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Psychiatry

Evaluating the likelihood to be helped or harmed after treatment with viloxazine extended-release in children and adolescents with attention-deficit/hyperactivity disorder

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Abstract

Aims: When clinicians evaluate potential medications for their patients, they must weigh the probability of a treatment's benefits against the possible risks. To this end, the present analyses evaluate the novel nonstimulant viloxazine extended-release (viloxazine ER) using measures of effect size to describe the potential benefits of its treatment in children and adolescents with attention-deficit/hyperactivity disorder (ADHD) as well as the risk of discontinuation because of intolerable adverse events.

Methods: These post hoc analyses use pooled data from four pivotal Phase 3 trials in paediatric patients treated with viloxazine ER. The Likelihood to be Helped or Harmed (LHH) effect size measure was calculated to describe the probability of patients benefiting from treatment vs discontinuing. The Number Needed to Treat (NNT) was calculated from frequently used thresholds of response. The Number Needed to Harm (NNH) was calculated using discontinuations because of adverse events.

Results: LHH values for viloxazine ER ranged from 5 to 13, suggesting that subjects were 5-13 times more likely to benefit from, rather than discontinue, viloxazine ER treatment. Specifically, NNT values for viloxazine ER treatment ranged from 6 to 7. NNH values for viloxazine ER treatment ranged from 31 to 74. By convention, single-digit NNTs (<10) suggest the intervention is potentially useful, while NNH values ≥10 for adverse events suggest it is potentially safe or tolerable.

Conclusions: These results indicate that patients with ADHD are likely to benefit from treatment with viloxazine ER, and are unlikely to discontinue, as viloxazine ER treatment was associated with favourable LHH, NNT, and NNH values. Clinicaltrials.gov: NCT03247530, NCT03247543, NCT03247517, NCT03247556.

What's known

Viloxazine extended-release (viloxazine ER) is a novel nonstimulant recently FDA-approved for the treatment of ADHD. Viloxazine ER has been shown to be effective in reducing symptoms

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of ADHD in children and adolescents by the first week of treatment. Viloxazine ER has a favourable safety and adverse event profile.

What's new

This analysis describes the clinical relevance of four pivotal Phase 3 trials in paediatric patients with ADHD treated with viloxazine ER, using measures of treatment effect that quantify both the benefits of treatment as well as its risks (defined as discontinuation because of adverse events).

Message for the Clinic

When considering ADHD treatments for their patients, clinicians must weigh the probability of a treatment's benefits against the potential risks. Ultimately, medications that are effective but poorly tolerated are likely to result in premature treatment cessation and are thus ineffective for the patient in the long term. Based on the results reported here, viloxazine ER may be a viable candidate for the treatment of ADHD because of its favourable efficacy, safety, and tolerability profiles.

1 | INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a neurobehavioural disorder characterised by a pattern of age-inappropriate inattentiveness, hyperactivity, and/or impulsivity that occurs across multiple settings (eg, school, home) and leads to various degrees of impairment.^{1,2} Diagnosed in approximately 6.1 million (9.4%) US children and adolescents³ and 2.5%-4.4% of adults,⁴⁻⁶ ADHD often persists into adulthood as a chronic, life-long disorder that requires continuous, flexible treatment approaches across the lifespan.^{7,8}

Current guidelines for pharmacotherapy recommend stimulants (eg, lisdexamfetamine, methylphenidate) as first-line therapy because of their greater efficacy in improving ADHD symptoms than nonstimulants (for a comprehensive review, see Cortese 2020).⁹⁻¹² However, stimulants must be used with caution, or may be contraindicated in patients with marked anxiety or agitation,¹³ substance use disorders,^{14,15} and bipolar disorder,¹⁶ and are associated with weight loss, decreased appetite, and insomnia.^{17,18} Stimulants also carry some risks of serious cardiovascular events^{13,16} and have a risk for abuse, misuse, and diversion.¹⁹⁻²¹ In children and adolescents for whom stimulant therapy is an option, 20%-30% have an inadequate response.²² Nonstimulants, while generally less effective and with slower onset of effect than stimulants,²³ tend to have fewer limitations, no significant risk of abuse, misuse, or diversion, and generally lower risk of cardiovascular events in patients with pre-existing risk factors.^{24,25}

When considering treatment with any medication, treating clinicians must weigh the potential benefits (ie, response to treatment) against the potential risks (ie, issues with safety and/or tolerability). Functionally, a medication that patients cannot tolerate and will eventually discontinue is of limited utility, even if patients find it beneficial in reducing ADHD symptoms. Likewise, patients, their caregivers, and physicians will have limited utility for a medication

that is well tolerated but does not provide benefit in reducing ADHD symptoms.

To quantify the potential benefits of ADHD treatments, clinical trials in ADHD are increasingly reporting efficacy results as the proportion of subjects having achieved pre-specified criteria of response, commonly based on the ADHD Rating Scale (ADHD-RS) or the Clinical Global Impressions - Improvement scale (CGI-I). Most commonly, the CGI-I (a quick, clinician-friendly assessment of overall change in illness) is used to convey the clinical relevance of a given treatment by reporting the percentage of subjects achieving a CGI-I level of 2 (*much improved*) or 1 (*very much improved*) after treatment, as a CGI-I assessment of *much improved* is conventionally thought to be the threshold indicative of clinically meaningful improvement.^{26,27} These analyses can also define responder rates in terms of symptom scales such as the ADHD-RS, using response criteria ranging from 20%²⁸ to 70%²⁹ improvement, with 30% being amongst the most frequent percentage cited in the literature.³⁰⁻³² Conversely, risks can be quantified in a variety of ways depending on the event of interest (eg, headaches, fatigue, syncope, cardiovascular events, death), or their frequency, intensity, or duration. Ultimately, study discontinuation because of adverse events (AEs) has been proposed and is frequently used as a practical measure of overall tolerability.³³

Viloxazine extended-release (viloxazine ER) is a bicyclic structurally distinct molecule with demonstrated in vitro activity as a moderate norepinephrine reuptake inhibitor ($IC_{50} = 0.269 \mu M$).³⁴ In a preclinical rodent model (microdialysis), viloxazine has also been shown to increase norepinephrine, serotonin, and dopamine levels in the prefrontal cortex, a region implicated in ADHD pathophysiology.³⁴ However, interspecies differences and limitations of this animal model preclude the functional translation of these data into humans. As such, additional research is needed to fully elucidate the mechanism of action of viloxazine ER beyond its noradrenergic activity.³⁴

Viloxazine ER has recently been FDA-approved for the treatment of ADHD in children and adolescents under the trade name Qelbree.TM The present post hoc analyses quantify and report the benefits and tolerability of viloxazine ER using data from four Phase 3 studies in children^{35,36} and adolescents.^{37,38} To this end, we use Likelihood to be Helped or Harmed (LHH) as an overall measure of treatment effects, which succinctly measures the benefit-risk ratio that clinicians, parents/caregivers, and patients must consider when selecting a treatment plan, and its component measures Number Needed to Treat (NNT), which describes the beneficial effect of treatment, and Number Needed to Harm (NNH), a measure of risk, such as discontinuations because of AEs. Unlike traditional measures of effect size such as Cohen's *d*, which are used to report the benefits of treatment, LHH also describes the risks associated with treatment and was thus selected because of its clinically relevant interpretation.

2 | METHODS

2.1 | Data sources

These analyses were conducted using pooled data from four pivotal Phase 3 trials assessing the efficacy and safety of viloxazine ER for the treatment of ADHD in children 6-11 years (study P301, NCT03247530³⁵ and study P303, NCT03247543³⁶) and adolescents 12-17 years (study P302, NCT03247517³⁷ and study P304, NCT03247556³⁸) (Table 1). All four trials were randomised, double-blind, placebo-controlled, multicentre, three-arm, parallel-group studies evaluating efficacy and safety of viloxazine ER (a novel non-stimulant with effects on norepinephrine and serotonin³⁴) in paediatric patients with ADHD. In each study, symptoms of ADHD were measured according to the diagnostic criteria of the Diagnostic and Statistical Manual, Fifth Edition, and the diagnosis of ADHD was confirmed with the Mini International Neuropsychiatric Interview for Children and Adolescents. All participants were required to have a minimum ADHD-RS (Fifth Edition; ADHD-RS-5) Total score of 28 at screening and baseline, and a minimum CGI-Severity (CGI-S) score of 4 (ie, *moderately ill*) at screening. Subjects were required to refrain from taking any ADHD medication (other than the study medication) starting at least 1 week prior to randomisation and continuing through end-of-study (EOS) or early termination. A trained

investigator/clinician administered the CGI-S at screening only, the ADHD-RS-5 at screening, baseline, and each post-baseline study visit, and the CGI-I at each post-baseline study visit.

Exclusion criteria included a current diagnosis of any major psychiatric disorders (a diagnosis of major depressive disorder was allowed if the subject was free of episodes at the time of screening and for six months prior), major neurological disorders or history of seizure disorder within the immediate family, current evidence of significant systemic disease, and/or evidence of suicidality within 6 months. Other exclusion criteria included a body mass index greater than 95th percentile for age and gender, history of receiving any investigational drug within the longer of 30 days or 5 half-lives prior to Day 1 dosing of viloxazine ER, or any other reason which might have prevented the subject from participating in the study (as determined by the Investigator).

Eligible participants were randomised at baseline in a 1:1:1 ratio to either placebo or one of the two doses of once-daily viloxazine ER as follows: children (6 to 11 years of age) received either 100 or 200 mg in study P301 and either 200 or 400 mg in study P303; adolescents (12 to 17 years of age) received either 200 or 400 mg in study P302 and either 400 or 600 mg in study P304 (Table 1). In P301, all subjects randomised to active treatment took an initial dose of 100 mg viloxazine ER on Week 1. Those subjects that were randomised to the 200 mg viloxazine ER arm were subsequently titrated up to 200 mg on Week 2. In P303, all subjects randomised to active treatment took an initial dose of 100 mg viloxazine ER on Week 1, and then were titrated up to 200 mg on Week 2. Those subjects that were randomised to the 400 mg viloxazine ER arm were subsequently titrated up to 300 mg on Week 3, and then 400 mg on Week 4. In P302, all subjects randomised to active treatment took an initial dose of 200 mg viloxazine ER on Week 1. Those subjects that were randomised to the 400 mg viloxazine ER arm were subsequently titrated up to 400 mg on Week 2. In P304, all subjects randomised to active treatment took an initial dose of 200 mg viloxazine ER on Week 1, and then titrated up to 400 mg on Week 2. Those subjects that were randomised to the 600 mg viloxazine ER arm were subsequently titrated up to 600 mg on Week 3. Regardless of the varied titration periods, subjects in all four studies maintained fixed-target, once-daily dosing for 5 weeks until EOS. The primary endpoint was the change from baseline at EOS in the ADHD-RS-5 Total score, and a key secondary endpoint was the mean CGI-I score at EOS.

TABLE 1 Summary of Phase 3 clinical trials evaluating viloxazine ER in paediatric populations

Age group	Children 6-11 years		Adolescents 12-17 years	
Study number	P301 ³⁵	P303 ³⁶	P302 ³⁷	P304 ³⁸
N ^a (randomized/completed)	477 / 399	310 / 266	313 / 281	297 / 276
Viloxazine ER doses (per day)	100 mg, 200 mg	200 mg, 400 mg	200 mg, 400 mg	400 mg, 600 mg
Weeks (t + m)	6 (1 + 5)	8 (3 + 5)	6 (1 + 5)	7 (2 + 5)
End of study assessment	Week 6 (Day 42)	Week 8 (Day 56)	Week 6 (Day 42)	Week 7 (Day 49)

Abbreviations: ER, extended-release; m, maintenance dosing; t, titration dosing.

^aN = total number of participants randomized to the study/who completed the study.

The 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. Parents or legal guardians provided written informed consent for all study procedures including protocol amendments. All versions of the informed consent were reviewed and approved by the IRB.

2.2 | Assessments

2.2.1 | ADHD rating scale, Fifth Edition

The ADHD-RS^{39,40} is an ADHD-specific rating scale designed and validated to assess current ADHD symptomatology as described in the Diagnostic and Statistical Manual, Fifth edition (DSM-5), currently in its Fifth Edition (ADHD-RS-5), and is a frequently used assessment in ADHD clinical trials. The scale consists of 18 items that directly correspond to the 18 DSM-5 ADHD symptoms, which are further subdivided into two subscales (nine symptoms/items per subscale): Inattention and Hyperactivity/Impulsivity. On the ADHD-RS-5 scale, the individual or caregiver rates the frequency of each symptom or behaviour over the preceding week on a 4-point Likert scale ranging from 0 (no or rare symptoms) to 3 (severe or frequent symptoms). The sum of scores for the 18 items provides the total score (ranging from 0 to 54). In the four Phase 3 trials, a trained investigator/clinician administered and scored the ADHD-RS-5 Home Version Child (P301/P303) or Adolescent (P302/P304) instrument at screening, baseline, and at each weekly post-baseline study visit through to EOS. The present analyses used the ADHD-RS-5 Total score change from baseline, expressed as a percent reduction (ie, improvement) of baseline scores.

2.2.2 | Clinical global impressions – improvement

The CGI-I scale is a single-item, stand-alone assessment of a clinician's view of a patient's overall functioning relative to an established baseline. Although the CGI-I is non-specific to any one disease, it is often used to measure the improvement/exacerbation of dysfunction as a result of a psychiatric disorder.^{26,41} The CGI-I is rated on a 7-point Likert scale from 1 (*very much improved*) to 7 (*very much worse*), with each score described as *very much improved*, *much improved*, *minimally improved*, *no change*, *minimally worse*, *much worse*, and *very much worse*. After an initial clinical evaluation, considering a patient's symptoms, behaviour, and circumstances, an experienced rater can complete the CGI-I in typically less than a minute. Successful therapy is indicated by a lower overall score in subsequent testing. In each of the four pivotal Phase 3 trials of viloxazine ER, the CGI-I was administered at each weekly post-baseline study visit to EOS (inclusive) to assess ADHD-specific clinical improvement.

2.3 | Statistical analyses

The risk-benefit balance of treatment is described by LHH (the ratio of NNH to NNT), which quantifies how much more likely a patient is to encounter a benefit vs harm from treatment, eg, if Drug A has an LHH value of 5, a patient taking Drug A is five times more likely to experience a benefit from treatment rather than harm.⁴²⁻⁴⁴ Thus, larger LHH values are considered more favourable, though specific rubrics for what constitutes a favourable, acceptable, or poor LHH value depends on the specific events in question (ie, an acceptable value describing a side effect of dry mouth will be smaller than that describing death).⁴²⁻⁴⁴ The components of LHH – NNT (which describes clinical treatment benefits) and NNH (which describes risks) – each quantify the likelihood of a response in a given patient by indicating how many patients would need to be treated with Drug A vs Drug B (eg, active vs placebo) in order to achieve one additional outcome of interest, such as a response to treatment (via NNT) or an adverse outcome (via NNH).⁴²⁻⁴⁴

NNT and NNH values were calculated by first computing the frequency of each event (ie, responses, discontinuations), then calculating the Attributable Risk Reduction (ARR; the difference in rates between the experimental group and the placebo group), and finally taking the inverse of the ARR⁴²⁻⁴⁴; ie, NNT or NNH = 1/ARR, where $ARR = f_a - f_b$, where f_a = the frequency of events for viloxazine ER, and f_b = the frequency of events for placebo:

$$\frac{1}{f_a - f_b} \quad (1)$$

Confidence intervals were calculated by taking the reciprocals of the values defining the confidence intervals for the ARR.⁴⁵ LHH values were calculated as the ratio of NNH over NNT (ie, LHH = NNH/NNT). When calculations resulted in a value other than a whole number, values were rounded to minimise bias and facilitate translation into clinical practice (ie, numbers of whole patients): NNT values were rounded up to the nearest whole number, and NNH and LHH values were rounded down.⁴⁵ NNT, NNH, and LHH calculations of values and confidence intervals were performed in SAS (version 9.4). When interpreting NNT, smaller values are more desirable, suggesting a bigger difference between Drug A and Drug B.⁴²⁻⁴⁴ Similarly, when comparing across multiple NNT values, smaller values indicate fewer patients need to be treated before one patient responds to treatment.⁴²⁻⁴⁴ Conversely, larger values are desirable for NNH,⁴²⁻⁴⁴ eg, an NNH = 50 would mean that fifty patients need to be treated in order for one patient to experience an adverse outcome (relative to the comparator treatment, eg, placebo). Similarly, larger values are desirable for LHH, indicating a more favourable risk-to-benefit ratio. By convention, single-digit NNTs (< 10) suggest the intervention is potentially useful, while NNH values ≥ 10 for adverse, unfavourable outcomes suggest it is potentially safe or tolerable.⁴²⁻⁴⁴ These measures can provide a clinical context to traditional statistical hypothesis testing (which conveys the probability that a treatment effect is not the results of chance, yet says nothing of the clinical significance) by describing the magnitude of the treatment effect.

NNT values were calculated based on the intent-to-treat population (defined as any subject with at least one post-randomisation score), and based on percent responders as defined by four criteria: (a) 30% improvement (ie, reduction from baseline) on the ADHD-RS-5 alone, (b) 50% improvement on the ADHD-RS-5 alone, (c) 30% improvement on the ADHD-RS-5 or response on the CGI-I (score of 1 or 2, *very much improved* or *much improved*, respectively), and (d) 50% improvement on the ADHD-RS-5 or response on the CGI-I (score of 1 or 2). The 30% response threshold was selected as it is amongst the most commonly cited threshold in ADHD studies,^{29,46-49} while the 50% response threshold was selected as it has been shown to be statistically linked with the CGI-I level *much improved* (CGI-I = 2),^{50,51} commonly used as the minimum threshold for clinically meaningful change.^{26,27} Response data were computed as the percent of subjects (treated with viloxazine ER vs receiving placebo) meeting the threshold for each criterion. NNH values were based on the safety population (defined as any subject having received at least one dose of study medication) using study discontinuation because of AEs, selected as a practical measure of overall tolerability.³³

3 | RESULTS

Demographic characteristics are shown in Table 2.

3.1 | Likelihood to be helped or harmed

When using only the ADHD-RS-5 criteria to define treatment responders, the overall LHH value for viloxazine ER was 8 at the 30% improvement level (children = 13, adolescents = 5), and 7 at the

TABLE 2 Demographic data and baseline characteristics

Characteristic	Children (P301 and P303)	Adolescents (P302 and P304)
N	761	593
Age, y		
Mean ± SD (range)	8.5 ± 1.7 (6-11)	13.9 ± 1.6 (12-17)
BMI		
Mean ± SD (range)	17.2 ± 2.3 (12.5-26.3)	21.3 ± 3.4 (13.5-32.6)
Sex, n (%)		
Male	484 (63.6%)	389 (65.6%)
Female	277 (36.4%)	204 (34.4%)
Race, n (%)		
White	395 (51.9%)	364 (61.4%)
Black or African American	326 (42.8%)	203 (34.2%)
Other	40 (5.3%)	26 (4.4%)

Note: Based on the intent-to-treat population.

Abbreviations: BMI, body mass index; n, number of subjects with that observation; N, total number of subjects; SD, standard deviation.

50% improvement level (children = 11, adolescents = 5) (Figure 1A). When response was defined by either the ADHD-RS-5 or CGI-I ≤ 2 criteria, the overall LHH value for viloxazine ER was 8 (children = 13, adolescents = 5), regardless of whether 30% or 50% improvement thresholds were used (Figure 1B). Table 3 shows the n's associated with these values and NNT/NNH values used to calculate LHH based on only ADHD-RS-5 criteria, and Table 4 shows these values for response defined by either the ADHD-RS-5 or CGI-I.

3.2 | Number needed to treat using ADHD-RS-5 criteria

When using only the ADHD-RS-5 criteria to define treatment responders, more subjects treated with viloxazine ER achieved response vs subjects receiving placebo. At the 30% ADHD-RS-5 improvement level, 58.6% of viloxazine ER-treated subjects met the definition of responders, vs 40.7% from the placebo group. When examined by age group, 55.4% of children treated with viloxazine ER responded, vs 37.7% receiving placebo, while 62.8% of adolescents treated with viloxazine ER responded, vs 44.5% receiving placebo. At the 30% response level, the NNT value for viloxazine ER for all groups was 6, regardless of age.

At the 50% ADHD-RS-5 improvement level, 40.7% of viloxazine ER-treated subjects met the definition of responders, vs 24.8% from the placebo group. When examined by age group, 37.3% of children

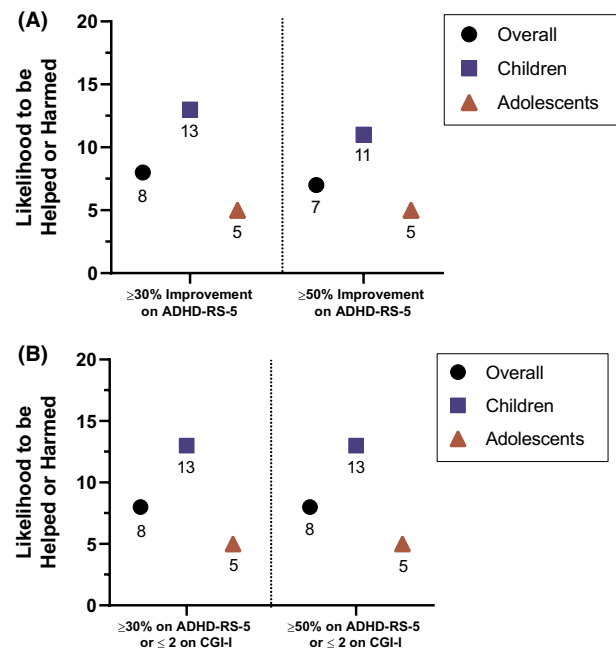


FIGURE 1 Likelihood to be helped or harmed. Likelihood to be Helped or Harmed (LHH) based on the rate of discontinuations because of adverse events and (A) ADHD-RS-5 criteria only or (B) either ADHD-RS-5 criteria or CGI-I criteria. LHH values under each symbol represent the likelihood of responding to treatment vs discontinuing treatment because of adverse events. ADHD-RS-5, Attention-Deficit Hyperactivity Disorder Rating Scale, Fifth Edition; CGI-I, Clinical Global Impressions – Improvement

TABLE 3 NNT (based only on ADHD-RS-5 criteria), NNH (based on discontinuations because of adverse events), and LHH

Subjects	NNT (95% CI)	N for NNT (viloxazine ER, Placebo)	NNH (95% CI)	N for NNH (viloxazine ER, Placebo)	LHH	Studies
30% Improvement on ADHD-RS-5						
All subjects (6-17 y)	6 (5 to 9)	902, 452	46 (26 to 167)	925, 463	8	P301, P302, P303, P304
Children (6-11 y)	6 (4 to 10)	509, 252	74 (-inf to -110) & (+27 to +inf) ^a	522, 262	13	P301 & P303
Adolescents (12-17 y)	6 (4 to 10)	393, 200	31 (18 to 88)	403, 201	5	P302 & P304
50% Improvement on ADHD-RS-5						
All subjects (6-17 y)	7 (5 to 10)	902, 452	46 (26 to 167)	925, 463	7	P301, P302, P303, P304
Children (6-11 y)	7 (5 to 11)	509, 252	74 (-inf to -110) & (+27 to +inf) ^a	522, 262	11	P301 & P303
Adolescents (12-17 y)	7 (5 to 13)	393, 200	31 (18 to 88)	403, 201	5	P302 & P304

Note: Abbreviations: ADHD-RS-5, Attention-Deficit Hyperactivity Disorder Rating Scale, Fifth Edition; CI, confidence interval; ER, extended-release; inf, infinity; LHH, likelihood to be helped or harmed; N, number of subjects; NNH, number needed to harm; NNT, number needed to treat.

^aThe ARR value and CI for children is 1.35 (-0.90 to 3.59). When the ARR CI includes zero, this results in an NNT CI that contains two ranges of numbers: a negative value to negative infinity, and a positive value to positive infinity,^{45,52,53} and suggests there exists no difference in event rates between patients treated with viloxazine ER and placebo.

TABLE 4 NNT (based on either ADHD-RS-5 or CGI-I criteria), NNH (based on discontinuations because of adverse events), and LHH

Subjects	NNT (95% CI)	N for NNT (viloxazine ER, placebo)	NNH (95% CI)	N for NNH (viloxazine ER, placebo)	LHH	Studies
30% Improvement on ADHD-RS-5 or CGI-I ≤ 2						
All Subjects (6-17 y)	6 (5 to 8)	902, 452	46 (26 to 167)	925, 463	8	P301, P302, P303, P304
Children (6-11 y)	6 (4 to 9)	509, 252	74 (-inf to -110) & (+27 to +inf) ^a	522, 262	13	P301 & P303
Adolescents (12-17 y)	6 (4 to 10)	393, 200	31 (18 to 88)	403, 201	5	P302 & P304
50% Improvement on ADHD-RS-5 or CGI-I ≤ 2						
All Subjects (6-17 y)	6 (5 to 8)	902, 452	46 (26 to 167)	925, 463	8	P301, P302, P303, P304
Children (6-11 y)	6 (4 to 9)	509, 252	74 (-inf to -110) & (+27 to +inf) ^a	522, 262	13	P301 & P303
Adolescents (12-17 y)	6 (4 to 10)	393, 200	31 (18 to 88)	403, 201	5	P302 & P304

Abbreviations: ADHD-RS-5, Attention-Deficit Hyperactivity Disorder Rating Scale, Fifth Edition; CGI-I, Clinical Global Impressions - Improvement scale; CI, confidence interval; ER, extended-release; inf, infinity; LHH, likelihood to be helped or harmed; N, number of subjects with that observation; NNH, number needed to harm; NNT, number needed to treat.

^aThe ARR value and CI for children is 1.35 (-0.90 to 3.59). When the ARR CI includes zero, this results in an NNT CI that contains two ranges of numbers: a negative value to negative infinity, and a positive value to positive infinity,^{45,52,53} and suggests there exists no difference in event rates between patients treated with viloxazine ER and placebo.

treated with viloxazine ER responded, vs 21.4% receiving placebo, while 45.0% of adolescents treated with viloxazine ER responded, vs 29.0% receiving placebo. At the 50% response level, the NNT value for viloxazine ER for all groups was 7, regardless of age. These NNT values and the 95% confidence intervals based only on ADHD-RS-5 criteria are shown in Figure 2A and Table 3.

3.3 | Number needed to treat using either ADHD-RS-5 or CGI-I criteria

When using either ADHD-RS-5 or CGI-I ≤ 2 response criteria at EOS, more subjects treated with viloxazine ER achieved response vs

subjects receiving placebo. Using 30% ADHD-RS-5 improvement or CGI-I ≤ 2 response criteria, 61.9% of viloxazine ER subjects met the definition of responders, vs 43.1% from the placebo group. When examined by age group, 59.5% of children treated with viloxazine ER responded, vs 40.9% receiving placebo, while 64.9% of adolescents treated with viloxazine ER responded, vs 46.0% receiving placebo. At this response level, the overall NNT value for viloxazine ER was 6 (regardless of age).

Using 50% ADHD-RS-5 improvement or CGI-I ≤ 2 response criteria at EOS, 53.3% of viloxazine ER subjects met the definition of responders, vs 34.7% from the placebo group. When examined by age, 51.9% of children treated with viloxazine ER responded, vs 33.3% receiving placebo, while 55.2% of adolescents treated

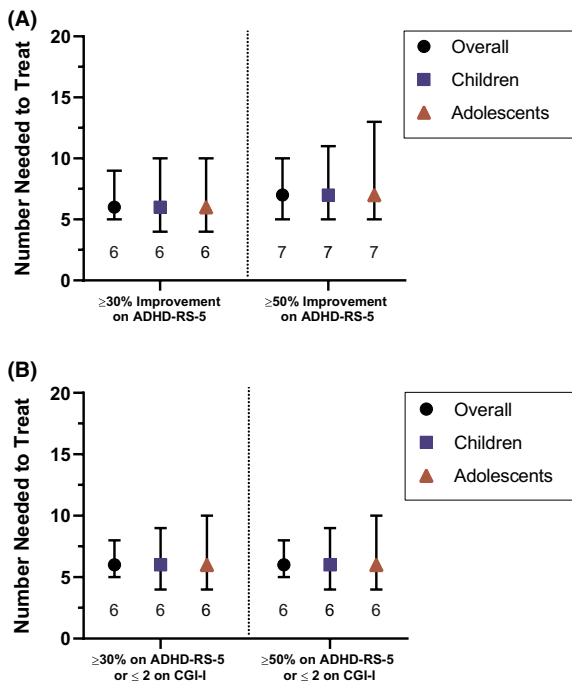


FIGURE 2 Number needed to treat. Number Needed to Treat (NNT; ± 95% confidence intervals) based on (A) ADHD-RS-5 criteria only or (B) either ADHD-RS-5 criteria or CGI-I criteria. NNT values under each symbol represent the number of patients who need to be treated before one patient responds. ADHD-RS-5, Attention-Deficit Hyperactivity Disorder Rating Scale, Fifth Edition; CGI-I, Clinical Global Impressions – Improvement

with viloxazine ER responded, vs 36.5% receiving placebo. At this response level, the overall NNT value for viloxazine ER was also 6 (regardless of age). These NNT values and the 95% confidence intervals based on either ADHD-RS-5 or CGI-I criteria are shown in Figure 2B and Table 4.

3.4 | Number needed to harm using discontinuations because of adverse events

Averaging across all four studies, discontinuations because of AEs occurred in 3.5% of subjects treated with viloxazine ER, and 1.3% of subjects receiving placebo. When examined by age group, discontinuations because of AEs were reported by 3.3% of children treated with viloxazine ER, and 1.9% of children receiving placebo. Similarly, discontinuations because of AEs were reported by 3.7% of adolescents treated with viloxazine ER, and 0.5% of adolescents receiving placebo. The overall NNH value for viloxazine ER was 46 (children = 74, adolescents = 31). The NNH values and 95% confidence intervals are shown in Figure 3 and Tables 3 and 4.

4 | DISCUSSION

The present post hoc analyses describe the results of four pivotal Phase 3 trials using the standardised measures LHH, NNT,

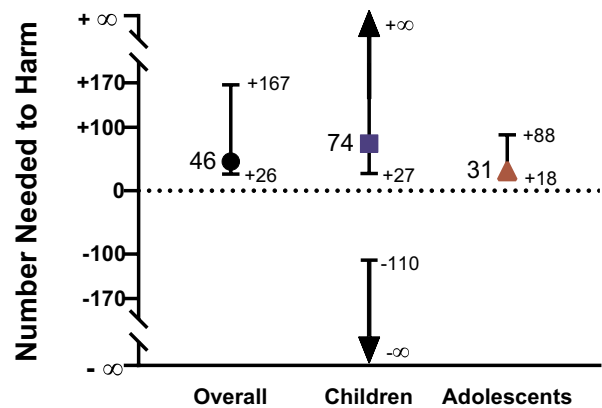


FIGURE 3 Number needed to harm. Number Needed to Harm (NNH; ± 95% confidence intervals) based on the rate of discontinuations because of adverse events. NNH values represent the number of patients who need to be treated before one patient discontinues treatment because of adverse events. Confidence intervals for NNH values that are not statistically significant (ie, Children, blue square) contain two ranges of numbers: negative infinity to a negative value (ie, -infinity to -110), and a positive value to positive infinity (ie, +27 to +infinity), and suggest that there exists no difference in event rates between patients treated with viloxazine ER and placebo. NNH values are to the left of each symbol, 95% upper- and lower-bound confidence intervals are to the right

and NNH. Across these Phase 3 studies (randomised N = 1,397), three of the four trials resulted in statistically significant improvements (vs placebo) on the primary endpoint (the change from baseline in ADHD-RS-5 Total score), as quickly as within one week of treatment.³⁵⁻³⁷ When analysed by response rates, ie, the percentage of subjects achieving 50% or more improvement on the ADHD-RS-5 (a key secondary endpoint), significantly more subjects treated with viloxazine ER improved (relative to participants receiving placebo).³⁵⁻³⁷

Based on response rates from these studies and the low rate of dropouts because of AEs (3.5% in the viloxazine ER group, vs 1.3% in the placebo group, averaged across all four studies), the present analyses report favourable LHH values that support the use of viloxazine ER in reducing ADHD symptoms, with a relatively low risk of discontinuing the drug. The large LHH values reported here (Figure 1) suggest patients are 5 to 13 times more likely to benefit from viloxazine ER than discontinue because of AEs (a common proxy for tolerability³³). Specifically, the NNT values (Figure 2) for viloxazine ER (ranging from 6 to 7) fall well within the convention of NNT <10 for a potentially useful intervention.^{43,44} This was true for all analysis pools, ie, both age groups had NNT values indicative of potentially useful treatment.

When interpreting NNT or NNH, the ARR value (the inverse of which is taken to compute NNT/NNH, see Equation 1, *Methods*) of the drug is considered statistically significant from the comparator (in this analysis, placebo) if both ends of the 95% confidence interval are positive or both ends are negative; if the ARR confidence interval includes zero, the value is not considered statistically significant

from its comparator.^{45,52,53} For all groups analysed (children, adolescents, and overall), all NNT 95% confidence intervals were positive (Figure 2), suggesting that the NNT values were statistically significant; in other words, the rates of response for participants treated with viloxazine ER were significantly different from those receiving placebo, consistent with reports from these data using traditional statistical hypothesis testing.³⁵⁻³⁷

Similarly, NNH values (ranging from 31 to 74; Figure 3) measuring overall tolerability are well beyond the conventional threshold of $\text{NNH} \geq 10$ for a potentially tolerable intervention.^{43,44} Using the overall data (overall $\text{NNH} = 46$, with a confidence interval spanning 26 to 167), this suggests that a clinician will have to treat 46 patients on average before one patient discontinues because of an AE, indicating that this treatment is likely to be very well tolerated.^{43,44} On this measure, modest differences between age groups were detected, as fewer discontinuations because of AEs were reported by children treated with viloxazine ER (3.3%, vs placebo = 1.9%) than by adolescents (3.7%, vs placebo = 0.5%). These differences—with the children's NNH value double that of the adolescents—are not likely to be clinically significant given the large overlap described by the 95% confidence intervals.

Interestingly, amongst children, the ARR value for discontinuations because of AEs was 1.35, with a confidence interval spanning -0.90 to 3.59 . As described above, when the confidence interval for the ARR value includes zero, the value is not considered statistically significant from its comparator. Because NNT and NNH values are the inverse of the ARR (see Equation 1, *Methods*), when converting a confidence interval which includes zero to confidence intervals for NNT or NNH values, this results in a confidence interval with two ranges: a positive value to positive infinity and a negative value to negative infinity.^{45,52,53} As such, the NNH value for the children in the present analysis includes two ranges: $+27$ to $+\infty$, and -110 to $-\infty$ (Figure 3), suggesting that the event rate of the drug is not considered statistically significant from its comparator (here, placebo).^{45,52,53} The confidence interval describing the range for the children's NNH value, therefore, can be interpreted to mean that the rate of AE-driven discontinuations between children treated with viloxazine ER and those receiving placebo was not significantly different.

The use of LHH to guide treatment decisions is likely to be more informative to clinicians than traditional measures of effect size, such as Cohen's *d*, odds ratios, or even NNT alone; as a measure of a treatment's overall effect, LHH quantifies the potential benefits and risks associated with a treatment, whereas traditional measures of effect size generally describe only the potential benefits. If exclusively considering a treatment's efficacy, clinicians may not fully consider the event rates of risks such as adverse events, safety considerations, or tolerability implications. The analyses here describe, in clinically relevant terms, how treatment with viloxazine ER is likely to affect individuals with ADHD with regard to clinical benefits and tolerability, which may help clinicians select a therapy that is both effective and unlikely to be prematurely discontinued.

Accordingly, data from randomised clinical trials (like those reported here) can be complemented by real-world data from

observational studies, providing clinicians with additional information on a medication's impact on patients. Such data can provide evidence of a medication's efficacy or safety on additional measures not easily captured during short-term treatment (eg, infrequent events not likely to occur in short time frames, such as a reduction of risk of injuries⁵⁴). Importantly, the LHH, NNT, and NNH values reported here were relatively consistent—regardless of how the response was defined, or which age group was analysed—suggesting that these data are likely to accurately represent the true effect in the population.

4.1 | Identifying clinically relevant improvement

Previous reports³⁵⁻³⁷ from three of these Phase 3 trials have demonstrated that treatment with viloxazine ER significantly reduces ADHD symptoms and improves overall functioning vs placebo in children and adolescents. Like all statistical hypothesis testing, these significant results demonstrate the low likelihood of these effects occurring by chance, yet do not fully describe the clinical relevance or the potential clinical impact on patients. To identify which response thresholds might be most indicative of meaningful clinical improvement, recent analyses linking the ADHD-RS with the CGI-I scale^{50,51} found that the commonly used 30% criteria threshold^{29,46-49} was linked with *minimally improved* on the CGI-I (associated with no clinically meaningful reduction of symptoms and very little change in functioning^{26,27}), while an improvement of 50% on the ADHD-RS was linked with *much improved*, which is typically assumed to be the threshold for clinically meaningful change.

Binary responder/non-responder efficacy results based on these or similar criteria lend themselves well to the measures NNT and NNH, clinically meaningful effect size measures which describe the results of a clinical trial in terms of the numbers of patients a clinician can expect to treat before one patient experiences the event of interest (eg, responds to therapy, drops out of treatment) vs a comparator treatment such as placebo. Regardless of which response criteria were used (ie, 30% or 50% improvement on the ADHD-RS-5 or $\text{CGI-I} \leq 2$), all viloxazine ER NNT values for children and adolescents were smaller than 10 (Figure 2), the conventional threshold for a potentially beneficial intervention.⁴³

4.2 | Medication discontinuation as an impediment to treatment

ADHD is a potentially lifelong disorder that is known to persist into adulthood,^{7,8} yet several studies have reported medication discontinuation rates that are significantly higher than the relative rates of reported ADHD symptoms and diagnosis,⁵⁵⁻⁵⁷ suggesting that many patients may be terminating treatment prematurely. While a variety of factors can cause a patient to discontinue treatment, intolerable AEs are consistently amongst the most cited reasons,⁵⁸ and present significant challenges to therapy. Although treatment

discontinuation rates in clinical trials tend to be lower than those in population-based studies (likely because clinical trials carefully select, monitor, and support patients throughout the study),⁵⁹ low early trial terminations as a result of AEs can indicate the likelihood that patients will continue treatment over the long term vs discontinuing prematurely.

The present analyses describe the likelihood of AE-induced treatment terminations using the effect size measure NNH. Using this measure, viloxazine ER had an overall NNH value of 46 (Figure 3), which exceeded the conventional NNH ≥ 10 threshold (indicating a potentially favourable tolerability profile), suggesting that a clinician would have to treat 46 patients with viloxazine ER before one patient found the medication intolerable. Because retrospective or longitudinal analyses tend to find higher rates of medication cessation than clinical trials,⁵⁹ these discontinuation rates—which are exclusively from randomised clinical trials—are likely to be an underestimation of the true frequency in clinical practice. This likely underestimation further emphasises the need to consider discontinuations as a barrier to treatment.

4.3 | Conclusions

Amongst children and adolescents with ADHD, treatment with viloxazine ER was associated with favourable LHH values, describing a medication that is likely to be clinically effective in treating ADHD symptoms and unlikely to result in premature medication cessation because of intolerability. Further, these analyses describe, in clinically relevant terms, how treatment with viloxazine ER is likely to affect patients and may help guide clinicians in understanding the potential impact of viloxazine ER treatment in patients (6-17 years of age) with ADHD. Although LHH is relatively simple to calculate from dichotomous data, an overwhelming majority of clinical trials fail to report it. In fact, many published NNT values are calculated during secondary meta-analyses (such as these analyses of stimulants⁶⁰ and atomoxetine⁶¹), rather than the original clinical trial reports. We believe reporting the LHH value resulting from clinical trials would increase the translational value of such studies and the clinical relevance for physicians, researchers, and patients alike, and we encourage authors to do so in their future studies.

DISCLOSURES

A Nasser, AR Kosheleff, T Liranso, P Qin, JT Hull, GD Busse, and J Rubin are employees of Supernus Pharmaceuticals, Inc For a list of M Fava's lifetime disclosures, please see this link. V Maletic is an employee of the University of South Carolina School of Medicine. He is a consultant for ACADIA Pharmaceuticals Inc; Alfasigma USA, Inc; Alkermes, Inc; Allergan; Eisai-Purdue; Intra-Cellular Therapies; Janssen; H. Lundbeck A/S; Otsuka America Pharmaceutical, Inc; Sage Pharmaceuticals; Sunovion Pharmaceuticals Inc; Supernus Pharmaceuticals, Inc; and Takeda Pharmaceutical Company Limited. He serves on the speakers' bureau of ACADIA Pharmaceuticals Inc; Alkermes, Inc; Allergan; Ironshore; Intra-Cellular; Janssen; H.

Lundbeck A/S; Otsuka America Pharmaceutical, Inc; Sunovion Pharmaceuticals Inc; and Takeda Pharmaceutical Company Limited; and his spouse serves on the speakers' bureau of Otsuka America Pharmaceutical, Inc F Lopez has served as a consultant to and received speaker fees and/or research support from Eli Lilly, GSK, Ironshore, Neos, Novartis, Noven, Pfizer, Shire, Sunovion, Supernus, and Tris.

DATA AVAILABILITY STATEMENT

The data are not available in a repository, but reasonable requests can be directed to anasser@supernus.com.

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