Executive Function Outcome of Treatment with Viloxazine Extended-Release Capsules in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder: A Post-Hoc Analysis of Four Randomized Clinical Trials

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Abstract

Aim The aim of this study was to evaluate the effect of viloxazine extended-release capsules (viloxazine ER; Qelbree™) on executive function deficits (EFDs) in pediatric subjects (6–17 years of age) with attention-deficit/hyperactivity disorder (ADHD).

Methods Data from four phase III placebo-controlled trials of 100–600 mg/day viloxazine ER (6–8 weeks of treatment) were used to evaluate the change from baseline (CFB) in the Conners 3rd Edition Parent Short Form—Executive Function (C3PS-EF) content scale T-score. Subjects were defined as EFD responders if they had C3PS-EF T-score > 70 at baseline and < 65 at end of study. ADHD symptoms were assessed with ADHD Rating Scale 5th Edition (ADHD-RS-5). Subjects were defined as ADHD symptom responders if they had a ≥ 50% reduction in CFB ADHD-RS-5 Total score at Week 6. The number needed to treat (NNT) and Cohen’s d effect sizes were estimated for EFD and ADHD symptoms.

Results A total of 1154 subjects were included in the analysis. Statistically significant improvements in EFDs were observed with viloxazine ER versus placebo (p = 0.0002). There were 52.5% of EFD or ADHD symptom responders in the viloxazine ER treatment group and 35.4% in the placebo group (p < 0.0001). The NNT was 5.8. The Cohen’s d effect size for EFD and ADHD symptoms was 0.31.

Conclusion Consistent with the efficacy of viloxazine ER demonstrated in pivotal trials, viloxazine ER significantly reduced EFDs in subjects with ADHD. Moreover, a substantial proportion of subjects treated with viloxazine ER had large improvements in EFDs, ADHD symptoms, or both.

Clinical Trial Registration Numbers NCT03247530, NCT03247517, NCT03247543, NCT03247556.

Key Points

Viloxazine ER significantly reduced executive function deficits in pediatric subjects with ADHD.

A substantial proportion of subjects treated with viloxazine ER had large improvements in executive function deficits, ADHD symptoms, or both.

Introduction

Executive functions are an array of cognitive processes, whereby individuals self-regulate their behavior, emotions, and cognition to optimize organization, planning, and problem-solving for an attainment of some goal [1]. Substantial evidence has shown that attention-deficit/hyperactivity disorder (ADHD) is associated with executive function deficits (EFDs). A meta-analysis of 24 studies comparing neuropsychological tests of adults with ADHD versus controls...
reported that ADHD was associated with small to moderate difficulties organizing information, planning, abstracting information, recalling information over short time spans, sustaining attention, and inhibiting inappropriate thoughts and behaviors [2]. Another meta-analysis of 41 studies found that children with ADHD exhibited deficits in planning compared with the typical development of their peers [3]. The impaired executive functioning in ADHD has been linked to behavioral disinhibition, altered reward sensitivity, and aversion to delay of rewards, potentially leading to risky decision making [4, 5]. The EFDs have also been associated with learning problems and poor school-related outcomes [6]. Interestingly, genome-wide association studies indicate that the etiologies of ADHD symptoms and EFDs share some common genetic variants [7, 8].

Prior studies of the medications used for the treatment of ADHD have found small to moderate improvements in executive functioning. A meta-analysis of the effects of methylphenidate on executive function in children and adults with ADHD demonstrated moderate improvements in response inhibition across 25 double-blind placebo-controlled studies [9]. This meta-analysis found similar results for sustained attention across 29 studies, but no significant effect on working memory. Several studies demonstrated significant effects of lisdexamfetamine dimesylate on executive function in children and adults [10, 11].

Improvements in EFDs in children and adults were also observed with atomoxetine treatment [12, 13]. Two identical studies using a double-blind, placebo-controlled, parallel design to evaluate 10-week atomoxetine treatment in adults demonstrated improvement in EFDs measured with the Stroop task [12]. An array of non-verbal executive function measures was assessed in a 12-week, open-label trial of atomoxetine in boys (8–16 years of age) [13]. The study showed improvements at 4 weeks and 12 weeks of treatment, although it was noted that the findings should be interpreted with caution as, in the absence of a placebo control, the changes in performance may be due to practice effects.

Studies with guanfacine extended-release showed mixed results. One study found small but significant effects on executive function when guanfacine extended-release was used as an adjunct therapy to psychostimulants in children with ADHD [14]. Another study evaluating cognitive-enhancing properties of guanfacine in healthy male volunteers found no improvement in executive or memory functions [15]. A phase II noninferiority laboratory classroom study showed that at doses that resulted in improvement in ADHD symptoms, guanfacine extended-release did not worsen cognitive task performance, with no significant differences found versus placebo on several measures of alertness and psychomotor functioning [16].

Viloxazine extended-release capsules (viloxazine ER; Qelbree™) is a novel nonstimulant medication that has been approved by the US Food and Drug Administration for the treatment of ADHD in children and adolescents (ages 6–17 years). Viloxazine has demonstrated activity at the norepinephrine transporter and has been shown to increase prefrontal cortex serotonin levels in preclinical studies, although how these latter changes in serotonin neurotransmitter levels translate into humans remains to be fully elucidated [17]. In phase III clinical trials in children and adolescents (6–17 years of age) with ADHD, viloxazine ER reduced ADHD symptoms [18–21]. There were also low discontinuation rates during the course of the trials, suggesting a tolerable and safe profile [18–21]. The objective of this post-hoc analysis was to evaluate the effects of viloxazine ER on EFD, which was measured in four pediatric phase III clinical trials using the Executive Function content scale of Conners 3rd Edition Parent Short Form (C3PS-EF). The C3PS is an assessment tool for ADHD and associated issues, validated in children ages 6–18 years [22]. It assesses behavior across six content scales scored on a 4-point Likert scale: inattention, hyperactivity/impulsivity, learning problems, executive function, defiance/aggression, and peer relations [22].

The current analysis expands the evidence base of ADHD treatment in several ways. First, this is the first study to evaluate the effect of viloxazine ER on EFDs. Second, the large sample size utilized in this analysis allows the evaluation of the magnitude of response in individuals with severe levels of EFDs at baseline. Third, the study provides clinically useful descriptions of response rates by using a norm-referenced scale (the C3PS), estimating the number needed to treat (NNT) [23], while also assessing individuals’ response in either executive functioning or ADHD symptom domains.

2 Methods

2.1 Data Description

We used data from four double-blind, three-arm, parallel-group, placebo-controlled, phase III clinical trials of viloxazine ER in children and adolescents (6–17 years of age) with ADHD (Table 1) [18–21].

All study protocols were approved by Advarra Institutional Review Board (IRB) and conducted in accordance with the Helsinki Declaration and the International Council for Harmonisation Note for Guidance on Good Clinical Practice. All versions of the informed consent/assent form were reviewed and approved by the IRB.

To participate in the study, subjects had to meet the following pre-determined inclusion criteria: diagnosis of ADHD based on DSM-5 criteria and confirmed by the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID), ADHD Rating Scale 5th Edition (ADHD-RS-5) Total score ≥ 28, and a Clinical Global Scale...
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Impression—Severity of Illness (CGI-S) score ≥ 4 [19]. Key predefined exclusion criteria were major psychiatric disorder or neurological disorder (excluding oppositional defiant disorder, or major depressive disorder if the subject was free of major depressive episodes within 6 months prior to screening), a history of allergic reaction to viloxazine or its excipients, any food allergy or intolerance that contraindicated trial participation, suicidal ideation, history of seizures, or significant systemic disease [19]. Children and adolescents had to weigh ≥ 20 kg and ≥ 35 kg, respectively, and have a body mass index > 95th percentile for the appropriate age and sex. After a screening period of up to 28 days, including a 7-day washout period of medications prohibited per study protocol, eligible subjects were randomized in a 1:1:1 ratio to receive one of the two doses of viloxazine ER or placebo (Table 1). The study medication capsules had to be taken daily by mouth in the morning, with or without food. The viloxazine ER and placebo capsules were identical in appearance. The capsules could be opened and the contents sprinkled over a spoon of soft food (e.g., apple sauce) if needed. Refraining from taking ADHD medications (other than the study medication) was required starting at least 1 week prior to randomization until the end of study (EOS).

Subjects returned weekly for efficacy and safety assessments until the EOS or early termination. The ADHD-RS-5 was measured at screening, baseline, and at post-baseline weekly visits. The C3PS was administered at baseline and the EOS.

### 2.2 Data Analyses

The ADHD-RS-5 data from all studies were integrated with a cutoff of 6 weeks of treatment (i.e., this was the common efficacy endpoint). Subjects were defined as ADHD symptom responders if the change from baseline (CFB) in ADHD-RS-5 Total score was reduced (improved) by ≥ 50% from baseline to Week 6. Subjects were defined as EFD responders if they had a C3PS-EF content scale T-score > 70 at baseline and < 65 at EOS (Week 6 or later in different trials as applicable; see Table 1). A cutoff T-score of 70 (very elevated) was chosen, because it falls above two standard deviations of the population mean, which is the standard method for defining severe impairment by T-scores [22]. A T-score < 65 (below elevated) was chosen, because it falls within 0.5 standard deviation, hence, this change would be reflective of a moderate effect [22].

The mixed model for repeated measures (MMRM) was used for these analyses (SAS version 9.4), with the responder status used as the dependent variable and the following fixed effects used as independent variables: C3PS-EF at baseline, treatment group (drug vs placebo), age, sex, and study site. To expand clinically useful information, two definitions of response were considered: (1) EFD response only and (2) EFD response or ADHD symptom response. Initial analysis included all subjects who had C3PS-EF measured at the EOS. Because some subjects did not exhibit EFDs at baseline, additional analysis included a subset of subjects who had a C3PS-EF T-score > 70 at baseline.

The effect size using Cohen’s d method was first calculated individually for EFD and ADHD symptoms [24]. Then the pooled effect size for both measures was jointly estimated using methodology proposed by Balduzzi et al. [25] and implemented with the R ‘meta’ package.

The effect size using NNT was calculated using the responder rate as an inverse of the absolute risk reduction (responder rate in the placebo group subtracted from responder rate in the treatment group) expressed as a decimal.

### Table 1  Overview of phase III randomized controlled trials providing data

| Study | Clinical trial identifiera | Age, years | Viloxazine ER dose, mg/day | Weeks (T+M) | N (ITT population) |
|-------|-----------------------------|------------|-----------------------------|-------------|-------------------|
|       |                             |            |                             |             | Total  | Viloxazine ER/placebo |
| 812P301 [19] | NCT03247530 | 6–11 | 100 | 6 (1 + 5) | 460 | 305/155 |
| 812P302 [18] | NCT03247517 | 12–17 | 200 | 6 (1 + 5) | 301 | 197/104 |
| 812P303 [21] | NCT03247543 | 6–11 | 200 | 8 (≤ 3 + 5) | 301 | 204/97 |
| 812P304 [20] | NCT03247556 | 12–17 | 400 | 7 (2 + 5) | 292 | 196/96 |

*aClinicalTrials.gov

*ITT* intent-to-treat, *M* maintenance, *T* titration, *Viloxazine ER* viloxazine extended-release capsules

△ Adis
3 Results

The total sample included 1154 subjects with ADHD (760 were treated with viloxazine ER and 394 with placebo). Of those, 739 were male and 941 had C3PS-EF T-score > 70 at baseline. C3PS-EF T-scores at baseline and EOS for each viloxazine ER dose are provided in Table 2. The mean baseline C3PS-EF T-score was > 70 (severe range) in all viloxazine ER treatment groups.

In the initial analysis, which included all subjects who had C3PS-EF measurement at EOS, a statistically significant improvement in the CFB C3PS-EF T-score was observed in the viloxazine ER treatment group (all doses pooled) versus placebo (− 2.7 ± 0.732; p = 0.0002). The MMRM analysis detected significant effects of baseline C3PS-EF T-score (F_{1,1150} = 193; p < 0.0001) and treatment group (F_{1,1150} = 14; p = 0.0002), with no significant effects of other variables (e.g., age or sex). The standardized mean difference (SMD) (difference between treatment means/pooled standard deviation [26]) between viloxazine ER and placebo was 0.11. When limiting the analysis to those with C3PS-EF baseline T-scores > 70, significant effects of baseline C3PS-EF score (F_{1,833} = 33; p < 0.0001) and treatment group (F_{1,833} = 11.9; p = 0.0006) were observed. However, no significant effects were detected for all the other tested variables. The SMD between viloxazine ER and placebo was 0.12.

The effect size estimated using Cohen’s d method for the EFD was 0.21. The pooled effect size for EFD and ADHD symptoms was 0.31. The effect sizes estimated among subjects with C3PS-EF baseline T-scores > 70 were similar: 0.24 for the EFD and 0.29 for EFD and ADHD symptoms combined.

When considering EFD or ADHD symptom responders (subjects who had either an ADHD-RS-5 Total score improvement of ≥ 50% from baseline to Week 6 or a decrease in the C3PS-EF score from > 70 to < 65), the response rates were 52.5% for the viloxazine ER group and 35.4% for the placebo group (X^2_1 = 22.1; p < 0.0001); the NNT was 5.8. When considering EFD responders only (subjects who had a decrease in the C3PS-EF T-score from > 70 to < 65), response rates were 38.6% for the viloxazine ER group and 27.4% for the placebo group (X^2_1 = 10.4;
Among the viloxazine ER-treated subjects, the correlation between the magnitude of EFd response and the magnitude of ADHD symptom response was 0.47 ($p < 0.0001$). Figure 1 shows the association between the C3PS-EF and ADHD-RS-5 change scores for the treatment group.

5 Conclusion

This post-hoc analysis of four randomized clinical trials demonstrated that viloxazine ER significantly reduced EFds in children and adolescents with ADHD. The average effects of viloxazine ER on EFds appeared to be clinically relevant as a substantial proportion of subjects had significant improvements in EFds. This work extends the previous findings [18–21] of viloxazine ER demonstrating improved ADHD symptoms, and may have implications for clinicians when planning treatment of children and adolescents with ADHD and EFD.
Declarations

Ethics approval This is a post-hoc analysis of integrated data from four clinical studies. In each study, informed consent/assent forms were signed as applicable. Each study protocol was approved by Advarra Institutional Review Board (IRB) and conducted in accordance with the Helsinki Declaration and the International Council for Harmonisation Note for Guidance on Good Clinical Practice. All versions of the informed consent/assent form were reviewed and approved by the IRB.

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Conflicts of Interest JTH, GDB, ZM, JR, and AN are employees of Supernus Pharmaceuticals, Inc. SYV received income, potential income, travel expenses, continuing education support and/or research support in the past year from Takeda, OnDosis, Tris, Otsuka, Arbor, Ironshore, Rhodes, Akili Interactive Labs, Enzymotec, Sunovion, Supernus, and Genomind. With his institution, he has US patent US20130217707 A1 for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. He also receives royalties from books published by Guilford Press: Straight Talk about Your Child’s Mental Health; Oxford University Press: Schizophrenia: The Facts; and Elsevier: ADHD: Non-Pharmacologic Interventions. He is Program Director of www.adhdsadults.com. RG was a paid consultant to Ironshore Pharmaceuticals; Sunovion Pharmaceuticals; Supernus Pharmaceuticals; Teva; Biomedical Science Institutes; Nanomini BVs; Laboratorios Liconsa; Massachusetts General Hospital; UCB; Recordati Rare Diseases; Indivior, Tris Pharma; F. Hoffmann-La Roche.

Authors’ contributions SF—contributed to analysis plan, data interpretation, writing and reviewing the manuscript drafts. RG—data analysis, data visualization, reviewing and updating the manuscript drafts. JTH—data curation and interpretation, quality review, and updating the manuscript drafts. GDB—data interpretation, reviewing and updating the manuscript drafts, publication management. ZM—data interpretation, data visualization, writing, reviewing and updating the manuscript drafts, publication management. JR—study conceptualization, interpretation, reviewing the manuscript drafts. AN—study design and conceptualization, oversight of all aspects of the study methods, analysis, and data interpretation, reviewing the manuscript drafts. All authors approved the final version of the manuscript for submission and agree to be accountable for the work described in the manuscript.

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Code availability Not applicable.

Consent to participate Each subject and parent(s)/legally authorized guardian(s) provided written informed consent/assent prior to screening or administration of any study-related procedures. The subject and the parent/guardian were informed about the nature and purpose of the study, as well as of its risks and benefits. It was explained that the subject could withdraw from the study at any time for any reason and that this would not have any effect on the subject’s potential future medical care.

Consent to publish Not applicable.

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