Viloxazine Extended Release in Adults With Attention-Deficit/Hyperactivity Disorder and Depression and/or Anxiety Symptoms:

Results From a Decentralized, Open-Label, Phase 4 Trial

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Abstract

Objective: Adult attention-deficit/hyperactivity disorder (ADHD) is commonly associated with comorbidities, including depression and anxiety; however, most ADHD treatment studies exclude people with these conditions. This phase 4, open-label, decentralized clinical trial (conducted March 25, 2024–December 11, 2024) evaluated viloxazine ER (extended-release capsules, an FDA-approved nonstimulant medication for ADHD) in adults with ADHD (based on *DSM-5-TR*) and comorbid depression and/or anxiety symptoms.

Methods: Participants received viloxazine ER (200–600 mg/d) for 14 weeks added to existing medications (including stimulant, antidepressant, or anxiolytic medications). Efficacy and safety measures (assessed via televisit, mobile phone app, and home monitoring devices) included clinician- and patient-reported scales evaluating ADHD, depression, and anxiety symptoms, treatment-emergent adverse events, blood pressure, pulse rate, weight, and suicidality assessment. The primary end point was change from baseline in Adult ADHD Investigator Symptom Rating Scale (AISRS) total score.

Results: Among participants receiving viloxazine ER (n = 161; mean age, 39.4 years; female, 75.8%), almost all (99.4%) had substantial depression and anxiety symptoms. AISRS total score was significantly reduced (improved) from baseline (mean [SD], 37.5 [6.53]; n = 150) at week 14/end of study (EOS) (mean [SD] change, −17.3 [11.34]; $P < .0001$); similar results were observed for patient-reported ADHD symptoms. Depression and anxiety rating scales were significantly improved from baseline to week 14/EOS (all $P < .0001$). Safety outcomes were consistent with previous viloxazine ER studies; 24 participants (14.9%) had adverse events leading to study discontinuation.

Conclusions: Viloxazine ER was well tolerated and associated with improvements in ADHD, depression, and anxiety symptoms in this real-world study of adults with ADHD and comorbid symptoms.

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Attention-deficit/hyperactivity disorder (ADHD) often overlaps with other conditions, including depression and anxiety, that complicate diagnosis and treatment.[1] Over half of adults with ADHD also have a co-occurring mood or anxiety disorder.[2,3] The presence of psychiatric comorbidities increases morbidity and mortality risk in people with ADHD,[4–6] with the risk incrementally increasing with comorbidity number.[4] Comorbidities can also add to long-term functional impairment for people living with ADHD.[3,5–7] Therefore, it is common for individuals with ADHD to receive concomitant treatments for ADHD, depression, anxiety, sleep disorders, and other conditions.[8]

Viloxazine ER (extended-release capsules; Qelbree®) is a US Food and Drug Administration (FDA)-approved nonstimulant medication for pediatric and adult ADHD.[9] In the US, viloxazine ER has only been evaluated for ADHD to date. However, studies from the 1970s demonstrated that viloxazine has antidepressant effects,[10] and viloxazine was approved and used in Europe as an immediate-release product for depression for approximately 30 years before being discontinued for commercial reasons unrelated to efficacy or safety.[11]

Recent preclinical studies have confirmed that viloxazine has a multimodal norepinephrine and serotonergic pharmacodynamic profile in the therapeutically relevant dosage range used to treat ADHD, which could contribute to symptomatic response. While viloxazine and atomoxetine both have action as selective norepinephrine transporter inhibitors, viloxazine also modulates specific serotonin (5-HT) receptors, displaying partial agonist activity at the 5-HT_{2C} receptor and antagonist activity at 5-HT_{2B} and 5-HT_7 receptors, which may explain viloxazine ER's observed ability to increase serotonin in the prefrontal cortex in animal models.[9,12–14] Whether these serotonin receptor effects contribute to the

Clinical Points

- Over half of adults with attention-deficit/hyperactivity disorder (ADHD) also experience depression and/or anxiety symptoms; however, patients with comorbid depression and/or anxiety are routinely excluded from clinical trials in ADHD.
- This phase 4, open-label, decentralized study evaluated the efficacy and safety of viloxazine extended-release (ER) in adults with ADHD and comorbid depression and/or anxiety symptoms.
- Participants treated with viloxazine ER (alone or added to concomitant medications for other psychiatric symptoms) experienced improved symptoms of ADHD, depression, and anxiety with acceptable safety and tolerability.

clinical response of viloxazine ER in ADHD is unknown and warrants further investigation.

Clinical trials for ADHD treatments, including viloxazine ER,[15] routinely exclude participants with psychiatric comorbidities. These exclusions, while perhaps desirable for achieving regulatory approval, can limit the capacity to measure effects on mood and anxiety symptoms in phase 3 trials (due to floor effects) and restrict generalizability of findings from a clinical trial to real-world populations. Therefore, we designed the phase 4 study reported here to evaluate viloxazine ER treatment in adults with ADHD who also experience prominent depression or anxiety symptoms. The trial was designed to represent real-world viloxazine ER use, with eligibility, dosing, and concomitant medication restrictions guided by the current FDA-approved prescribing information. The trial design was fully decentralized to reduce entry barriers. Participants were recruited online, and data were collected via a mobile app and televisits with clinical raters or psychiatric nurse practitioners trained in the rating scales employed in the trial. Here, we present primary efficacy and safety results from this trial.

METHODS

Study Design, Participants, and Treatment

This phase 4, open-label, flexible-dose, decentralized study (NCT06185985) evaluated the efficacy and safety of viloxazine ER in adults with ADHD and comorbid depression and/or anxiety symptoms. Eligibility criteria were designed to reflect real-world viloxazine ER use. Prospective participants were recruited using digital tools; participation was open to adults (aged ≥18 years) who owned a functioning smartphone, had internet access, and were willing to download and use the study app. Eligible participants had a primary diagnosis of ADHD based on the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision,* as confirmed by the Mini-International Neuropsychiatric Interview for ADHD Studies (MINI-AS), an Adult ADHD Investigator Symptom Rating Scale (AISRS[16]) total score ≥24, a Clinical Global Impression of Severity (CGI-S) score ≥3, and a Montgomery-Asberg Depression Rating Scale (MADRS[17]) total score >22 and/or a Hamilton Anxiety Rating Scale (HAM-A[18]) total score >22. During the screening televisit, trained raters conducted the MINI-AS, AISRS, and CGI-S evaluations and depression and anxiety symptom ratings (using the Structured Interview Guide for the MADRS [SIGMA] and Structured Interview Guide for the HAM-A [SIGH-A], respectively). The use of stimulant medications for ADHD and medications for other medical or psychiatric conditions, including depression or anxiety, was allowed. Additional details are provided in the Supplementary Methods.

The study comprised a 4-week screening period, 14-week treatment period, and 1-week safety follow-up period (Figure 1A). The study was fully decentralized; clinician-reported outcomes (CROs) and safety were assessed during televisits conducted by qualified raters or assessors who were trained on the evaluated scales, and participants provided patient-reported outcome (PRO) data through the study mobile app. During the treatment period, participants were instructed to take viloxazine ER 200 mg once daily in the morning during week 1 and 400 mg once daily in the morning during week 2 onward until the next contact with the study investigator. Televisits were conducted at weeks 4, 9, and 14 of treatment, and a safety follow-up televisit was conducted 1 week after the last viloxazine ER dose.

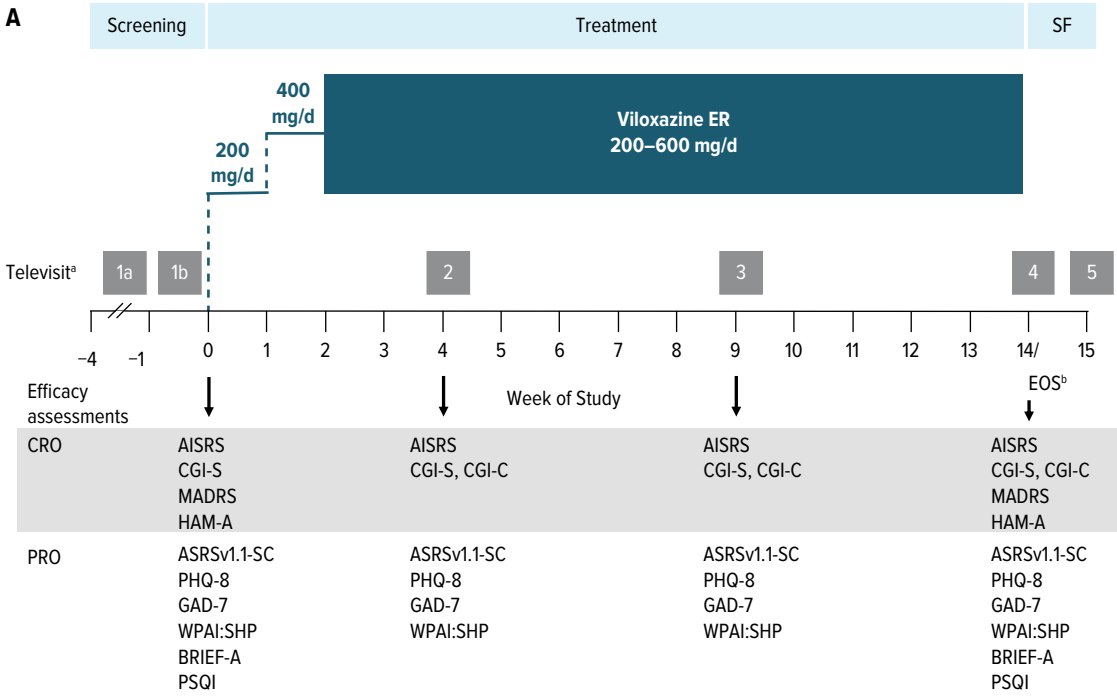
The study was approved by an institutional review board; followed guidance of US regulatory bodies, Good Clinical Practice regulations, and standards set by the International Conference on Harmonisation; and was conducted in accordance with the Declaration of Helsinki. All participants provided informed consent.

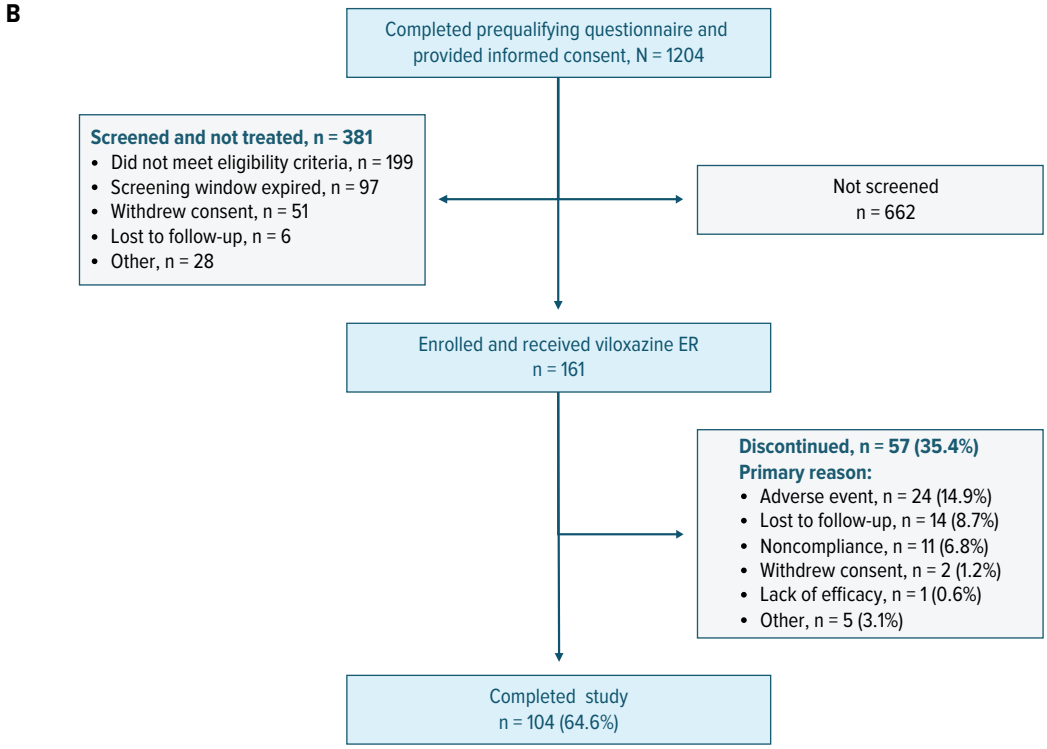
Efficacy Assessments

The primary end point was change from baseline in AISRS total score. Secondary clinician-reported efficacy end points included change from baseline in AISRS subscale (inattention and hyperactivity/impulsivity) scores, CGI-S score,[19] MADRS total score, and HAM-A total score. Clinical Global Impression of Change (CGI-C) score was also assessed. Secondary PRO efficacy end points included change from baseline in Adult ADHD Self-Report Scale version 1.1 Symptoms Checklist (ASRSv1.1-SC) total and subscale (inattention and hyperactivity/impulsivity) scores[20]; Patient Health Questionnaire-8 item (PHQ-8) total score[21]; General Anxiety Disorder 7-item scale (GAD-7) total score[22]; Behavioral Rating Inventory of Executive Function–Adult Version (BRIEF-A[23]) Global Executive Composite (GEC), Behavioral Regulation Index (BRI), and Metacognition Index (MI) scores (converted to T-scores; consistent with

Figure 1.

(A) Study Design and (B) Participant Disposition





[a]Televisit 1a was conducted within 3 weeks after obtaining informed consent, and televisit 1b occurred within 1 week before the first dose of study medication. If participants preferred, televisits 1a and 1b could be combined and completed in a single visit.
[b]EOS analyses were based on assessments assigned to the nominal week 14 visit. Early termination visits were mapped to the next scheduled analysis visit according to the study schedule.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, AISRS = Adult ADHD Investigator Symptom Rating Scale, ASRSv1.1-SC = Adult ADHD Self-Report Scale version 1.1 Symptoms Checklist, BRIEF-A = Behavior Rating Inventory of Executive Function–Adult Version, CGI-C = Clinical Global Impression of Change, CGI-S = Clinical Global Impression of Severity, CRO = clinician-reported outcome, EOS = end of study, ER = extended release, GAD-7 = General Anxiety Disorder 7-item scale, HAM-A = Hamilton Anxiety Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, PHQ-8 = Patient Health Questionnaire-8 item, PRO = patient-reported outcome, PSQI = Pittsburgh Sleep Quality Index, SF = safety follow-up, WPAI:SHP = Work Productivity and Activity Impairment: Specific Health Problem Questionnaire.

previous viloxazine ER studies[15,24]); Work Productivity and Activity Impairment: Specific Health Problem Questionnaire (WPAI:SHP)[25]; and Pittsburgh Sleep Quality Index (PSQI) global score.[26] Post hoc efficacy assessments included the proportion of participants achieving ≥30% or ≥50% reduction from baseline in AISRS total score (thresholds considered clinically meaningful improvements; consistent with those used in a phase 3 study of viloxazine ER in adults[15]) or clinically meaningful responses or published remission criteria according to MADRS, PHQ-8, HAM-A, or GAD-7 total scores.[22,27,28]

Safety Assessments

Safety assessments included the incidence of treatment-emergent adverse events (TEAEs), including investigator-assessed TEAE severity, seriousness, relationship to study medication, and whether TEAEs led to discontinuation. Additional safety assessments included the absolute values and change from baseline for systolic and diastolic blood pressure (SBP/DBP), pulse rate, and body weight, and presence of suicidal ideation and behavior (assessed at all televisits using the Columbia-Suicide Severity Rating Scale [C-SSRS]). Post hoc safety assessments included incidence of TEAEs by stimulant use.

Statistical Methods

Data were summarized descriptively. Nominal *P* values and 95% CIs were calculated for primary and secondary end points using *t* test. Week 14/end of study (EOS) analyses were based on assessments assigned to the nominal week 14 visit. Early termination visits were mapped to the next scheduled analysis visit according to the study schedule. Participants who were lost to follow-up or did not complete an early termination visit were excluded.

RESULTS

Participants

Of 1204 potential participants who provided informed consent, 662 were unable to be contacted or scheduled for a screening visit, 381 were not enrolled (primarily due to not meeting eligibility criteria, expired screening window, or withdrawn consent), and 161 received viloxazine ER treatment (Figure 1B). Of the 161 treated participants, 104 (64.6%) completed the study. Among the 161 enrolled participants (Table 1; Supplementary Table 1), most were female (75.8%), and the mean (SD) age was 39.4 (10.64) years. Mean baseline AISRS, MADRS, and HAM-A scores were consistent with moderate-to-severe ADHD, depression, and anxiety symptoms, respectively. All participants had substantial depression symptoms at baseline (MADRS >22), and almost all (99.4%) had substantial anxiety symptoms (HAM-A >22). Viloxazine ER dose distribution is shown in Supplementary Table 2. During the study, 28.6% of participants took stimulants, 44.7% took antidepressants, and 14.9% took anxiolytic and/or hypnotic medications (Supplementary Table 3).

Efficacy

Participants in the full analysis set (n = 150) showed clinically significantly reduced clinician- and patient-reported ADHD symptom scores at all study visits; at week 14/EOS, mean (SD) change from baseline was −17.3 (11.34) for AISRS total score ($P < .0001$; Figure 2A) and −28.4 (14.89) for ASRSv1.1-SC total score ($P < .0001$; Figure 2B), representing reductions from baseline of −45.3% (27.31%) and −50.9% (24.88%), respectively. The proportion of participants achieving ≥30% and ≥50% reduction in AISRS total score at week 14/EOS was 71.8% and 45.6%, respectively (Supplementary Figure 1). AISRS and ASRS inattention and hyperactivity/impulsivity subscale scores were also significantly reduced at all study visits (all $P < .0001$; Table 2). Substantial improvements in ADHD severity were also demonstrated by over a 1-category change in CGI-S score from baseline to week 14/EOS (mean [SD] of −1.4 [1.06]) and a mean (SD) week 14/EOS CGI-C score of 2.3 (0.97), with 63.1% of participants rated as "very much improved" or "much improved" per the CGI-C (Table 2; Supplementary Table 4).

Clinician- and patient-reported depression and anxiety scores were nominally significantly reduced at all study visits (all $P < .0001$). At week 14/EOS, mean (SD) change from baseline in MADRS total score was −15.5 (7.12; Figure 2C) and in PHQ-8 total score was −10.6 (5.24; Figure 2D). The mean (SD) change from baseline to week 14/EOS in HAM-A total score was −14.2 (5.79; Figure 2E) and in GAD-7 total score was −8.5 (5.33; Figure 2F). For MADRS, PHQ-8, HAM-A, and GAD-7, ≥50% reduction in total score from baseline at week 14/EOS was achieved by 57.5%, 78.4%, 70.8%, and 67.6% of participants, respectively (Supplementary Figure 2A), and symptom remission was achieved by 28.3%, 48.6%, 24.2%, and 43.2% (Supplementary Figure 2B). Executive functioning and sleep measures showed significant mean reductions from baseline in BRIEF-A GEC, BRI, and MI T-scores and PSQI global scores following viloxazine ER treatment (Table 2). Work productivity impairment was significantly improved at week 14/EOS (mean [SD] change from baseline in WPAI:SHP percentages: −5.89 [20.170; $P < .05$] for absenteeism, −23.08 [26.072; $P < .0001$] for presenteeism, −36.06 [24.230; $P < .0001$] for regular activity, and −22.32 [26.915; $P < .0001$] for work productivity).

Table 1.

Baseline Demographics and Clinical Characteristics

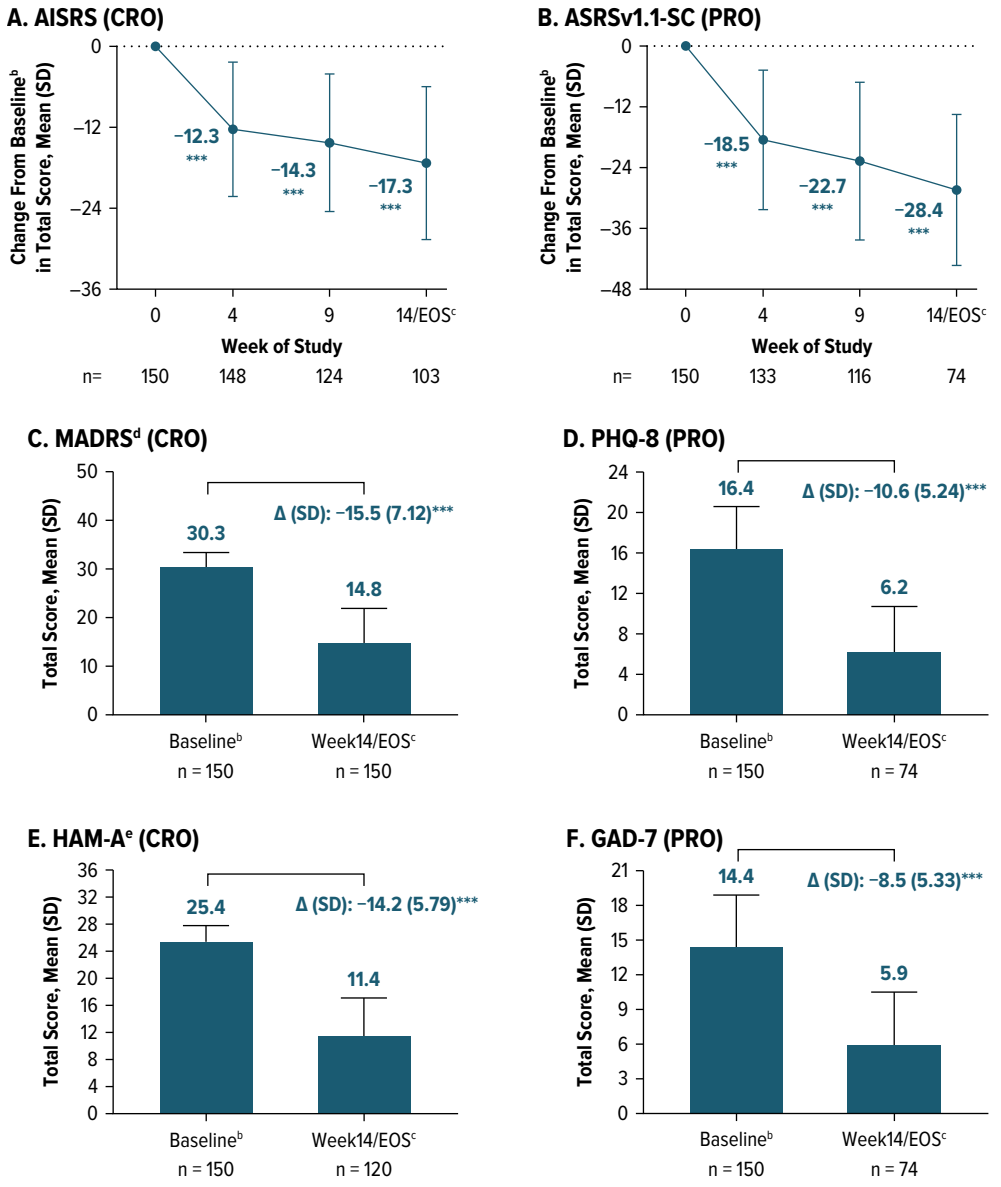
Characteristic	Viloxazine ER (n = 161)
Age, y, mean (SD)	39.4 (10.64)
Female, n (%)	122 (75.8)
Race, n (%)	
White	129 (80.1)
Black or African American	11 (6.8)
Asian	7 (4.3)
Multiple	12 (7.5)
Unknown	2 (1.2)
Ethnicity, Hispanic or Latino, n (%)	11 (6.8)
BMI, kg/m^2, mean (SD)	31.70 (9.00)
Employed (full time, part time, or contracted), n (%)	117 (72.7)
Employment status, n (%)	
Yes, fully or partially	100 (62.1)
Yes, contracted	17 (10.6)
No, not employed	44 (27.3)
Antidepressant use, n (%)	72 (44.7)
Stimulant use, n (%)	46 (28.6)
Anxiolytic use (and/or medications with hypnotic effects), n (%)	24 (14.9)
Caffeine use, n (%)	145 (90.1)
Nicotine use, n (%)	24 (14.9)
Cannabis/marijuana use, n (%)	49 (30.4)
Meeting diagnostic criteria per MINI-AS, n (%)	
ADHD	161 (100)
Combined	143 (88.8)
Predominantly inattentive	17 (10.6)
Predominantly hyper/impulsive	1 (0.6)
Major depressive disorder	154 (95.7)
Major depressive episode	161 (100)
Generalized anxiety disorder	149 (92.5)
Social anxiety disorder	32 (19.9)
Posttraumatic stress disorder	6 (3.7)
Agoraphobia	2 (1.2)
Anorexia nervosa	1 (0.6)
Binge-eating disorder	1 (0.6)
Panic disorder	1 (0.6)
AISRS total score, mean (SD)	37.5 (6.53)[a]
AISRS IA subscale score, mean (SD)	20.4 (3.34)[a]
AISRS HI subscale score, mean (SD)	17.1 (4.24)[a]
ASRS total score, mean (SD)	53.5 (8.51)[a]
MADRS total score, mean (SD)	30.3 (3.12)[a]
HAM-A total score, mean (SD)	25.4 (2.38)[a]
MADRS total score >22, n (%)	161 (100)
HAM-A total score >22, n (%)	160 (99.4)
MADRS total score >22 and HAM-A total score >22, n (%)	160 (99.4)
GAD-7 total score, mean (SD)	14.4 (4.54)[a]
PHQ-8 total score, mean (SD)	16.4 (4.16)[a]
BRIEF-A GEC T-score, mean (SD)	79.8 (9.78)
BRIEF-A BRI T-score, mean (SD)	71.2 (11.85)[a]
BRIEF-A MI T-score, mean (SD)	82.6 (9.19)[a]
PSQI global score, mean (SD)	10.8 (3.38)

[a]Measured among participants in the full analysis set (n = 150).

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, AISRS = Adult ADHD Investigator Symptom Rating Scale, ASRS = Adult ADHD Self-Report Scale, BMI = body mass index, BRI = Behavioral Regulation Index, BRIEF-A = Behavior Rating Inventory of Executive Function–Adult Version, ER = extended release, GAD-7 = General Anxiety Disorder 7-item scale, GEC = Global Executive Composite, HAM-A = Hamilton Anxiety Rating Scale, HI = hyperactivity/impulsivity, IA = inattention, MADRS = Montgomery-Asberg Depression Rating Scale, MI = Metacognition Index, MINI-AS = Mini-International Neuropsychiatric Interview for ADHD Studies, PHQ-8 = Patient Health Questionnaire-8 item, PSQI = Pittsburgh Sleep Quality Index.

Figure 2.

Changes in ADHD, Depression, and Anxiety Symptoms[a]



[a](A) Mean (SD) change from baseline by visit in AISRS total score. (B) Mean (SD) change from baseline by visit in ASRSv1.1-SC total score. (C) Mean (SD) absolute scores and change from baseline at week 14/EOS in MADRS total score. (D) Mean (SD) absolute scores and change from baseline at week 14/EOS in PHQ-8 total score. (E) Mean (SD) absolute scores and change from baseline at week 14/EOS in HAM-A total score. (F) Mean (SD) absolute scores and change from baseline at week 14/EOS in GAD-7 total score.

[b]Measured among participants in the full analysis set (n = 150).

[c]Week 14/EOS analyses were based on assessments assigned to the nominal week 14 visit. Early termination visits were mapped to the next scheduled analysis visit according to the study schedule. Participants who were lost to follow-up or did not complete an early termination visit were excluded.

[d]MADRS score range of 0–60 (0–6, "normal"; 7–19, "mild"; 20–34, "moderate"; >34, "severe").

[e]HAM-A score range of 0–56 (≤17, "mild anxiety severity"; 18–24, "moderate anxiety severity"; 25–30, "moderate-to-severe anxiety severity"; ≥31, "severe anxiety)."

***Nominal $P < .0001$.

Abbreviations: Δ = mean change from baseline, ADHD = attention-deficit/hyperactivity disorder, AISRS = Adult ADHD Investigator Symptom Rating Scale, ASRSv1.1-SC = Adult ADHD Self-Report Scale version 1.1 Symptoms Checklist, CRO = clinician-reported outcome, EOS = end of study, GAD-7 = General Anxiety Disorder 7-item scale, HAM-A = Hamilton Anxiety Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, PHQ-8 = Patient Health Questionnaire-8 item, PRO = patient-reported outcome.

Table 2.

Change From Baseline in AISRS and ASRSv1.1-SC Inattention and Hyperactivity/Impulsivity Subscale Scores, CGI-S Scores, CGI-C Scores, BRIEF-A T-scores, and PSQI Global Score

Measure	Baseline, mean (SD) (FAS)	Change from baseline, mean (SD)		
		Week 4	Week 9	Week 14/EOS
AISRS IA subscale score (CRO)	20.4 (3.34) (n = 150)	−6.8 (5.21)*** (n = 148)	−7.6 (5.57)*** (n = 124)	−8.9 (6.04)*** (n = 103)
AISRS HI subscale score (CRO)	17.1 (4.24) (n = 150)	−5.6 (5.51)*** (n = 148)	−6.8 (5.67)*** (n = 124)	−8.4 (6.20)*** (n = 103)
ASRSv1.1-SC IA subscale score (PRO)	29.1 (4.16) (n = 150)	−9.7 (7.75)*** (n = 133)	−12.0 (8.61)*** (n = 116)	−14.9 (7.83)*** (n = 74)
ASRSv1.1-SC HI subscale score (PRO)	24.4 (5.71) (n = 150)	−8.8 (6.80)*** (n = 133)	−10.7 (7.83)*** (n = 116)	−13.5 (7.82)*** (n = 74)
CGI-S score (CRO)	4.7 (0.57) (n = 149)	−1.0 (0.80)*** (n = 147)	−1.2 (0.85)*** (n = 123)	−1.4 (1.06)*** (n = 102)
CGI-C score (CRO)	…	2.7 (0.81) (n = 148)	2.6 (1.09) (n = 124)	2.3 (0.97) (n = 103)
BRIEF-A GEC T-score	79.9 (9.84) (n = 150)	…	…	−16.2 (13.75)*** (n = 89)
BRIEF-A BRI T-score	71.2 (11.85) (n = 150)	…	…	−13.1 (12.45)*** (n = 90)
BRIEF-A MI T-score	82.6 (9.19) (n = 150)	…	…	−16.4 (13.79)*** (n = 89)
PSQI global score	10.8 (3.29) (n = 150)	…	…	−2.2 (4.05)*** (n = 90)

***Nominal $P < .0001$.

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, AISRS = Adult ADHD Investigator Symptom Rating Scale, ASRSv1.1-SC = Adult ADHD Self-Report Scale version 1.1 Symptoms Checklist, BRI = Behavioral Regulation Index, BRIEF-A = Behavior Rating Inventory of Executive Function–Adult Version, CGI-C = Clinical Global Impression of Change, CGI-S = Clinical Global Impression of Severity, CRO = clinician-reported outcome, EOS = end of study, FAS = full analysis set, GEC = global executive composite, HI = hyperactivity/impulsivity, IA = inattention, MI = Metacognition Index, PRO = patient-reported outcome, PSQI = Pittsburgh Sleep Quality Index.

Table 3.

Safety Overview and Most Common TEAEs[a]

Parameter	Viloxazine ER (n = 161), n (%)
Any TEAE	114 (70.8)
Mild	72 (44.7)
Moderate	35 (21.7)
Severe	7 (4.3)
Serious TEAE	6 (3.7)
TEAE considered related to viloxazine ER	111 (68.9)
TEAE leading to viloxazine ER withdrawal	24 (14.9)
TEAE leading to death	0
Most common TEAEs[b]	
Nausea	34 (21.1)
Insomnia	31 (19.3)
Constipation	22 (13.7)
Headache	17 (10.6)
Fatigue	15 (9.3)
Somnolence	14 (8.7)
Decreased appetite	12 (7.5)
Migraine	12 (7.5)
Dry mouth	11 (6.8)

[a]Adverse events were coded for preferred terms using the Medical Dictionary for Regulatory Activities (version 27.0).

[b]Most common TEAEs defined as those occurring in ≥5% of participants.

Abbreviations: ER = extended release, TEAE = treatment-emergent adverse event.

Safety

Viloxazine ER was generally well tolerated. TEAEs were experienced by 70.8% of participants; most were mild to moderate in severity (Table 3). The most common adverse events (≥5% of participants) were nausea, insomnia, constipation, headache, fatigue, somnolence, decreased appetite, migraine, and dry mouth. For 24 participants (14.9%), TEAEs led to viloxazine ER discontinuation; TEAEs leading to discontinuation of study drug in ≥3 participants included insomnia (n = 8), nausea (n = 5), decreased appetite (n = 4), migraine (n = 4), somnolence (n = 4), dizziness (n = 3), and suicidal ideation (n = 3; 2 considered serious, moderate in severity, and related to treatment; both reported on day 3 of study treatment). Six participants (3.7%) experienced serious TEAEs, including the 2 participants with suicidal ideation described above and 1 participant each with migraine (day 65, considered severe and possibly related to treatment, participant remained in the study), sensation of foreign body (reported term “lump in throat”; day 28, considered moderate and related to treatment, led to treatment discontinuation), and Addison disease (day 11, considered severe and unrelated to treatment, participant remained in the study). There was also 1 participant with serious adverse events of hepatic enzymes increased (day 38) and cyclic vomiting syndrome (day 64). The event of hepatic enzymes increase was considered severe and possibly related to treatment due to possible temporal association with viloxazine ER, and led to treatment discontinuation. The event of cyclic vomiting syndrome occurred 23 days after the participant discontinued study medication and was likely due to underlying gastrointestinal issues; the event was considered severe and not related to treatment. This participant also experienced TEAEs of blood cholesterol increased, thyrotoxicosis, gallbladder disease, and biliary

tract disease and was taking rosuvastatin for the TEAE of blood cholesterol increased and tirzepatide for a medical history of type 2 diabetes mellitus. Viloxazine ER treatment was generally well tolerated among both participants who were or were not receiving stimulants (Supplementary Table 5). The mean (SD) number of baseline concomitant medications was higher among patients with vs without treatment-related TEAEs that were severe, serious, or led to withdrawal (3.4 [2.61], n = 28 vs 2.3 [2.50], n = 133, respectively).

There were modest increases in mean SBP, DBP, and pulse rate at all visits and a mean decrease in body weight at all visits (Supplementary Table 6). Overall at week 14/EOS, 20.0% and 13.3% of participants had a >15 mm Hg increase in SBP or DBP, respectively, and 10.2% had a >20 beats per minute increase in pulse rate; however, these were seldom considered TEAEs (heart rate increased, n = 3 [1.9%]; hypertension, n = 2 [1.2%]; palpitations, n = 1 [0.6%]; blood pressure increased, n = 1 [0.6%]). Five participants (3.1%) reported TEAEs of suicidal ideation (of these, 3 withdrew from the trial due to these TEAEs); suicidal ideation resolved in all cases. The proportion of participants reporting suicidal ideation on the C-SSRS during the treatment period was 5.3% (Supplementary Table 7). No suicidal behavior was reported on C-SSRS (nor as an adverse event) during viloxazine ER treatment. One patient (0.6%) reported suicidal behavior in the 6-month period before screening.

DISCUSSION

Adults with ADHD and comorbid depression and anxiety symptoms experienced substantial improvement in all 3 conditions while taking viloxazine ER treatment (alone or added to existing treatments) in this decentralized, phase 4, open-label trial (Supplementary Figure 3). Efficacy and safety results were consistent with previous phase 3 studies of viloxazine ER in adults with ADHD,[15,24] and improvements in depression symptoms aligned with the past use of immediate-release viloxazine as an antidepressant in Europe.[11] Measures of executive function and work productivity also improved with viloxazine ER treatment. These findings suggest that the established efficacy of viloxazine ER may extend to adults with ADHD and comorbid depression and/or anxiety symptoms, who typically represent over half of people with ADHD.[2,3]

Though often exclusively considered a selective norepinephrine reuptake inhibitor, early and contemporaneous pharmacology studies consistently showed that viloxazine also affects 5-HT neurotransmission.[10,12–14,29–32] In drug discovery efforts, the 5-HT_{2B} and 5-HT_{2C} receptors are considered therapeutic targets for mood regulation and reduction of impulsivity, anxiety, and weight,[33–38] and 5-HT_7 antagonism has been identified as a therapeutic target to improve cognition, sleep regulation, and mood regulation.[39–42] Viloxazine has previously been shown to be effective for treating depression[11]; whether effects on depression symptoms in this study are direct or secondary to ADHD improvement is unknown and requires evaluation in a controlled study.

Despite the high prevalence of comorbid psychiatric conditions in ADHD, including individuals with comorbid disorders (eg, anxiety, depression) in clinical studies of ADHD pharmacotherapies is uncommon. This study is the first trial of viloxazine ER in adults with ADHD to include participants with comorbid depression and/or anxiety and allow concomitant medication use for these conditions. This study had a higher proportion of female participants and higher mean baseline body weight and HAM-A scores compared with a previous adult phase 3 study population; participants in the current study also had a higher degree of executive dysfunction (according to baseline BRIEF-A T-scores) than those in the adult phase 3 trial.[15] Results from the current study provide important insights into the utility of viloxazine ER treatment for people with ADHD and comorbid conditions, which comprise a large proportion of the real-world ADHD population.

Simultaneous treatment of ADHD and depression and/or anxiety symptoms can be challenging, partly due to safety concerns about combining medications.[3] In a recent study evaluating stimulant use combined with other psychiatric medications, approximately half of people receiving stimulants also used antidepressants and one-third used anxiolytics, sedatives, and/or hypnotics,[8] but the safety (and effectiveness) of such treatment combinations is not well studied.[8] Polypharmacy can increase the risk of drug-drug interactions and TEAEs, but excluding potentially beneficial medications may also create safety risks[43]; whether medications like viloxazine ER could reduce co-occurring symptoms and allow reducing other medications warrants further study. Further analysis of safety outcomes is needed to uncover whether TEAEs in the current study were influenced by concomitant medication patterns (eg, medication class, duration) and/or other factors, including medical comorbidities or cannabis use. Still, preliminary safety findings from the current study are encouraging and suggest viloxazine ER can be used with other psychiatric medications with careful monitoring.

The decentralized nature of the study is a unique feature for ADHD clinical trials. This approach is encouraged by the FDA to facilitate including participants with baseline characteristics and psychiatric history that represent the real-world ADHD population.[44,45] Although decentralized trials may be limited by challenges, such as ensuring validity of patient-reported data, they can also reduce participant burden and reach participants who cannot travel to a

research center (due to geographical/logistical restrictions or impaired executive function).[44,45] By using a decentralized design, the current study helps provide representation of viloxazine ER treatment effects in real-world populations of people with ADHD.

Strengths of this study include the real-world nature and representation of people with comorbid depression and/or anxiety symptoms (who are typically excluded from other ADHD clinical trials), its decentralized nature, and the use and high level of correlation between CROs and PROs. Limitations of the study include the open-label design (which may introduce bias and potential overestimation of treatment effects), absence of a comparator group, and lack of long-term follow-up. These analyses were conducted to descriptively characterize changes over time in an open-label, single-arm study, not to support formal confirmatory inference; no multiplicity adjustments were applied, and statistical findings across visits should be interpreted descriptively. The study was not designed to evaluate whether improvements in depression/anxiety symptoms were a direct effect of viloxazine ER or a secondary effect of ADHD symptom improvement. Concomitant medication changes or their impact on efficacy and safety have not yet been evaluated. Other limitations may include challenges inherent in a decentralized design, such as potential difficulty in consistently obtaining PROs without an in-person clinic visit, self-selection bias (considering that participants were recruited online and participated voluntarily), and inability to include individuals without online access or smartphones. The study population was mostly White and female, which could influence generalizability of the findings.

In conclusion, adults with ADHD and mood symptoms who received viloxazine ER (alone or added to existing treatments) experienced substantial improvements in ADHD, depression, and anxiety symptoms with acceptable safety and tolerability. These findings support the use of viloxazine ER to treat people with ADHD and comorbid depression and/or anxiety symptoms.

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The Journal of Clinical Psychiatry

Supplementary Material

Article Title: Viloxazine Extended Release in Adults With Attention-Deficit/Hyperactivity Disorder and Depression and/or Anxiety Symptoms: Results From a Decentralized, Open-Label, Phase 4 Trial

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

Supplementary Methods

Study Design, Participants, and Treatment

Prospective participants were aged ≥18 years, living in the contiguous United States, and recruited using digital tools (eg, social media, advertising). Potential participants were directed to a website where they could access basic information about the study, provide their contact information, and answer prequalifying questions. Those who met the prequalifying criteria were contacted to schedule a screening televisit and received an email invitation to download the study app. After downloading the mobile app, potential participants received study details, an electronic informed consent form, and contact information for the principal investigator and virtual clinical trial support team. Female participants were required to be nonpregnant (confirmed by home pregnancy test mailed to participant), and participants capable of bearing children had to agree to use acceptable contraception. Exclusion criteria included a history of substance use disorder (except nicotine or cannabis) within 6 months of screening; presence of an unstable, clinically significant cardiovascular condition; a history of schizophrenia, schizoaffective disorder, bipolar disorder, or psychiatric condition that in the investigator's judgement would interfere with study participation; a history of moderate or severe head trauma or neurological or systemic medical disease likely to affect central nervous system functioning; or significant risk of suicide (based on investigator opinion, attempted suicide ≤6 months before screening, or answering "yes" to Columbia Suicide Severity Rating Scale [C-SSRS] suicidal ideation questions 4 or 5, or C-SSRS suicidal behavior questions). Potential participants were also excluded if they had taken viloxazine ER (extended-release capsules; Qelbree®) within 3 months of screening, were currently taking another nonstimulant medication (atomoxetine, clonidine, or guanfacine) for attention-deficit/hyperactivity disorder or were using a medication contraindicated with viloxazine ER per the US Food and Drug Administration–approved prescribing information.

Raters were initially screened by a review of their curriculum vitae and their responses to a Rater Qualification Questionnaire. Specific training was provided for the screening assessment (Mini-International Neuropsychiatric Interview for ADHD Studies [MINI-AS]) and efficacy assessments (Adult ADHD Investigator Symptom Rating Scale [AISRS], Montgomery–Åsberg Depression Rating Scale [MADRS], Hamilton Anxiety Rating Scale [HAM-A], and Clinical Global Impression of Severity/Change [CGI-S/C]), and qualified raters were certified upon completion of the training. When possible, participants had the same raters at subsequent visits.

The screening period consisted of up to 2 televisits. The first screening televisit, conducted within 3 weeks after obtaining informed consent, collected the participant's demographic information; medical, psychiatric, and social history; Mini-International Neuropsychiatric Interview for ADHD Studies; prior and concomitant medications; and baseline C-SSRS. The second screening televisit, conducted within 1 week before the first dose of viloxazine ER, collected baseline clinician-reported outcomes and concomitant medications. The 2 screening televisits could be combined into a single televisit. Participants who met the eligibility criteria used the study mobile app to complete baseline patient-reported outcomes. At the discretion of the investigator based on response and tolerability, investigators could adjust the participant's dose in up to 200 mg increments once per week, to a minimum of 200 mg/day or up to the maximum recommended dosage of 600 mg/day. Based on tolerability, investigators could also instruct the participant to take the medication in the evening. Per the study protocol, efficacy assessments were not completed for any visit (including the end of study [EOS] visit) where the participant had not taken ≥1 dose of viloxazine ER within the 7 days before that study visit.

Assessments

At each televisit, participants were asked if they missed any doses of study medication since the prior televisit. Study medication dosage changes were recorded at each study visit. Participants were instructed to return all study medication bottles (empty or not) at the end of their study participation, and the remaining capsules in the returned bottles were counted. Concomitant medication use or changes were recorded at each study visit.

The MADRS measures depression severity in patients with mood disorders using a 10-item investigator-rated diagnostic questionnaire.[1]Each item is rated on a 7-point Likert scale (0 [no abnormality] to 6 [severe]), with a possible score range of 0–60. A higher total score indicates more severe depression (0–6, “normal”; 7–19, “mild”; 20–34, “moderate”; >34, “severe”).[1]

The HAM-A is a clinical measure of anxiety symptoms rated on a 5-point Likert scale (0 [not present] to 4 [very severe]).[2]The ratings/scores of all 14 items are summated to yield a total score (ranging from 0 to 56), where ≤ 17 indicates “mild anxiety severity,” 18 to 24 indicates “moderate anxiety severity,” 25 to 30 indicates “moderate to severe anxiety severity,” and ≥ 31 indicates “severe anxiety.”[2]

Clinically meaningful responses for depression and anxiety symptoms were defined as ≥50% reduction from baseline in MADRS, PHQ-8, HAM-A, or GAD-7 total score, which are considered clinically meaningful improvements in depression/anxiety clinical trials. Remission of depression and anxiety symptoms was defined as MADRS total score ≤10, PHQ-8 total score ≤5, HAM-A total score ≤7, or GAD-7 total score ≤4.[3-5]

For blood pressure and pulse readings, all participants received the same blood pressure device model (certified for remote physiological monitoring) and instructions for use. At

screening (baseline measurement), participants measured their blood pressure and pulse rate and recorded the values in the study mobile app before dosing. At all other televisits (week 4 to week 14/EOS), participants measured their blood pressure and pulse rate during the televisit and reported the results to the study team.

Analysis Populations

Safety data were summarized for the safety analysis population, which included all participants who provided informed consent and received ≥1 dose of viloxazine ER. C-SSRS outcomes were summarized using the number and percent of participants by categories for suicidal ideation, suicidal behavior, suicidal ideation or behavior, and nonsuicidal self-injurious behavior. Efficacy analyses were conducted among the full analysis set, defined as participants in the safety analysis population who had a valid Adult ADHD Investigator Symptom Rating Scale (AISRS) assessment at baseline and ≥1 valid AISRS postbaseline assessment.

Statistical Methods

Statistical analyses were performed using SAS version 9.4 or higher. No formal hypothesis testing was planned, and no statistical power calculation was considered in determining the sample size for this decentralized open-label study. No adjustments for multiplicity were performed. Between-group difference in the number of concomitant medications was evaluated using Wilcoxon rank-sum test. Continuous variables were summarized using means, standard deviations and 95% confidence intervals, while categorical variables were summarized using counts and percentages.

Supplementary References

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Supplementary Table 1. Baseline Social Characteristics

Characteristic, n (%)	Viloxazine ER (n = 161)
Highest level of education	
Never attended school or less than high school	0
Completed some high school	2 (1.2)
High school graduate	11 (6.8)
Attended college, but no degree	43 (26.7)
Skilled trade or technical certificate	8 (5.0)
Associate's degree or equivalent 2-year college degree	20 (12.4)
Bachelor's degree (4-year college degree)	38 (23.6)
Some graduate school, but no degree	5 (3.1)
Master's degree	27 (16.8)
Doctoral degree	7 (4.3)
Prefer not to say	0
Income level	
<$15,000/year	14 (8.7)
$15,000 to <$30,000/year	27 (16.8)
$30,000 to <$65,000/year	37 (23.0)
$65,000 to <$100,000/year	40 (24.8)
$100,000 to <$125,000/year	16 (9.9)
$125,000 to <$150,000/year	12 (7.5)
$150,000 to <$175,000/year	4 (2.5)
$175,000 to <$200,000/year	3 (1.9)
≥$200,000/year	3 (1.9)
Prefer not to say	5 (3.1)
Marital status	
Never married, single	42 (26.1)
Never married, living with partner	24 (14.9)
Married or in civil union	62 (38.5)
Married but separated	3 (1.9)
Divorced, single	21 (13.0)
Divorced, living with partner	7 (4.3)
Widowed, single	2 (1.2)
Widowed, living with partner	0

Abbreviations: ER, extended release.

Supplementary Table 2. Summary of Planned and Confirmed Viloxazine ER Dose

Parameter	Planned Dose[a]	Confirmed Dose[b]
Viloxazine ER dose, mg, mean (SD), [range]		
Week 1	200.0 (0) [200–200]	N/A[c]
Weeks 2–4	400.0 (0) [400–400]	356.0 (83.13) [200–400]
Weeks 5–9	362.7 (84.67) [200–600]	357.9 (84.58) [200–600]
Weeks 10–14/EOS	373.5 (89.66) [200–600]	369.7 (81.09) [200–600]
Dosing category, n (%)		
Week 1		
200 mg	161 (100)	N/A
Weeks 2–4		
200 mg	N/A	33 (20.5)
400 mg	150 (93.2)	117 (72.7)
600 mg	N/A	0
Weeks 5–9		
200 mg	26 (16.1)	28 (17.4)
300 mg	2 (1.2)	2 (1.2)
400 mg	104 (64.6)	102 (63.4)
600 mg	2 (1.2)	1 (0.6)
Weeks 10–14		
200 mg	19 (11.8)	18 (11.2)
300 mg	2 (1.2)	1 (0.6)
400 mg	87 (54.0)	88 (54.7)
600 mg	5 (3.1)	2 (1.2)

[a]Dose that was prescribed per the study protocol.

[b]Dose that participants reported they had been taking; queried at the week 4, week, 9, and week 14/EOS televisits.

[c]After week 1, no scheduled visit took place until week 4; therefore, confirmed dose could not be determined during this interval.

Abbreviations: EOS, end of study; ER, extended release, N/A, not applicable.

Supplementary Table 3. Concomitant Medication Use

Medication Category,[a] n (%)	Viloxazine ER (n = 161)
Antidepressants	72 (44.7)
Selective serotonin reuptake inhibitors	36 (22.4)
Bupropion-containing medications[b]	28 (17.4)
Serotonin and norepinephrine reuptake inhibitors	12 (7.5)
Trazodone	7 (4.3)
Tricyclic antidepressants	5 (3.1)
Vilazodone	2 (1.2)
Mirtazapine	2 (1.2)
Hypericum perforatum (St John's wort)	1 (0.6)
Stimulants	46 (28.6)
Amphetamine products	39 (24.2)
Methylphenidate products	8 (5.0)
Phentermine	1 (0.6)
Anxiolytics and/or medications with sedative-hypnotic effects	24 (14.9)
Nonspecific antihistamines[c]	12 (7.5)
Benzodiazepines	6 (3.7)
Buspirone	6 (3.7)
Melatonin	3 (1.9)
Benzodiazepine-related hypnotics	1 (0.6)
Beta-blocking agents	11 (6.8)
Anticonvulsants	8 (5.0)
Second-generation antipsychotics	4 (2.5)
Opiates	2 (1.2)
Acamprosate	1 (0.6)
Antiemetics with dopamine blocking properties	1 (0.6)
Buprenorphine hydrochloride/naloxone hydrochloride	1 (0.6)
Dopamine agonists	1 (0.6)
Withania somnifera (Indian ginseng)	1 (0.6)

[a]Concomitant medications were defined as medications continuing or starting after the first dose of viloxazine ER through the end of study. Medications were coded using the World Health Organization Drug Dictionary version Global September 2023. Concomitant medications were categorized based on commonly referenced categories and were not based on the indication for which they were being used.

[b]Includes patients taking bupropion with dextromethorphan (n = 2).

[c]Dicyclomine, diphenhydramine, hydroxyzine, or dicycloverine.

Abbreviations: ER, extended release.

Supplementary Table 4. Proportion of Participants With CGI-S and CGI-C Scores of 1 or 2

Parameter	Viloxazine ER
CGI-S score of either 1 (asymptomatic) or 2 (borderline), n/n (%)	
Baseline	0/149
Week 4	3/147 (2.0)
Week 9	10/123 (8.1)
Week 14/EOS	19/102 (18.6)
CGI-C score of either 1 (very much improved) or 2 (much improved), n/n (%)	
Week 4	60/148 (40.5)
Week 9	67/124 (54.0)
Week 14/EOS	65/103 (63.1)

Abbreviations: CGI-C, Clinical Global Impression of Change; CGI-S, Clinical Global Impression of Severity; EOS, end of study; ER, extended release.

Supplementary Table 5. Safety Outcomes by Baseline Concomitant Stimulant Use[a]

Parameter, n (%)	With Stimulant (n = 46)	Without Stimulant (n = 115)
Any TEAE	32 (69.6)	82 (71.3)
TEAE considered related to viloxazine ER	31 (67.4)	80 (69.6)
TEAE leading to viloxazine ER withdrawal	5 (10.9)	19 (16.5)
Serious TEAE considered related to viloxazine ER	3 (6.5)	2 (1.7)
Severe TEAE	2 (4.3)	5 (4.3)
Most common TEAEs in the overall study population[b]		
Nausea	12 (26.1)	22 (19.1)
Insomnia	9 (19.6)	22 (19.1)
Fatigue	8 (17.4)	7 (6.1)
Migraine	5 (10.9)	7 (6.1)
Constipation	4 (8.7)	18 (15.7)
Decreased appetite	4 (8.7)	8 (7.0)
Suicidal ideation	4 (8.7)	1 (0.9)
Somnolence	3 (6.5)	11 (9.6)
Abdominal discomfort	3 (6.5)	3 (2.6)
Headache	2 (4.3)	15 (13.0)
Dry mouth	1 (2.2)	10 (8.7)

[a]Evaluated in the safety analysis population (n = 161). Concomitant medications were defined as medications continuing or starting after the first dose of viloxazine ER through the end of study.

[b]Most common TEAEs defined as those occurring in ≥5% of participants in either group.

Abbreviations: ER, extended release; TEAE, treatment-emergent adverse events.

Supplementary Table 6. Baseline Values and Change From Baseline in Blood Pressure, Pulse Rate, and Body Weight

Parameter, Mean (SD)	Viloxazine ER
Systolic blood pressure, mmHg[a]	
Baseline value (n = 158)	117.5 (11.62)
Change from baseline at week 4 (n = 140)	6.0 (12.47)
Change from baseline at week 9 (n = 118)	7.7 (13.75)
Change from baseline at week 14/EOS (n = 90)	3.0 (14.38)
Diastolic blood pressure, mmHg[a]	
Baseline value (n = 158)	76.6 (9.16)
Change from baseline at week 4 (n = 140)	4.6 (10.08)
Change from baseline at week 9 (n = 118)	4.7 (10.29)
Change from baseline at week 14/EOS (n = 90)	2.9 (10.46)
Pulse rate, beats per minute[a]	
Baseline value (n = 158)	79.6 (11.46)
Change from baseline at week 4 (n = 136)	5.2 (12.66)
Change from baseline at week 9 (n = 116)	4.7 (12.41)
Change from baseline at week 14/EOS (n = 88)	5.5 (11.30)
Body weight, kg	
Baseline value (n = 161)	90.0 (26.78)
Change from baseline at week 4 (n = 149)	−0.7 (5.03)
Change from baseline at week 9 (n = 131)	−0.8 (5.50)
Change from baseline at week 14/EOS (n = 108)	−1.6 (5.69)

[a]Measured while sitting.

Abbreviations: EOS, end of study; ER, extended release.

Supplementary Table 7. Suicidality Evaluation by C-SSRS[a]

Parameter, n (%)	Screening, Lifetime (n = 161)	Screening, Past 6 Months (n = 161)	Week 4, Since Last Visit (n = 149)	Week 9, Since Last Visit (n = 123)	Week 14/EOS, Since Last Visit (n = 103)	Overall (n = 150)
Suicidal ideation	82 (50.9)	25 (15.5)	6 (4.0)	3 (2.4)	1 (1.0)	8 (5.3)
Wish to be dead	82 (50.9)	24 (14.9)	6 (4.0)	3 (2.4)	1 (1.0)	8 (5.3)
Nonspecific suicidal thought	39 (24.2)	6 (3.7)	4 (2.7)	0	0	4 (2.7)
Suicidal ideation, no intent	24 (14.9)	2 (1.2)	0	0	0	0
Ideation with intent, no plan	23 (14.3)	0	0	0	0	0
Ideation with plan/intent	23 (14.3)	0	0	0	0	0
Suicidal behavior	20 (12.4)	1 (0.6)	0	0	0	0
Actual attempt	18 (11.2)	0	0	0	0	0
Interrupted attempt	10 (6.2)	0	0	0	0	0
Aborted attempt	5 (3.1)	0	0	0	0	0
Suicidal behavior	0	1 (0.6)	0	0	0	0
Suicidal ideation or behavior	82 (50.9)	26 (16.1)	6 (4.0)	3 (2.4)	1 (1.0)	8 (5.3)
Nonsuicidal self-injurious behavior	0	0	0	0	0	0

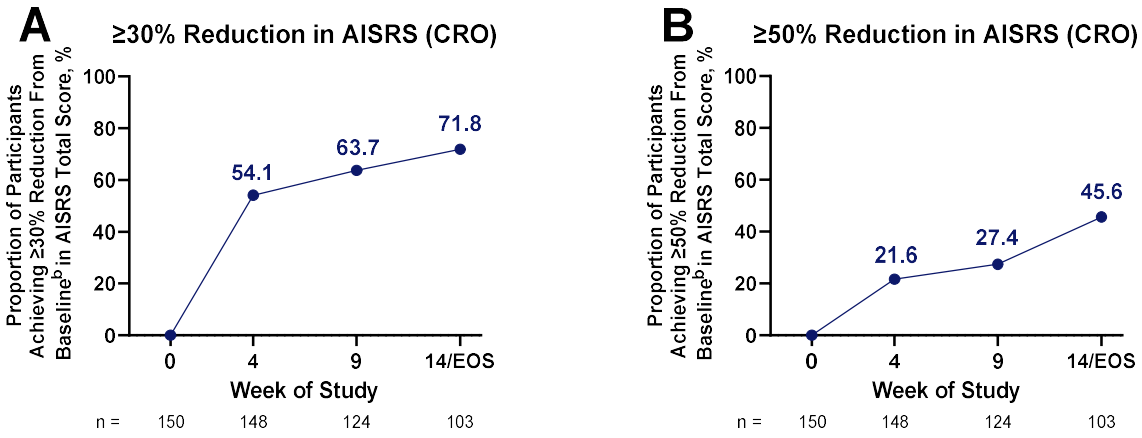
[a]Measured among participants in the safety analysis population (n = 161).
Abbreviations: C-SSRS, Columbia Suicide Severity Rating Scale; EOS, end of study.

Supplementary Figure 1. Achievement of ≥30% or ≥50% reduction from baseline in AISRS total score.[a]

[a]Proportion of participants achieving (A) ≥30% or (B) ≥50% reduction from baseline by visit in AISRS total score. The 30% and 50% reduction from baseline thresholds were assessed post hoc and were selected for consistency with a phase 3 clinical trial of viloxazine ER in adults (Nasser A, et al. *CNS Drugs*. 2022;36(8):897-915). Week 14/EOS analyses were based on assessments assigned to the nominal week 14 visit. Early termination visits were mapped to the next scheduled analysis visit according to the study schedule. Participants who were lost to follow-up or did not complete an early termination visit were excluded.

[b]Measured among participants in the full analysis set (n = 150).

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AISRS, Adult ADHD Investigator Symptom Rating Scale; CRO, clinician-reported outcome; EOS, end of study.

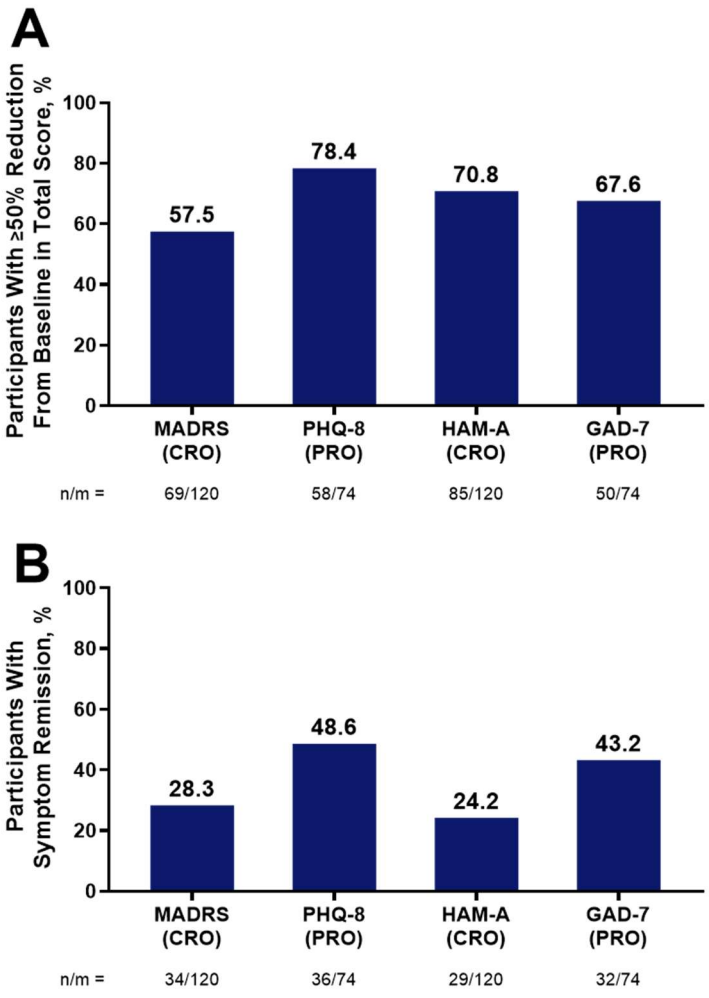


Supplementary Figure 2. Achievement of response or remission for depression and anxiety symptoms at week 14/EOS.[a,b]

[a]Proportion of participants achieving (A) ≥50% reduction from baseline in MADRS, PHQ-8, HAM-A, or GAD-7 total score or (B) symptom remission, defined as MADRS total score ≤10, PHQ-8 total score ≤5, HAM-A total score ≤7, or GAD-7 total score ≤4.[3–5]

[b]Week 14/EOS analyses were based on assessments assigned to the nominal week 14 visit. Early termination visits were mapped to the next scheduled analysis visit according to the study schedule. Participants who were lost to follow-up or did not complete an early termination visit were excluded.

Abbreviations: CRO, clinician-reported outcome; EOS, end of study; GAD-7, General Anxiety Disorder 7-item scale; HAM-A, Hamilton Anxiety Rating Scale; n, number of responders; m, number of participants with nonmissing data at each visit; MADRS, Montgomery-Åsberg Depression Rating Scale; PHQ-8, Patient Health Questionnaire-8 item; PRO, patient-reported outcome.



Supplementary Figure 3. Graphical Abstract