimulant effect without apparent dependence, few trials have evaluated the efficacy and safety of viloxazine for the treatment of ADHD in the past decade. Several placebo-controlled trials, including NCT02633527, NCT03247530, NCT03247543, NCT03247517, and NCT03247556, were conducted in a full-fledged manner during 2016–2019 to evaluate the efficacy and safety of viloxazine for the treatment of ADHD in children. An open-label extension of a double-blind placebo-controlled trial (NCT02736656) is ongoing to establish the long-term efficacy and safety of viloxazine. The timeline representing the journey of viloxazine from inception to US FDA approval is depicted in Fig. 1 [11].

In the US, viloxazine is approved for the treatment of ADHD in patients aged 6–17 years. For children aged 6–11 years, the recommended initial dose is 100 mg/day, which can be titrated up to 400 mg/day by weekly increments of 100 mg. For older children between 12 and 17 years of age, the recommended starting dose is 200 mg/day, which can be increased up to 400 mg/day. Viloxazine capsules may be either swallowed whole or opened and sprinkled on applesauce [12].

Mechanism of action

It is essential to understand the basic pathophysiology of ADHD in order to understand the mechanism of viloxazine. The prefrontal cortex (PFC) is mainly responsible for regulating behavior and attention. A circuit of neurons connecting the PFC, striatum, and cerebellum control behavior, thoughts, concentration, and movement. The neurotransmitters release acts on postsynaptic receptors and systematize attention, focus, and organization of thoughts and actions. Norepinephrine activates this neural circuit [13].

Viloxazine was sold as a racemic mixture containing the (S) and (R) isomers, with the former being five times more active. Viloxazine binds to the norepinephrine transporter (NET), and the inhibitor constant Ki was 0.63 µM. Viloxazine inhibits the reuptake of norepinephrine, with a minimal inhibitory concentration (IC_{50}) of 0.2 µM [14]. Viloxazine has a multimodal mechanism of action involving the norepinephrine and serotonergic systems, which can be a serotonin norepinephrine modulating agent (SNMA) (Fig. 2). It acts as an agonist at the 5-$HT2_C$ receptor and an antagonist at the 5-$HT2_B$ receptor, and increases serotonin and norepinephrine levels in the PFC. Viloxazine causes a minimal increase in dopamine levels in the nucleus accumbens, making it a novel drug for ADHD with the least abuse potential [15].

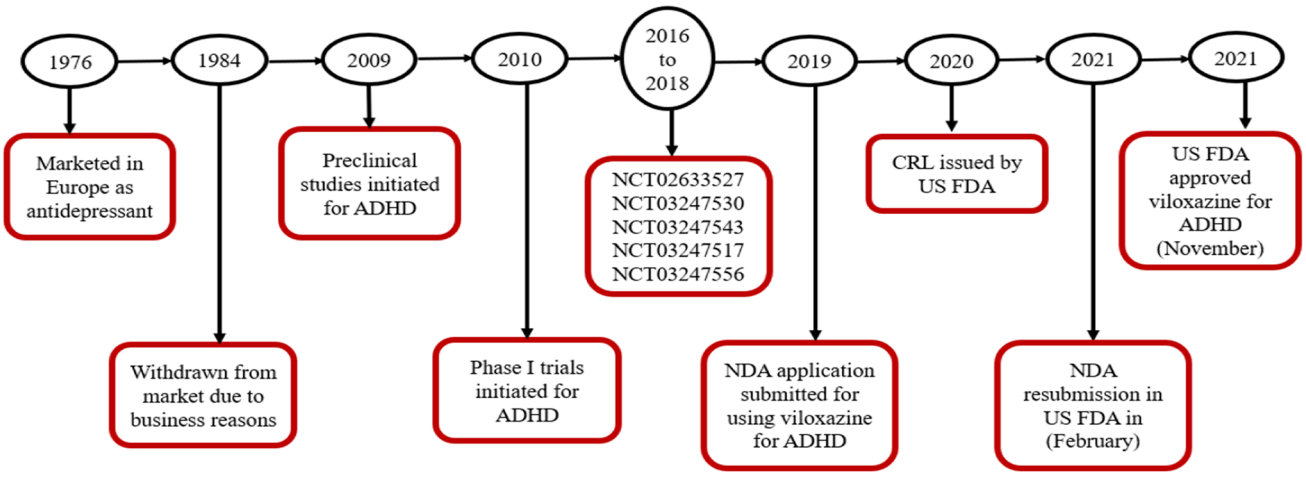

Fig. 1 Timeline for viloxazine approval for use in the treatment of ADHD. *ADHD* attention-deficit hyperactivity disorder, *CRL* complete response letter, *NDA* new drug application

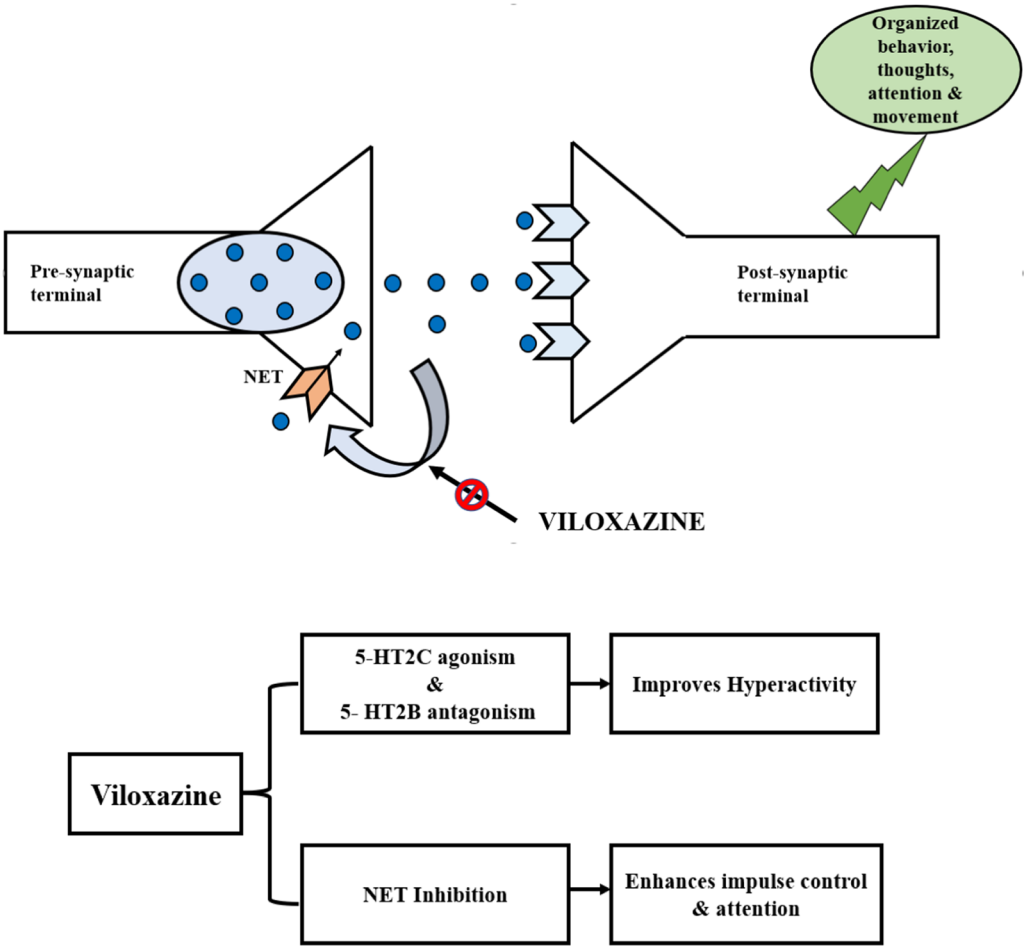

Fig. 2 Mechanism of action of viloxazine. *NET* norepinephrine transporter

Pharmacokinetics

Viloxazine achieves steady-state concentration after 2 days of administration, and the maximum concentration (C_{max}) is reached in a median time (T_{max}) of 5 h (range 6–9 h). The half-life of the drug is ≈ 7 h with 80% plasma protein binding. The administration of viloxazine with high-fat meals decreases the C_{max} and area under the curve (AUC) by ≅ 10%, and increases T_{max} by 2 h. Almost 90% of the drug gets eliminated by the kidney.

Viloxazine is mainly metabolized by the cytochrome P450 (CYP) 2D6, UDP-glucuronosyltransferase (UGT) 1A9, and UGT2B15 enzymes, and 5-hydroxy-viloxazine glucuronide is the major metabolite detected in plasma. Modest variation in C_{max} was detected in poor CYP2D6 metabolizers compared with extensive metabolizers (less than twofold), with moderate drug–drug interactions observed with a strong CYP2D6 inhibitor (paroxetine). Simultaneous administration of viloxazine with methylphenidate or lisdexamphetamine does not affect the C_{max} or AUC of either drug. Viloxazine is a potent inhibitor of CYP1A2 and significant drug interactions are expected. Concomitant use of a monoamine oxidase inhibitor (MAO-I) may lead to a hypertensive crisis.

No data are available regarding the use of viloxazine in the elderly population, pediatric population < 6 years of age, or patients with hepatic impairment. The drug should be discontinued during pregnancy. Furthermore, in patients with renal impairment, the starting dose is 100 mg, with a weekly increment of 50 mg up to a maximum dose of 200 mg/day [12].

Clinical trials

The efficacy of viloxazine has been established in several different clinical trials, and long-term safety is being assessed in ongoing open-label trials. This section discusses the five clinical trials that evaluated the efficacy and safety of viloxazine in children with ADHD (Table 1).

In an essential, randomized, double-blind, phase II, placebo-controlled trial, the efficacy and safety of SPN-812

Table 1 Efficacy and tolerability profile of viloxazine [16–20]

Trial description	Age group, years	Comparators	Efficacy	Tolerability of VLX-ER
Johnson et al. (2020) [16]	6–12	VLX-ER 100, 200, 300, 400 mg/day ($n = 198$) vs. PLB ($n = 24$)	Δ from PLB in LSM change in ADHD-RS-IV: − 6.2 (100 mg/day). − 7.9* (200 mg/day), − 8.1* (300 mg/day), − 8.5 (400 mg/day)	The most frequent AEs (≥ 15%) were somnolence, headache, and decreased appetite
			Δ from PLB in LSM change in CGI-I: − 0.4 (100 mg/day), − 0.4 (200 mg/day), − 0.8* (300 mg/day), − 0.6 (400 mg/day)	Most of the TEAEs were mild to moderate in severity No SAEs or deaths occurred during the entire study period
			Δ from PLB in LSM change in CGI-S: − 0.6 (100 mg/day), − 0.8* (200 mg/day), − 0.8* (300 mg/day), − 0.9* (400 mg/day)	None of the participants presented with clinically relevant changes in ECG
Nasser et al. (2021) [17]	12–17	VLX-ER 200, 400 mg/day ($n = 194$) vs. PLB ($n = 104$)	Δ from PLB in LSM change in ADHD-RS-5: − 4.5* (200 mg/day), − 5.1* (400 mg/day)	The most frequent AEs were somnolence (13.7%), decreased appetite (6.9%), fatigue (4.9%), and nausea (4.9%)
			Δ from PLB in responder rate ADHD-RS-5: 18.8%* (200 mg/day) and 17.6%* (400 mg/day)	No cardiovascular events leading to discontinuation were observed in any of the group, and no ECG-related AEs were reported during the study
			Δ from PLB in responder rate CGI-I at EOS: 19.4%* (200 mg/day) and 20.7%* (400 mg/day)	Suicidal ideation was noted in a few participants but no deaths occurred during the entire study period
Nasser et al. (2020) [18]	6–11	VLX-ER 100, 200 mg/day ($n = 305$) vs. PLB ($n = 155$)	Δ from PLB in LSM change in ADHD-RS-5: − 5.7* (100 mg/day), − 6.8* (200 mg/day)	The most frequent AEs were somnolence (8.9%), decreased appetite (6%) and headache (5.4%)
			Δ from PLB in responder rate ADHD-RS-5: 14.4%* (100 mg/day) and 21.4%* (200 mg/day)	No deaths occurred during the entire study period
			Δ from PLB in responder rate CGI-I: 15.2%* (100 mg/day) and 20.9%* (100 mg/day)	One case of ECG T-wave inversion occurred in the 100 mg/day SPN-812 treatment group (0.6%)
			Δ from PLB in LSM change in C3PS: − 4.3* (100 mg/day), − 4.4* (200 mg/day)	A total of seven participants left the study due to TEAEs that were mild to moderate in severity
			Δ from PLB in LSM change in WFIRS-P: − 0.14* (100 mg/day), − 0.17* (200 mg/day)	No suicidal ideation was noted in the viloxazine-treated group
Nasser et al. (2021) [19]	6–11	VLX-ER 200, 400 mg ($n = 204$) vs. PLB ($n = 97$)	Δ from PLB in LSM change in ADHD-RS-5: − 6.0* (200 mg/day), − 5.8* (400 mg/day)	Treatment-related AEs included somnolence (14%), decreased appetite (7.7%), fatigue (7.2%), and headache (6.8%)
			Δ from PLB in responder rate ADHD-RS-5: 10.2%* (200 mg/day) and 15.4%* (400 mg/day)	Severe suicidal ideation was noted in one subject

Table 1 (continued)

Trial description	Age group, years	Comparators	Efficacy	Tolerability of VLX-ER
			Δ from PLB in responder rate CGI-I: 11.5%* (200 mg/day) and 11.3%* (400 mg/day)	Cardiovascular-related AEs and ECG abnormalities were infrequent
			Δ from PLB in LSM change in C3PS: − 3.8* (200 mg/day), − 2.5 (400 mg/day)	Three SAEs were reported and no deaths occurred during the entire study period
Nasser et al. (2021) [20]	12–17	VLX-ER 600, 400 mg (n = 199) vs. PLB (n = 97)	Δ from PLB in LSM change in ADHD-RS-5: − 5.1* (400 mg/day), − 3.5 (600 mg/day)	Treatment-related AEs included somnolence (15.1%), fatigue (10.6%), headache (8%), and nausea (6.5%)
			Δ from PLB in responder rate ADHD-RS-5: 15.3% (400 mg/day) and 13.1% (600 mg/day)	Syncope and suicidal ideation were noted as SAEs
			Δ from PLB in responder rate CGI-I: 26.3% (400 mg/day) and 14.2% (600 mg/day)	A total of nine participants left the study due to TEAEs (4.5%)

ADHD-RS-5 Attention-Deficit Hyperkinetic Syndrome Rating Scale-5, *AEs* adverse events, *CGI-I* Clinical Global Impression Scale–Improvement, *CGI-S* Clinical Global Impression Scale–Severity, *C3PS* Conners 3rd Edition–Parent Short Form, *ECG* electrocardiogram, *EOS* end of study, *LSM* least-square mean, *PLB* placebo, *SAEs* serious adverse events, *TEAEs* treatment-emergent adverse events, *VLX-ER* viloxazine extended-release, *WFIRS-P* Weiss Functional Impairment Rating Scale–Parent Report, **Δ** indicates difference

*$p < 0.05$

(viloxazine extended-release [VLX-ER]) 100, 200, 300, and 400 mg/day were evaluated in 222 children aged 6–12 years. The study consisted of a 3-week titration phase followed by a 5-week maintenance phase. The primary efficacy endpoint was change from baseline (CFB) to end of study (EOS) in the Attention-Deficit Hyperactivity Rating Scale (ADHD-RS-IV) total score, while the secondary endpoints were CFB to EOS in Clinical Global Impression–Severity (CGI-S) and Clinical Global Impression–Improvement (CGI-I) scores. At the end of the study, relative to placebo, a statistically significant ($p \leq 0.03$) improvement in the ADHD-RS-IV scale was demonstrated in the viloxazine 200, 300, and 400 mg/day groups (Table 1). A similar trend was observed for CGI-S, as a significant ($p \leq 0.03$) improvement relative to placebo was noted in viloxazine doses of 200, 300, and 400 mg/day (Table 1). However, in the CGI-I score, significant improvement relative to placebo was noted only with viloxazine 300 mg/day ($p = 0.01$) (Table 1) [16].

Based on the findings from the phase II trial, the efficacy and safety of VLX-ER 200 and 400 mg/day were evaluated in children aged 12–17 years in a randomized, double-blind, placebo-controlled, phase III trial. This study involved 104 participants in the placebo arm and 197 participants in the drug-treated arm. The duration of the study was 6 weeks, including a 1-week titration phase and a 5-week maintenance phase. The primary efficacy endpoint was CFB in ADHD-RS-5 total score at EOS. As secondary endpoints, the responder rate in ADHD-RS-5 and CGI-I was assessed. ADHD-RS-5 responders were defined as the proportion of participants showing ≥ 50% improvement in the total score, while CGI-I responders were defined as the proportion of patients who had a score of 1 (very much improved) or 2 (much improved). Other secondary endpoints were CFB in the Conners 3rd Edition–Parent Short Form (C3PS) composite T score and Weiss Functional Impairment Rating Scale–Parent Report (WFIRS-P) at EOS.

A significant ($p \leq 0.023$) CFB was observed in the ADHD-RS-5 scale with viloxazine compared with placebo (Table 1). The responder rate for ADHD-RS-5 was significantly ($p \leq 0.0089$) higher with viloxazine 200 and 400 mg/day than with placebo (45.8% and 44.6% vs. 27%). Similarly, a significantly ($p < 0.05$) higher CGI-I responder rate was observed with viloxazine 200 and 400 mg/day versus placebo at week 1 (14.1% and 16.5% vs. 4.8%), with these improvements generally remaining significant through EOS. A statistically significant difference was not observed in other secondary efficacy endpoints (i.e., C3PS and WFIRS-P) (Table 1) [17].

In another 6-week, randomized, double-blind, placebo-controlled, phase III trial, the efficacy and safety of VLX-ER (100 and 200 mg/day) were evaluated in 460 children aged 6–11 years. The study duration was 6 weeks, including an initial 1-week titration phase followed by a maintenance

phase of 5 weeks. The endpoints were similar to the previous trial: CFB in ADHD-RS-5 total score, C3PS, and WFIRS-P at EOS, and responders' rate in ADHD-RS-5 and CGI-I. A significant ($p \leq 0.004$) CFB was observed in the ADHD-RS-5 scale in the viloxazine arm compared with the placebo arm (Table 1). The responder rate for ADHD-RS-5 and CGI-I was significantly ($p \leq 0.0244$) higher with viloxazine 100 and 200 mg/day versus placebo (34.2% and 41.2% vs. 19.8%, and 44.9% and 50.6% vs. 27.9%, respectively). Similarly, a statistically significant difference was also observed in other secondary efficacy endpoints, i.e., C3PS and WFIRS-P, in both doses compared with placebo (Table 1) [18].

Another phase III, randomized, double-blind, pivotal trial evaluated the efficacy and safety of VLX-ER (200 and 400 mg/day) in children aged 6–11 years. The study involved 97 participants in the placebo arm and 204 participants in the drug-treated arm. The duration of the study was 8 weeks, the initial 2 weeks of which were designated as the titration phase. The endpoints were similar to the previous trials. A statistically significant ($p \leq 0.006$) CFB relative to placebo was noted in the ADHD-RS-5 score at EOS in both the 200 and 400 mg groups (Table 1). The response rate for ADHD-RS-5 and CGI-I was also significantly ($p \leq 0.0099$) higher in the viloxazine 200 and 400 mg/day groups than in the placebo group (36% and 41.2% vs. 25%, and 47.6% and 47.4% vs. 36.1%, respectively). The CFB in the C3PS score was statistically significant versus placebo for the 200 mg/day dose ($p = 0.006$) but not for the 400 mg/day dose [19].

A similar randomized, double-blind, placebo-controlled, phase III clinical trial also assessed the efficacy and safety of VLX-ER (400 and 600 mg/day) in adolescents. The trial duration was 7 weeks, the initial 2 weeks of which were designated as the titration phase. The endpoints were similar to the previous trials. A statistically significant CFB was noted in the ADHD-RS-5 score at EOS in the viloxazine 400 mg/day group but not in the 600 mg/day group (Table 1). The responder rate for ADHD-RS-5 and CGI-I was numerically higher with viloxazine 400 and 600 mg/day versus placebo (48.2% and 46% vs. 32.9%, and 60.6% and 48.5% vs. 34.3%, respectively). The CFB in the C3PS score and WFIRS-P was not statistically significant from placebo for either dose (Table 1) [20].

Adverse effects

For safety analysis, AEs or treatment-emergent AEs (TEAEs) were recorded throughout the study periods (Table 1). The most common AEs noted with the use of viloxazine were either neurological or gastrointestinal. The neurological AEs included somnolence, headache, and insomnia, while the gastrointestinal AEs included nausea and decreased appetite.

In five randomized, double-blind, placebo-controlled, phase II or III trials, TEAEs were observed in 47.9–68.4% and 29.6–45.8% of viloxazine and placebo recipients, respectively [16–20].

Upon pooling the data from the clinical trials, the overall incidence of TEAEs was 37.5% and 59.2% in the placebo and VLX-ER groups, respectively. The incidence of somnolence (14.1% vs. 3%), headache (8.0% vs. 4.5%), and decreased appetite (7.6% vs. 0.8%) was numerically higher in the VLX-ER group than in the placebo group. Very few serious AEs were reported in both groups (0% vs. 0.89%); the reported serious AEs included syncope, suicidal ideation, suicidal attempt, suicidal behavior, and conduct disorder. Accordingly, the US FDA issued a black-box warning for suicidal thoughts and behaviors [16–20]. Hence, parents/caretakers should be made aware of this alarming AE and all patients treated with viloxazine should be monitored closely for the emergence or worsening of suicidal thoughts and behaviors, especially during the first few months of viloxazine treatment and at times of dosage adjustment. Heart rate and blood pressure monitoring should be performed periodically throughout the treatment (Table 1) [10].

Place of viloxazine therapy

As discussed earlier, the pharmacotherapy of ADHD includes stimulant and non-stimulant drugs [4]. In a systematic review and meta-analysis, the comparative efficacy and tolerability of oral medications for ADHD in children, adolescents, and adults were analyzed [21]. In studies using ADHD core symptoms rated by clinicians in children and adolescents, interventional drugs such as amphetamines, methylphenidate, and atomoxetine were found to be more efficacious than placebo. For scores rated by teachers, only methylphenidate and modafinil were found to be more efficacious than placebo. In terms of tolerability, amphetamines were found to be inferior to placebo in both children and adolescents, and guanfacine was also found to be inferior to placebo in children and adolescents [21]. As stimulants are often associated with undesirable AEs, a new non-stimulant medication may benefit children with ADHD. The US FDA approved viloxazine, a non-stimulant drug, for the treatment of ADHD in pediatric patients aged 6–17 years [11], at dose ranges of 100–400 mg/day depending on the efficacy and tolerability [11].

The significant advantage of viloxazine is devoid of cardiovascular AEs/sudden cardiac death and abuse liability compared with already-approved drugs [22]. Viloxazine has shown efficacy relative to placebo in numerous endpoints such as the ADHD-RS-IV, ADHD-RS-5, CGI-I, C3PS, and

WFIRS-P with mostly tolerable adverse effects [16–20]. Very few serious AEs were reported, making viloxazine a well-tolerated alternative. On the flip side, a black-box warning has been issued for suicidal ideation or behavior. An ongoing open-label extension study (NCT02736656) will further determine the efficacy and safety of viloxazine in children with ADHD.

A systematic review and meta-analysis by Faraone et al. noted that although ADHD medications showed superior efficacy compared with placebo, heterogeneous placebo effects have been found for all efficacy outcomes [23]. Further clinical trials comparing viloxazine with other agents, along with real-world studies, would be of interest to establish the effectiveness of viloxazine for the treatment of ADHD.

Declarations

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Consent to participate Not applicable.

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Author contributions All authors contributed equally to this work.

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