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Viloxazine: A New Non-Stimulant Treatment for Attention-Deficit/Hyperactivity Disorder (ADHD)

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ABSTRACT

Introduction

Viloxazine is an antidepressant medication classified as an SNRI (serotonin and norepinephrine reuptake inhibitor). In April 2021, it received FDA approval in the United States for the treatment of ADHD in children aged 6 to 17. Subsequently, in May 2022, it was also approved for the treatment of adults with ADHD [1]. Viloxazine, available in extended-release capsules, represents novel non-stimulant medication option for patients with ADHD.

Aim of the study

Our aim was to review the viloxazine in the fields of ADHD treatment, summarize current knowledge and analyze the first treatment results.

Methods and materials

A review of the literature available in the PubMed database was performed, using the key words: „Viloxazine" ; „ADHD treatment" ; „ADHD", „attention deficit hyperactivity disorder", „attention deficit hyperactivity disorder treatment"; „ADHD non-stimulant treatment"; „ADHD non-stimulant"; „ADHD non-stimulant drugs", „SPN-812"

Conclusion

Viloxazine presents a promising non-stimulant alternative for ADHD treatment with more favorable pharmacokinetics, new way of possible administration and fewer adverse effects, particularly within the cardiovascular system, than other available ADHD medication options. While these findings are encouraging, continual research is imperative to establish the long-term safety profile.

Key words :viloxazine; ADHD treatment; ADHD; attention deficit hyperactivity disorder; ADHD non-stimulant drug; ADHD non-stimulant treatment; ADHD non-stimulants; attention deficit hyperactivity disorder treatment; SPN-812

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by three primary symptoms: inattention, hyperactivity, and impulsivity. ADHD primarily manifests in childhood, and for a long time, it was believed to remit in adolescence. It is now understood to persist into adulthood, with attention deficits being particularly prevalent [2]. The absence of diagnosis is detrimental to an individual's academic, social, familial, and occupational trajectories [3]. Untreated individuals exhibit a higher rates of risky driving behavior, obesity, suicidal thoughts, and drug use/addictive behavior [2]. The treatment of ADHD can be categorized into two main groups of registered medications - stimulants and non-stimulants. Stimulants such as methylphenidate, lisdexamfetamine and amphetamine are considered first-line medications [4], while non-stimulants like atomoxetine, guanfacine, and clonidine are often employed when patients either do not tolerate stimulant medications [5] or due to comorbidities such as sleep disorders, or substance abuse [6]. Approximately 20-40% of patients using stimulants may not achieve treatment response or symptomatic remission. [7]. Hence, there is a need to explore and register new medications to effectively treat all individuals with ADHD. In April 2021, the FDA approved a new medication in the USA, viloxazine - for the treatment of ADHD in children aged 6 to 17. In May 2022, the FDA also approved it for the treatment of adults with ADHD.

2. Methodology

A review of the literature available in the PubMed database was performed using the keywords: "Viloxazine," "ADHD treatment," "ADHD," "attention deficit hyperactivity disorder", "attention deficit hyperactivity disorder treatment", „ADHD non-stimulant treatment", „ADHD non-stimulant".

3. State of knowledge

Viloxazine is a drug classified as an SNRI (Serotonin-Norepinephrine Reuptake Inhibitor). Viloxazine received its first endorsement in the United Kingdom in 1971 as an antidepressant. Subsequently, it received approvals in several other countries. However, it was discontinued in 2002 due to commercial reasons, unrelated to either its therapeutic efficacy or safety. [8,9]. In in vivo preclinical studies, viloxazine has demonstrated an ability to elevate levels of serotonin (5-HT), norepinephrine, and dopamine in the prefrontal cortex, which is closely associated with ADHD pathophysiology. Importantly, only a small and transient increase in dopamine levels was noted in the nucleus accumbens, a brain region involved in substance use disorders, suggesting a low abuse potential for viloxazine [2,10,11]. Due to its mechanism of action, viloxazine is categorized within the group of non-stimulant ADHD medications.

4. Effects of the treatment

Phase III clinical trials were conducted to assess the effectiveness of viloxazine extended-release [ER] in ADHD treatment in both the pediatric age group (6-17 years) and adults. The studies demonstrated significant statistical efficacy of viloxazine ER in ADHD treatment compared to placebo in both groups [2,3,12,13]. The phase III trials data report suggest a well-tolerated clinical profile of viloxazine with a low incidence and mild severity of adverse effects [14,15], including a small number of cardiovascular abnormalities [16] and liver enzyme elevations [2, 17]. Viloxazine was reported effective in reducing ADHD symptoms in children such as inattention and hyperactivity/impulsivity [3, 18], significantly reduces the impairment of peer relations and social activities in children and adolescents with ADHD [19] as well as school learning problems [20]. The trial results demonstrated the efficacy of viloxazine for ADHD symptoms, which can manifest as early as week 1 of treatment, along with a safe and well-tolerated clinical profile. Additional studies have indicated that viloxazine ER has a diminished impact on the cardiovascular system, which was frequently a concern in the administration of ADHD drugs for patient treatment. It has been demonstrated that viloxazine ER has no effect on cardiac repolarization or other ECG parameters in healthy adults, suggesting that it is not associated with a risk of cardiac arrhythmias or other electrocardiographic abnormalities [21] as well as the minimal effects on blood pressure (BP) and heart rate (HR), particularly in children, serve as a potential distinguishing factor from

currently available ADHD medications [22]. There are also reports that pediatric and adult ADHD patients who have experienced less than optimal response to atomoxetine demonstrate rapid improvement in inattention and hyperactivity/impulsivity with greater tolerability on extended-release viloxazine [23]. Besides it's beneficial impact on ADHD, it has been demonstrated that viloxazine exhibits antiepileptic properties at low doses. However, individuals undergoing concurrent administration of phenytoin and carbamazepine are prone to increased serum concentrations and correlated toxicity, which resolves upon discontinuation of viloxazine therapy [24].

5.1 Pharmacokinetics

Studies indicate a relatively quick onset of action of viloxazine in the 400-mg/d and 200 mg/d group throughout the entire treatment period [2, 25]. Improvement versus placebo was observed starting at week 1 for both doses. The observation is particularly noteworthy, considering the delayed onset of action observed with some current FDA-approved non-stimulant medications for ADHD, such as atomoxetine or guanfacine [26]. To date, stimulants have been recognized for their rapid onset of action in reducing symptoms of ADHD. The emergence of a new non-stimulant medication with a potentially quicker onset, shorter than the typical 4-6 weeks, is promising. Furthermore, viloxazine extended-release (ER) can be ingested either by sprinkling it on applesauce or as intact capsules, with or without meals, without significantly altering its pharmacokinetics [27, 28], which is also a welcome change compared to other treatment options available on the market. The applesauce with sprinkled capsule content should be consumed in its entirety (without chewing) within 2 h and should not be stored for future use [29]. The new option of drug administration enables a larger number of patients, including children facing challenges with swallowing or those who prefer not to consume pills, such as individuals with autism, sensory processing disorder, or other developmental disabilities, to adhere to the treatment [30].

5.2 The co-administration with stimulant medications

A study on the safety of combining viloxazine with the first-line stimulant medication, methylphenidate, revealed no significant impact on the pharmacokinetics of either drug [6, 28, 31]. Similarly, the co-administration of viloxazine extended-release and lisdexamfetamine did not alter the pharmacokinetics of viloxazine or d-amphetamine in comparison to individual

drug administration. After a single-dose administration, the combination was reported well-tolerated and safe [32].

5.3 Drug holidays

Measurements of viloxazine and its primary metabolite, 5-HVLX-gluc, were taken following missed doses. The study demonstrated that, after brief interruptions in drug administration ranging from 1 to 4 days, viloxazine concentrations typically return rapidly to steady-state levels. This implies that the occasional missed dose is unlikely to result in a notable clinical impact on systemic exposure [33]. These findings underscore the resilience of viloxazine ER in maintaining its therapeutic and safety characteristics even in the event of occasional missed doses.

6. Adverse effects

In children, adverse events related to treatment, occurring in ≥5% of subjects in any viloxazine ER treatment group, and with a higher percentage than the placebo, included somnolence (8.9%), decreased appetite (6.0%), and headache (5.4%) [3]. Additionaly, recent case was published involving a 10-year-old child with partial priapism associated with the administration of 300 mg/day of viloxazine, which is probable considering it's multimodal mechanism of action at the norepinephrine transporter-adrenergic and serotonin receptors systems [34].

In adults the most common treatment-related adverse events that occurred in ≥5% of subjects mainly during second week of receiving viloxazine ER were insomnia (14.8%), fatigue (11.6%), nausea (10.1%), decreased appetite (10.1%), dry mouth (9.0%), and headache (9.0%). Viloxazine ER was well tolerated, with a discontinuation rate of 9.0% due to adverse events compared with 4.9% in the placebo group [12].

In adolescent group (12-17 years) the most common treatment-related adverse events that occurred in ≥5% of subjects and were greater in percentage than placebo, were somnolence (13,7%) decreased appetite (6,9%), nausea (4,9%), and fatigue (4,9%). The adverse event–related discontinuation rates were <5% [2].

Considering mechanism of action as a noradrenergic agent, it is imperative to acknowledge that viloxazine may potentially trigger manic or mixed episodes in individuals diagnosed with bipolar disorder, excesive somnolence and fatigue. Screening for bipolar disorder risk should

be conducted in patients intended for viloxazine treatment before the initiation of such therapy [29].

Viloxazine may cause potential maternal harm when used during pregnancy, as indicated by findings from animal reproduction studies. It is crucial to stop administration when pregnancy occurs [35].

7. Conclusions

The review provides a comprehensive overview of the evolving landscape of ADHD treatment, emphasizing the significant impact of viloxazine in addressing the challenges associated with this neurodevelopmental disorder. The introduction of viloxazine as a non-stimulant medication marks a crucial advancement in the therapeutic options available for both pediatric and adult ADHD patients. Results from phase III clinical trials strongly support the efficacy of viloxazine ER in treating ADHD symptoms, demonstrating statistical significance compared to placebos in both pediatric and adult populations and proves well-tolerability of the treatment and minimal adverse effects. The unique pharmacokinetic features, such as a relatively quick onset of action, the flexibility of administration and safety of combining with stimulant medications, contribute to viloxazine's practicality of use. Additionaly, the SNRI profile of viloxazine may offer benefits for individuals experiencing depression in addition to ADHD [36, 37]. While the review highlights the promising aspects of viloxazine, it also emphasizes the importance of ongoing research and monitoring. Considering the short duration of trials, long-term safety cannot be established.

Author’s contribution

Conceptualization Wiktoria Wilanowska, Bartosz Mazur and Aleksandra Kłos; methodology, Mateusz Pawlicki; software, Dawid Mika; check, Dawid Mika and Maciej Lambach; formal analysis, Aleksandra Mazurek and Bartosz Mazur; investigation, Kamila Turek and Wiktoria Wilanowska; resources, Anna Greguła; data curation, Anna Greguła; writing - rough preparation, Wiktoria Wilanowska; writing - review and editing, Kamila Turek, Maciej Lambach,; visualization, Wiktoria Wilanowska; supervision, Mateusz Pawlicki and Karol Stachyrak; project administration, Karol Stachyrak; receiving funding, Aleksandra Mazurek.

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