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ORIGINAL RESEARCH ARTICLE

Extended-Release Viloxazine Compared with Atomoxetine for Attention Deficit Hyperactivity Disorder

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Abstract

Background and Objective In our outpatient pediatric and adult psychiatry centers, we reserve psychostimulants for predominantly inattentive attention deficit hyperactivity disorder (ADHD) due to the potential for appetite and growth suppression, insomnia, wear off, exacerbation of mood, anxiety, and tics, or misuse. We utilize extended-release (ER) alpha-2 agonists primarily for hyperactivity/impulsivity but find them less effective for inattention, and they can cause sedation and hypotension. Oftentimes, we need to combine an alpha-2 agonist for behavior with psychostimulants for inattention. We employ atomoxetine or viloxazine ER (VER) for combined ADHD. However, our patients' insurers mandate a trial of generic atomoxetine prior to covering branded VER. The objective of this study was to determine whether pediatric and adult patients taking atomoxetine for DSM-5-TR ADHD combined type would experience improvement in ADHD symptoms following voluntary, open-label switch to VER.

Methods 50 patients (35 children) received mean doses of atomoxetine 60 mg (25–100 mg once daily) followed by VER 300 mg (100–600 mg once daily) after a 5-day atomoxetine washout. Both atomoxetine and VER were flexibly titrated according to US Food and Drug Administration (FDA) guidelines. The pediatric ADHD-Rating Scale-5 (ADHD-RS-5) and the Adult Investigator Symptom Rating Scale (AISRS) were completed prior to starting atomoxetine, and 4 weeks after treatment with atomoxetine or upon earlier response or discontinuation due to side effects, whichever occurred first; the same protocol was used after treatment with VER. We conducted a blinded, de-identified, retrospective review of charts from these 50 patients in the regular course of outpatient practice. Statistical analysis was performed using a within-subject, 2-tailed *t*-test with significance level of $p < 0.05$.

Results From the baseline total ADHD-RS-5 mean score (40.3 ± 10.3), improvements were greater on VER (13.9 ± 10.2) than atomoxetine (33.1 ± 12.1; $t = -10.12$, $p < 0.00001$) in inattention ($t = -8.57$, $p < 0.00001$) and in hyperactivity/impulsivity ($t = -9.87$, $p < 0.00001$). From the baseline total AISRS mean score (37.3 ± 11.8), improvements were greater on VER (11.9 ± 9.4) than atomoxetine (28.8 ± 14.9; $t = -4.18$, $p = 0.0009$) in inattention (t = − 3.50, $p < 0.004$) and in hyperactivity/impulsivity ($t = -3.90$, $p < 0.002$). Of patients on VER, 86% reported positive response by 2 weeks versus 14% on atomoxetine. A total of 36% discontinued atomoxetine for side effects, including gastrointestinal (GI) upset (6 patients), irritability (6), fatigue (5), and insomnia (1), versus 4% who discontinued VER due to fatigue. A total of 96% preferred VER over atomoxetine, with 85% (22 out of 26) choosing to taper psychostimulants following stabilization on VER.

Conclusions Pediatric and adult ADHD patients who have experienced less than optimal response to atomoxetine demonstrate rapid improvement in inattention and in hyperactivity/impulsivity with greater tolerability on extended-release viloxazine.

1 Introduction

This study compares the effectiveness and tolerability of viloxazine ER (VER) to atomoxetine in the treatment of pediatric and adult attention deficit hyperactivity disorder (ADHD). In our outpatient pediatric and adult psychiatry centers, we reserve psychostimulants for predominantly inattentive ADHD due to the potential for appetite and growth

Key Points

Compared with atomoxetine, viloxazine ER seems to produce greater improvement in total ADHD symptoms than atomoxetine in both children and adults.

Viloxazine ER also seems to produce greater improvement in both inattention and in hyperactivity/impulsivity and to work more rapidly than atomoxetine and was better tolerated.

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suppression, insomnia, wear off, exacerbation of mood, anxiety, and tics, or misuse. We utilize extended-release (ER) alpha-2 agonists primarily for hyperactivity/impulsivity but find them less effective for inattention, and they can cause sedation and hypotension. Oftentimes, we need to combine an alpha-2 agonist for behavior with psychostimulants for inattention. We employ atomoxetine or VER for combined ADHD. However, challenges we have encountered with atomoxetine are that it is often only mildly effective, takes several weeks to work, and requires dosage adjustment for poor cytochrome P450 (CYP) 2D6 metabolizers, and capsules cannot be opened for young children. Viloxazine was marketed as an antidepressant in Europe for 30 years [1], and it was recently reformulated as an ER and approved by the US Food and Drug Administration (FDA) for pediatric and adult ADHD in the USA. Potential advantages of VER are improvements in ADHD symptoms by 1 week in children and by 2 weeks in adults, no adjustment required for CYP2D6 (it is a CYP1A2 inhibitor), and the ability to open capsules [2, 3]. Although both medications are norepinephrine reuptake inhibitors (NRIs), viloxazine demonstrates less inhibition of norepinephrine (NE) reuptake (Ki = 2300 nM) than atomoxetine (Ki = 3.4 nM), negligible serotonin (5-HT) reuptake inhibition (Ki > 10,000 nM) versus atomoxetine (Ki = 390 nM), and no dopamine (DA) reuptake inhibition versus atomoxetine (Ki = 1750 nM) [4]. In contrast, viloxazine is a 5-HT_{2B} antagonist, 5-HT_{2C} partial agonist, and 5-HT_7 antagonist associated with increases in prefrontal cortex 5-HT, NE, and DA levels in vivo [5]. Our patients' insurers mandate a trial of generic atomoxetine prior to covering branded VER. We wanted to know whether patients taking atomoxetine for DSM-5-TR ADHD combined type would experience improvement in ADHD symptoms following voluntary, open-label switch to VER.

2 Participants and Methods

A total of 50 patients (35 children; Table 1) who presented to our centers with a chief complaint and primary diagnosis of ADHD combined type according to DSM-5-TR criteria and had no other concurrent psychiatric, medical, or substance-related comorbidities as per clinical diagnostic interview or prior exposure to either atomoxetine or VER received mean doses of atomoxetine 60 mg (25–100 mg once daily) followed by VER 300 mg (100–600 mg once daily) after a 5-day atomoxetine washout. All patients were allowed to stay on stable doses of concomitant psychostimulant medication throughout both treatments. All patients received "a non-stimulant ADHD medication for inattentiveness and hyperactivity/impulsivity called atomoxetine" prior to receiving VER as per their insurance prior authorization requirement. Following up to a 4-week trial of atomoxetine, as tolerated, all 50 patients voluntarily opted for a trial of a "similar, non-stimulant ADHD medication called viloxazine ER" either due to side effects or insufficient response. Both atomoxetine [6] and VER [7] were flexibly titrated and administered at either daytime or nighttime, as tolerated, according to the following FDA guidelines: For atomoxetine, children 6 years and older and < 70 kg received 0.5 mg/day for 3 days, increased to a maximum of 1.2 mg/kg/day after at least 2 weeks, and children 6 years and older and > 70 kg and adults received 40 mg/day for 3 days, increased to a maximum of 100 mg/day after at least 2 weeks. For VER, children ages 6–11 years received 100 mg/day for 1 week, increasing by 100 mg/day each week to a maximum of 400 mg/day; children ages 12 years and older received 200 mg/day for 1 week, increasing to a maximum of 400 mg/day; and adults received 200 mg/day for 1 week increasing by 200 mg/day per week to a maximum of 600 mg/day. Patients were seen weekly for titration and monitoring. The pediatric ADHD-Rating Scale-5 (ADHD-RS-5) [8] and the Adult Investigator Symptom Rating Scale (AISRS) [9] were completed prior to starting atomoxetine; 4 weeks after treatment with atomoxetine or upon earlier response or discontinuation due to side effects, whichever occurred first; and 5 days after discontinuing atomoxetine, which re-established baseline ADHD scores; the same protocol was used after treatment with VER. As per our clinical protocol, a maximum time frame of a 4-week trial on each treatment to observe response was chosen to balance the time required for treatments to take effect with the natural urgency for both children and adults to experience some

Table 1 Demographic and baseline characteristics

Variables	Pediatric	Adult
Population, *N*	35	15
Age, years		
Mean ± SD	11.9 ± 2.9	29.3 ± 9.0
Median (min, max)	12 (6, 17)	28 (20, 51)
Sex, *n* (%)		
Male	33 (94.3%)	11 (73.3%)
Female	2 (5.7%)	4 (26.7%)
Race, *n* (%)		
White	33 (94.3%)	14 (93.3%)
Non-white	2 (5.7%)	1 (6.7%)
Hispanic/Latino	1 (2.9%)	1 (6.7%)
Black	1 (2.9%)	0 (0%)
Asian	0 (0%)	0 (0%)
Concurrent stimulant, *n* (%)	15 (42.9%)	11 (73.3%)

Max maximum, *min* minimum, *n* number of subjects, *N* number of subjects in the population, *SD* standard deviation

relief of ADHD symptoms that are impairing their daily functioning. We obtained informed consent from participants and Institutional Review Board (IRB) approval prior to conducting a blinded, de-identified, retrospective review of charts from these 50 patients in the regular course of outpatient practice between 1 July and 30 October 2022. Statistical analysis was performed using a within-subject, 2-tailed *t*-test with significance level of $p < 0.05$. Power analysis indicated that a sample size of 35 children per treatment group with an estimated Cohen's *d* effect size between the VER and the atomoxetine groups of 0.819, which we calculated from this sample, yielded a statistical power of 92.3%. Power analysis indicated that a sample size of 15 adults per treatment group with an estimated Cohen's *d* effect size between the VER and the atomoxetine group of 1.36 that we calculated from this sample yielded a statistical power of 94.7%.

3 Results

From the baseline total ADHD-RS-5 mean score (40.3 ± 10.3), improvements were greater on VER (13.9 ± 10.2) than atomoxetine (33.1 ± 12.1; $t = -10.12$, $p < 0.00001$) in inattention ($t = -8.57$, $p < 0.00001$) and in hyperactivity/impulsivity ($t = -9.87$, $p < 0.00001$; Fig. 1). From the baseline total AISRS mean score (37.3 ± 11.8), improvements were greater on VER (11.9 ± 9.4) than atomoxetine (28.8 ± 14.9; $t = -4.18$, $p = 0.0009$) in inattention ($t = -3.50$, $p < 0.004$) and in hyperactivity/impulsivity ($t = -3.90$, $p < 0.002$; Fig. 2). Of the children on VER, 89% reported positive response by 2 weeks versus 14% on atomoxetine (Fig. 3). Of the adults on VER, 87% reported positive response by 2 weeks versus 13% on atomoxetine (Fig. 4). No patients discontinued treatment prior to 4 weeks due to lack of response. A total of 36% discontinued atomoxetine for side effects, including gastrointestinal (GI) upset (6 patients), irritability (6), fatigue (5), and insomnia (1), versus 4% who discontinued VER due to fatigue. A total of 96% preferred VER over atomoxetine, with 85% (22 out of 26) choosing to taper psychostimulants following stabilization on VER, specifically 100% (15 out of 15) of children and 64% (7 out of 11) of adults.

4 Discussion

Pediatric and adult ADHD diagnoses have been rising over the past decade [10] alongside increasing numbers of prescriptions for psychostimulant medications [11]. While psychostimulants have demonstrated superiority to non-stimulants in rapidly improving inattention [12], risk for abuse and side effects, such as insomnia, appetite suppression, wear off, and potential exacerbation of mood, anxiety, and tics [13], give clinicians cause to consider prescribing non-stimulants either as monotherapy or in combination with psychostimulants to enhance efficacy and/or mitigate side effects of psychostimulants [14]. While the alpha-2 agonists, ER clonidine and ER guanfacine, can help manage symptoms of hyperactivity/impulsivity, they are less effective for inattentive symptoms compared with psychostimulants [15]. As an NRI, atomoxetine can potentially address the full spectrum of inattentive and hyperactive/impulsivity symptoms, albeit more modestly compared with psychostimulants for inattention [16] and ER alpha-2-agonists for hyperactivity/impulsivity [17]. When VER was introduced to the US market for ADHD in 2021, it was classified as another NRI and equated with atomoxetine in terms of its mechanism of action and corresponding mild efficacy in ADHD [18]. However, additional serotonin receptor targets have been more recently identified that may better explain its primary mechanism of action beyond the NE reuptake inhibition that distinguishes it from atomoxetine pharmacologically

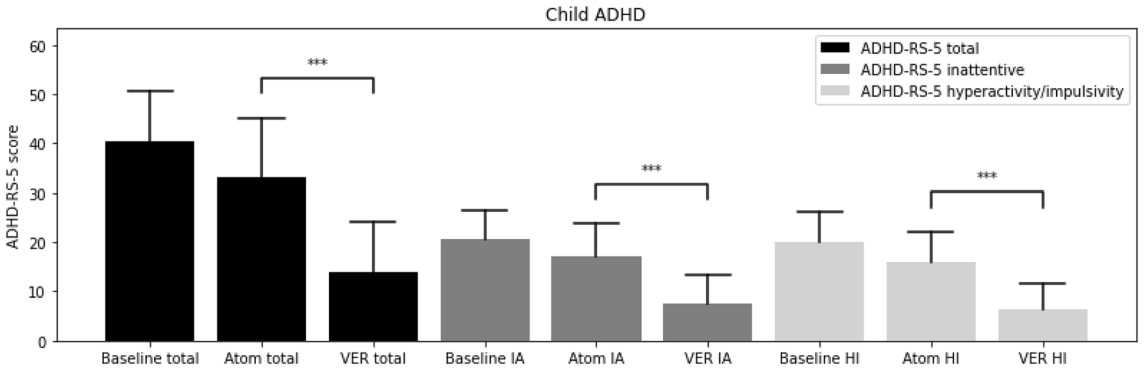

Fig. 1 ADHD-Rating Scale-5 (ADHD-RS-5) at baseline, on atomoxetine (Atom), on extended-release viloxazine (VER). ***$p < 0.00001$. *ADHD* attention-deficit hyperactivity disorder, *Atom* atomoxetine, *HI* hyperactivity/impulsivity, *IA* inattentive, *RS* rating scale, *VER* viloxazine extended-release

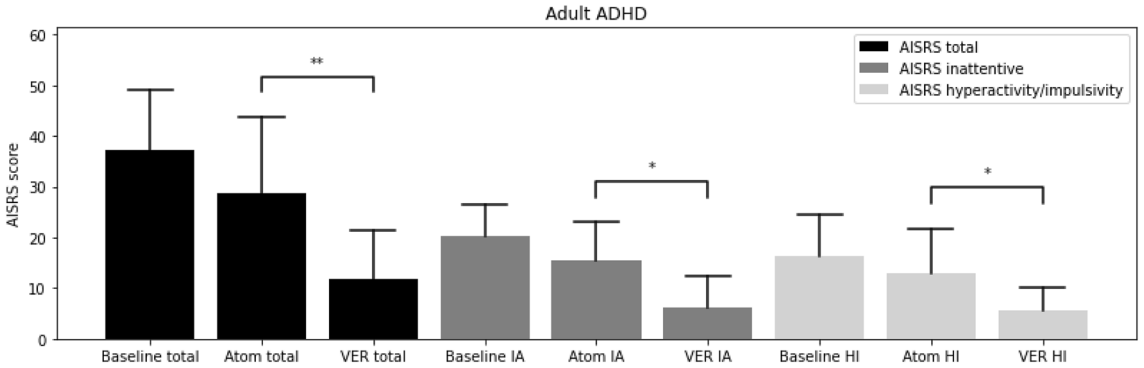

Fig. 2 Adult Investigator Symptom Rating Scale (AISRS) at baseline, on atomoxetine (Atom), on extended-release viloxazine (VER). *$p < 0.005$. **$p < 0.001$. *ADHD* attention-deficit hyperactivity disorder, *AISRS* Adult Investigator Symptom Rating Scale, *Atom* atomoxetine, *HI* hyperactivity/impulsivity, *IA* inattentive, *VER* viloxazine extended-release

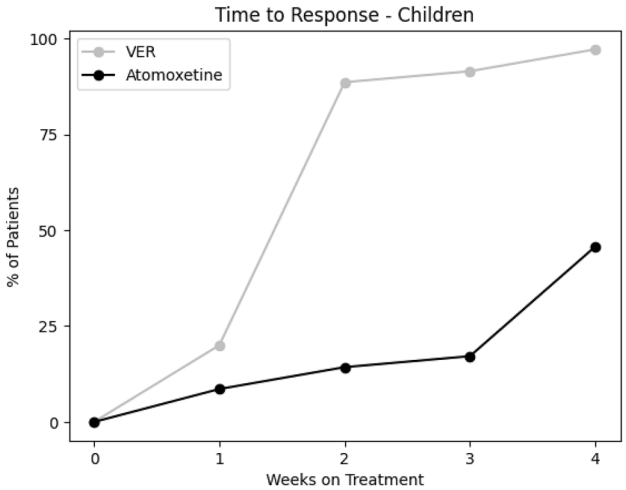

Fig. 3 Cumulative percent of children with positive response per week to viloxazine ER (VER) compared with atomoxetine. *VER* viloxazine extended-release

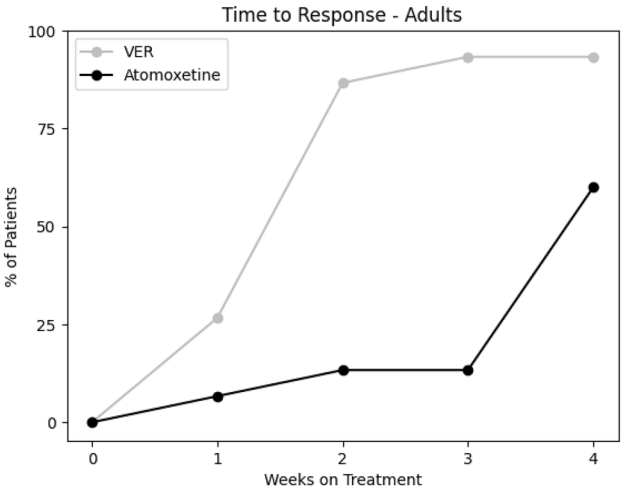

Fig. 4 Cumulative percent of adults with positive response per week to viloxazine ER (VER) compared with atomoxetine. *VER* viloxazine extended-release

[5]. Using a within-subject, crossover design from atomoxetine to VER, this study is important in differentiating the clinical utility, speed of onset, and tolerability of VER from atomoxetine. Compared with baseline total ADHD-RS-5 and AISRS scores, these participants who were initially moderately to severely impaired by their ADHD symptoms were much to very much improved after 2 weeks on VER. Over half of study participants had been previously exposed to stable doses of psychostimulants, and the vast majority were able to reduce or discontinue their psychostimulant use as the addition of VER became effective after 2 weeks. Furthermore, the common aforementioned side effects found with psychostimulants did not present causes for discontinuation of VER. Likewise, the most common reason for discontinuation of atomoxetine, gastrointestinal upset, was also not a cause for discontinuation of VER. During the 5-day washout period from atomoxetine, side effects from atomoxetine abated, and participants reverted back to their baseline ADHD symptoms. Given the superior efficacy for both inattentive and hyperactivity/impulsivity symptoms, speed of onset, and tolerability of VER over atomoxetine, we recommend considering VER as a first-line non-stimulant option for addressing the full spectrum of ADHD symptoms, either as a monotherapy in patients for whom psychostimulants are not ideal or as an adjunct to psychostimulants. Limitations of this study were that it was an unblinded, open-label, single arm, retrospective analysis of a relatively small, heterogeneous sample of children and adults, without a comparison group or placebo control. Placebo effect, period effect, or carry-over effect could not be excluded. Future double-blind studies with larger sample sizes, greater representation of females and minority groups, and weekly ADHD-RS-5 and AISRS

administered over longer periods of time are warranted. A more rigorous study would include two parallel arms with random groups, one starting with atomoxetine prior to use of VER and one starting with VER prior to use of atomoxetine to take into account the improvements of each first starting treatment, where the baseline of each group would be the reference to investigate improvements. However, this was not possible in our real-world clinical practice setting where patients' insurance mandated a trial of atomoxetine prior to providing coverage for VER, and all patients previously taking atomoxetine voluntarily chose to switch to VER.

5 Conclusions

Pediatric and adult ADHD patients who have experienced less-than-optimal response to atomoxetine demonstrate rapid improvement in inattention and in hyperactivity/impulsivity with greater tolerability on extended-release viloxazine.

Declarations

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Conflicts of Interest Maxwell Z. Price certifies that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript. Richard L. Price has received honoraria from AbbVie, Alkermes, Idorsia, Intra-Cellular Therapies, Janssen, Jazz, Lundbeck, Neuronetics, Otsuka, and Supernus, and discloses no other conflicts of interest in this work.

Data Availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval This research study was conducted retrospectively from data obtained for clinical purposes and performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. We consulted extensively with WCG IRB, who determined that our study did not need ethical approval. An IRB official waiver of ethical approval (#1-1597751-1) was granted from WCG IRB.

Consent to Participate Informed consent was obtained from all individual participants included in the study (or their parent or legal guardian in the case of children under 16 years).

Consent for Publication Not applicable.

Code Availability Not applicable.

Authors' Contributions Both authors substantially contributed to the conception and design of the work, drafting the work, and approving the final version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy of any part of the work are appropriately investigated and resolved. Both authors read and approved the final version of the manuscript and agree to be accountable for the work.

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