A Double-Blind, Placebo-Controlled, Parallel-Group, Flexible-Dose Study of Venlafaxine Extended Release Capsules in Adult Outpatients With Panic Disorder

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Objective: To evaluate the efficacy, safety, and tolerability of venlafaxine extended release (ER) in short-term treatment of panic disorder.

Method: In this multicenter, double-blind study, conducted from April 2001 to December 2002, 343 adult outpatients who met criteria for panic disorder (with and without agoraphobia) according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, were randomly assigned to flexible-dose venlafaxine ER (75–225 mg/d) or placebo for 10 weeks (N = 155 per group, intent-to-treat population). The primary outcome measure was the percentage of panic-free patients as assessed using the Sheehan Panic and Anticipatory Anxiety Scale. Key secondary measures included the Panic Disorder Severity Scale (PDSS) score and Clinical Global Impressions-Improvement (CGI-I) scale response (score = 1 or 2). Last-observation-carried-forward data were analyzed, and statistical significance was set at $p \leq .05$.

Results: At week 10, the percentage of patients who were free from full-symptom panic attacks was 52% in the venlafaxine ER group and 43% in the placebo group ($p = .11$). Mean change from baseline in PDSS total score was significantly ($p = .006$) greater for the venlafaxine ER group (–9.3) than for the placebo group (–7.5), and significantly ($p = .03$) more venlafaxine ER–treated patients achieved CGI-I response (71%) than did those receiving placebo (59%) at week 10. Treatment with venlafaxine ER was generally safe and well tolerated. Adverse events were the primary or secondary cause for discontinuation for 7 placebo patients (4%) and 12 venlafaxine ER patients (7%).

Conclusions: Venlafaxine ER appears to be effective, safe, and well tolerated in short-term treatment of panic disorder, although the results fell just short of significance on the primary outcome measure.

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Panic disorder is estimated to have a lifetime prevalence between 1% and 4% in the general U.S. population and is frequently comorbid with other psychiatric disorders.[1] A disabling, multidimensional illness, panic disorder varies in the severity and frequency of panic attacks and associated symptoms, such as chest pain, heart palpitations, and interepisode anxiety.[2–4] Adequate assessment and treatment of panic disorder requires measuring improvement across 5 principal domains: panic attack frequency and intensity, anticipatory anxiety, phobic avoidance, functional impairment in daily life, and overall illness severity and well-being.[4,5] Expert clinical guidelines have recommended selective serotonin reuptake inhibitors (SSRIs) as first-line pharmacotherapy for the management of panic disorder because of their broad efficacy and favorable tolerability for the treatment of both depression and anxiety.[4] The Food and Drug Administration

(FDA) has approved 3 SSRIs—paroxetine,[5–7] sertraline,[8–10] and fluoxetine[11–13]—for the treatment of panic disorder.

The efficacy and safety of the serotonin-norepinephrine reuptake inhibitor venlafaxine extended release (ER) has been well established and approved by the FDA for the treatment of major depressive disorder (MDD),[14,15] generalized anxiety disorder (GAD),[16–18] and social anxiety disorder (SAD).[19–22] Venlafaxine ER also was approved by the FDA for the treatment of panic disorder in November 2005.[23]

The efficacy and safety of venlafaxine for panic disorder have been demonstrated in small open-label and double-blind trials with venlafaxine immediate-release (IR),[24–26] in 2 large-scale, double-blind, randomized, placebo-controlled, active-comparator, fixed-dose trials of venlafaxine ER,[27,28] and in 1 large-scale, double-blind, randomized, placebo-controlled trial of flexible-dose venlafaxine ER.[29] The purpose of this double-blind, randomized, placebo-controlled trial was to further evaluate the efficacy, safety, and tolerability of flexible-dose venlafaxine ER for the treatment of panic disorder in adult outpatients with and without agoraphobia. Specifically, we hypothesized that flexible-dose venlafaxine ER would demonstrate superior efficacy compared with placebo on the primary efficacy outcome, the percentage of patients free of full-symptom panic attacks as measured with the Panic and Anticipatory Anxiety Scale (PAAS),[30] as well as superior efficacy on secondary efficacy outcomes, including total score on the Panic Disorder Severity Scale (PDSS)[31] and response rate on the Clinical Global Impressions-Improvement (CGI-I)[32] scale.

METHOD

Study Design

This multicenter, phase III, randomized, double-blind, parallel-group, placebo-controlled trial compared flexible-dose venlafaxine ER (75–225 mg/d) and placebo in adult outpatients who met criteria for panic disorder (with or without agoraphobia) according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV).[33] The study was conducted from April 2001 to December 2002. The protocol received institutional review board/independent ethics committee approval at each of the 56 sites (7 in Canada and 49 in the United States) and was conducted according to the Declaration of Helsinki and its amendments. The Canadian portion of the study was conducted according to the Therapeutic Products Directorate Good Clinical Practice Consolidated Guideline.[34] Participants were new, referred, or existing patients and provided written informed consent before enrollment.

Patients

Eligible participants were healthy outpatients aged 18 years and older who met DSM-IV criteria for panic disorder for at least 3 months before study day 1 (baseline) and had sufficient symptoms to require anxiolytic drug therapy. Patients were required to have a score ≥ 4 on the Clinical Global Impressions-Severity of Illness (CGI-S) scale,[32] at least 8 full-symptom panic attacks within 4 weeks of screening, a minimum of 4 full-symptom panic attacks during the 14(± 3)-day placebo lead-in period between screening and baseline, and a Covi Anxiety Scale[35] total score greater than the Raskin Depression Scale[36] total score. Patients were excluded from the trial if they had DSM-IV–diagnosed GAD or MDD considered by the investigator as primary (i.e., causing a higher degree of distress or impairment than panic disorder); patients with a secondary major depression or GAD were eligible provided that other exclusionary requirements were not met. Patients were excluded if they had any other clinically significant Axis I or Axis II disorders, other than panic disorder (with or without agoraphobia), current or predominant within 6 months of baseline; had a history or presence of bipolar affective disorder, organic brain disorder, seizure disorder, or any psychotic illness; or were acutely suicidal or had a history of drug or alcohol dependence or abuse within 1 year of baseline. Also excluded were patients with a screening or baseline 17-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$)[37] score ≥ 18, a screening or baseline $HAM\text{-}D_{17}$ item 1 (depressed mood) score > 2, a screening or baseline Raskin Depression Scale single-item score > 3, or a Raskin total score > 9.

In addition, patients were excluded if they had received prior treatment with venlafaxine or venlafaxine ER within 6 months of baseline or had a known hypersensitivity to venlafaxine; had taken investigational drugs, antipsychotics, fluoxetine, sumatriptan, naratriptan, or zolmitriptan within 30 days of baseline; had regularly used benzodiazepines within 14 days of screening; had taken herbal products (intended to treat anxiety, insomnia, or depression), antidepressants, monoamine oxidase inhibitors, nonbenzodiazepine anxiolytics, or psychopharmacologic drugs (including anxiolytics, other antidepressants, lithium, stimulants, and sedative hypnotics other than zaleplon or zolpidem [which were permitted up to 10 mg at bedtime through study day 14 at a maximum of 3 times per week]) within 14 days of baseline; had taken nonpsychopharmacologic drugs with psychotropic effects within 7 days of baseline, unless taken at a stable dose for at least 3 months before baseline; had received electroconvulsive therapy within 6 months of baseline; had had cognitive-behavioral therapy (CBT) within 30 days of baseline; or had initiated or changed the intensity of formal psychotherapy within 60 days of baseline. Other reasons for exclusion were the presence of clinically significant abnormal findings on laboratory tests, physical examination, electrocardiogram (ECG), or vital signs, or a history or presence of clinically important medical conditions. Women who were pregnant or lactating were excluded

Table 1. Description of Assessment Scales Used to Measure Severity of Panic Symptoms and Associated Functional Impairment

Scale	Description
Panic and Anticipatory Anxiety Scale (PAAS)[30]	Measures the frequency, average duration, average intensity, and type of attack (full-symptom or limited-symptom and expected or unexpected), percentage of time awake spent having anticipatory anxiety, and the intensity of the anticipatory anxiety
Panic Disorder Severity Scale (PDSS)[11,31,47]	A 7-item clinical interview assessment instrument designed to measure the severity of panic disorder symptoms. It rates core features of panic disorder, including frequency of full-symptom and limited-symptom panic attacks, distress caused by panic attacks, anticipatory anxiety, agoraphobic fear/avoidance, panic-related sensation fear/avoidance, and work and social impairment
Phobia Scale[39]	Evaluates the extent of fear and the avoidance of things or situations that patients fear (if any)
Sheehan Disability Scale (SDS)[40]	Includes 3 specific domains that capture key aspects of patient disability (work, social life/leisure, family life/home responsibilities). Responses on these 3 domains are scored on an 11-point (0 to 10) discrete analog scale with higher scores representing greater impairment (0 = not at all impaired, 10 = very severely impaired). Also includes a 5-point work and social disability scale (1 = normal activity, 5 = symptoms prevent normal work or social activities)
Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)[41]	Includes domains that measure physical health/activities, subjective feelings of well-being, work, household duties, school/coursework, leisure time, social relations, general well-being, satisfaction with medication, and overall life satisfaction. Responses are measured on a 5-point Likert scale with higher scores indicating better functioning

from the study, as were women of childbearing age who were not on medically acceptable contraception.

Treatment

After a 14 (± 3)-day, single-blind, placebo lead-in period, eligible patients were randomly assigned at baseline to receive flexible doses of venlafaxine ER (75–225 mg/d) or placebo for up to 10 weeks of treatment, followed by a taper period of up to 14 days. On study days 1 through 4, patients in the venlafaxine ER group received 37.5 mg/d (1 capsule), and the dose was increased to 75 mg/d (1 capsule) on days 5 to 14. If clinically indicated to improve response, the daily dose could be increased to 150 mg/d (2 capsules) on day 15 and to the maximum dose of 225 mg/d (3 capsules) on day 22. Dosage could have been reduced at any time during the study to improve tolerance, but after study day 7, the minimum daily dose allowed was 75 mg/d (1 capsule). Patients continued taking active treatment or placebo through day 70 or early withdrawal. During the 2-week taper period, doses were reduced at weekly intervals. Patients who had received 2 capsules or 3 capsules (150 or 225 mg/d) during the on-therapy period tapered their dose by taking 1 less capsule each week; patients who had received 75 mg/d during the double-blind period did not need to have their dose tapered. Patients assigned to placebo continued receiving it for 2 weeks. The taper period could have been omitted or prolonged if medically indicated. Poststudy evaluations were obtained 4 to 10 days after the study medication had been discontinued or after the completion of the taper period for all patients who received study treatment.

Measurements

Assessment tools used in the study to measure the severity of panic symptoms and associated functional impairment are described in Table 1. The primary efficacy instrument was the PAAS,[30] which was administered at screening, baseline, and weeks 1, 2, 3, 4, 6, 8, and 10. PAAS data were derived from patient diary cards, on which patients recorded daily details of panic attack frequency (including symptoms and whether situational or unexpected) and anticipatory anxiety. The investigator completed the PAAS after interviewing the patient to verify and clarify the information in the daily diary. The primary outcome measure, based on the PAAS, was the percentage of patients who were free of full-symptom panic attacks (defined as panic attacks with 4 or more symptoms) at the end of the study period.

The first key secondary efficacy outcome was the total score on the PDSS,[31] which was administered at screening, baseline, and weeks 2, 3, 4, 6, 8, and 10. The second key efficacy outcome was response rate on the CGI-I[32] scale (responder score = 1 or 2), which was administered at weeks 1, 2, 3, 4, 6, 8, and 10.

Other secondary efficacy outcomes were the number and intensity of full-symptom and limited-symptom panic attacks extracted from the PAAS, the PDSS average item score, and responder rates on the PDSS (defined as a 40% reduction in total score from baseline). In addition, secondary efficacy outcomes included scores on the Hamilton Rating Scale for Anxiety (HAM-A),[38] which was administered at baseline and week 10, and scores on the CGI-S[32] and Phobia Scale,[39] which were administered at screening, baseline, and weeks 1, 2, 3, 4, 6, 8, and 10. Remission also was measured and defined as 0 full-symptom panic attacks on the PAAS and either a CGI-I score of 1 (very much improved) or a CGI-S score of 1 or 2 (not ill or borderline mentally ill). Additional secondary efficacy measures were patient-rated health outcomes assessments, the Sheehan Disability Scale[40] (SDS) and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q),[41] which were administered at baseline and week 10.

Safety evaluations performed at screening, baseline, and weeks 1, 2, 3, 4, 6, 8, and 10 included assessment of vital signs, recording of adverse events (AEs) and concomitant treatments, and review of treatment compliance. A physical examination, laboratory determinations, and 12-lead ECG were performed at screening and week 10. Weight was recorded at screening, baseline, and week 10. Poststudy evaluations were conducted 4 to 10 days after the last dose of double-blind or taper study medication was taken.

Data Analyses

The primary analysis population for efficacy variables was the intent-to-treat (ITT) population. Secondary analyses were performed on the per-protocol patients and the "all-randomized" patients. Results of the primary analysis population, the ITT population, are presented in this article. Patients in the ITT population were those who had a baseline PAAS evaluation and at least 1 double-blind, on-therapy evaluation of the primary efficacy variable during visits 3 to 10 and within 3 days of stopping the study medication before taper. On-therapy evaluation for the PAAS was defined as a period ≥ 7 days of double-blind PAAS data.

Efficacy was assessed at each evaluation period and was analyzed using the last-observation-carried-forward (LOCF) and observed-cases (OC) data sets. The LOCF method was used to account for the results of early terminators, whereas the OC analysis used only data that were collected at each visit, without estimating missing information. Both OC and LOCF data are presented for the primary and 2 key secondary outcome measures—the percentage of patients free of PAAS full-symptom panic attacks, PDSS total score, and CGI-I response rate, respectively. For the HAM-A, SDS, and Q-LES-Q, only OC data were analyzed and are presented. For all other measures, only LOCF data are presented. The safety population included all randomly assigned patients who received at least 1 dose of double-blind study medication.

The primary end point for all efficacy variables was the week 10 LOCF evaluation. The primary outcome measure, the percentage of patients free of full-symptom panic attacks, was analyzed using logistic regression with treatment group and sites as factors. If the treatment effect was significant, the treatment-by-center interaction term was explored and tested at an α level of .10. In addition, the median change in panic attack frequency and the anticipatory anxiety data from the PAAS were analyzed by the Wilcoxon rank sum test. Because the values measured in the PAAS are usually nonnormal in nature, log transformations were applied. Geometric means of the log transformations were employed. Analysis of covariance (ANCOVA) was applied to these data using logs of the baseline values as covariates. If a patient did not report any full-symptom panic attacks for a particular study period, the 0 value was converted to 0.5 before the log transformations were completed.

The remission, CGI-I responder, and PDSS responder data were analyzed using the Fisher exact test with statistical significance set at $p \leq .05$. The PDSS, Phobia Scale, $HAM\text{-}D_{17}$, CGI-I, CGI-S, SDS, and Q-LES-Q were analyzed by ANCOVA. One-way analysis of variance was used to test for comparability of treatment groups with respect to baseline continuous variables such as age. The χ^2 test or Fisher exact test was used to compare treatment groups with respect to baseline nominal variables such as sex. Statistical significance was set at $p \leq .05$.

A sequential testing strategy with a prespecified order of testing was planned to control for multiplicity in the primary efficacy variable (PAAS full-symptom panic attack frequency) and the 2 key secondary efficacy variables (PDSS total score; CGI-I response rate). If the comparison of venlafaxine ER versus placebo was significant at the ≤ .05 level for the primary efficacy variable, then the subsequent pairwise comparison for the first of the 2 key secondary efficacy variables (PDSS total score) was to be made and was to be declared significant if the p value was ≤ .05. The other key secondary efficacy variable (CGI-I response rate) was to be considered significant only if both of the previous comparisons were significant and the p value was ≤ .05. The primary end point was not statistically significant; therefore, all pairwise comparisons presented here should be considered exploratory.

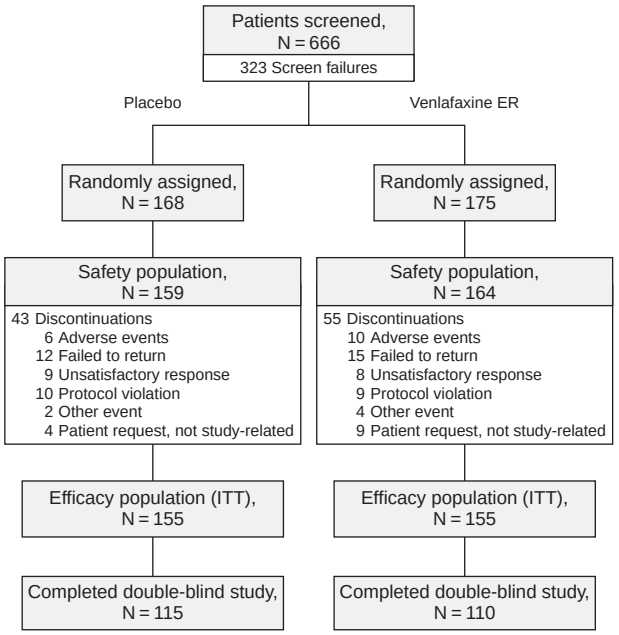
Sample size estimates were based on the literature. The percentage of patients free from panic attacks was estimated to be about 50% in the venlafaxine ER–treated group compared with 30% in the placebo-treated group. It was estimated that 140 ITT patients per treatment arm would be needed to provide 90% power for a 2-sided test at the .05 level of significance. To compensate for the estimated 15% of patients who might not qualify for the ITT criteria, the planned enrollment was 165 patients per treatment group.

RESULTS

Patients

A total of 343 patients were randomly assigned to treatment, 175 to venlafaxine ER and 168 to placebo. Of these, 323 patients (94%) were evaluated for safety (20 patients had no data after baseline). The ITT population had 310 patients (90%); 13 patients were excluded because they did not have a primary efficacy evaluation (PAAS) on therapy (Figure 1). Overall, 98 patients (30%) in the safety population prematurely discontinued double-blind treatment. Failure to return was the most common reason for withdrawal in both the venlafaxine ER group (9%) and placebo group (8%). No significant differences between the 2 treatment groups were observed in the

Figure 1. Flowchart of Double-Blind, Placebo-Controlled Study of Venlafaxine ER in Adult Outpatients With Panic Disorder[a]



[a]The a priori study analysis plan defined a *completer* as a patient who completed a Panic and Anticipatory Anxiety Scale (PAAS) evaluation on or after at least 9 weeks (64 days) of taking study medication. During the course of this study, there was 1 venlafaxine ER patient who had both discontinued the study and had the final evaluation on day 64. By definition, this patient is included in both the completer group and the discontinuation population. The same scenario also occurred in the placebo group for 1 patient who also discontinued and had a final study evaluation on day 64. The placebo group also included 2 patients whom the investigator considered to have completed the study even though they did not have a final PAAS evaluation on or after study day 64. These 2 patients have not been included in either the completer group or the discontinuation population but have been included in all LOCF and safety analyses.

Abbreviations: ER = extended release, ITT = intent to treat, LOCF = last observation carried forward.

Table 2. Baseline and Demographic Characteristics of ITT Population by Treatment Group (N = 310)

Characteristic	Placebo (n = 155)	Venlafaxine ER (n = 155)
Age, mean ± SD, y	36.7 ± 12.0	36 ± 12.4
Sex, n (%)[a]		
Male	63 (41)	44 (28)
Female	92 (59)	111 (72)
Current panic disorder episode duration, mean ± SD, y	6.3 ± 9.3	6.1 ± 7.8
No. of baseline PAAS full-symptom panic attacks, mean ± SD	12.1 ± 13.0	13.3 ± 15.8
No. of full-symptom panic attacks, n (%)		
2–7	70 (45)	63 (41)
8–14	49 (32)	56 (36)
15–28	23 (15)	19 (12)
≥ 29	12 (8)	16 (10)
Baseline CGI-S score, n (%)		
3	1 (1)	1 (1)
4	80 (52)	72 (46)
5	62 (40)	64 (41)
6	12 (8)	17 (11)
7	0	1 (1)
Baseline HAM-D_{17} total score, mean ± SD	9.5 ± 4.4	9.3 ± 4.3

[a]Significant difference between groups for sex (p = .023, χ^2 test); no other significant between-group differences.

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, ER = extended release, HAM-D_{17} = 17-item Hamilton Rating Scale for Depression, ITT = intent to treat, PAAS = Panic and Anticipatory Anxiety Scale.

primary reasons for withdrawal during the double-blind period. One patient (< 1%) withdrew during the taper or poststudy period. In the ITT population, the only significant difference in baseline characteristics was in the distribution of men and women (p = .023) (Table 2). The mean (± standard deviation) daily doses of venlafaxine ER for completers ranged from 128.3 (± 31.6) mg at week 3 to 188.3 (± 49.1) mg at week 10.

Efficacy Evaluation

Primary efficacy measure. The number of patients free of PAAS full-symptom panic attacks was not significantly different at any time point in the LOCF analysis for the venlafaxine ER group compared with the placebo group. At week 10, the percentage of patients who were free from full-symptom panic attacks was 51.6% in the venlafaxine ER group compared with 43.2% in the placebo group (p = .11; Table 3). However, in the OC analysis, the difference between treatment groups was significant at weeks 8 (55.3% for venlafaxine ER vs. 41.1% for placebo; p = .03) and 10 (63.6% for venlafaxine ER vs. 49.6% for placebo; p = .02).

Secondary efficacy measures. The median reduction in PAAS full-symptom panic attacks from baseline was not significantly different between venlafaxine ER and placebo groups at LOCF week 10 (–6.0 vs. –4.9, respectively; p = .08). A comparison of log-transformed data for PAAS full-symptom panic attacks also showed no significant reductions from baseline to LOCF week 10 for venlafaxine ER versus placebo (–1.82 vs. –1.56, respectively; p = .09; effect size [ES] = 0.19; Table 4).

The effect of treatment on limited-symptom panic attacks was consistent with the findings for full-symptom panic attacks. At the LOCF week 10 evaluation, 54.8% of venlafaxine ER patients were free of limited-symptom panic attacks versus 52.9% of placebo patients (p = .69; Table 3). A comparison of log-transformed data for PAAS limited-symptom panic attacks also showed no significant reductions from baseline for venlafaxine ER versus placebo at LOCF week 10 (–0.67 vs. –0.61, respectively; p = .63; ES = 0.06; Table 4).

PAAS anticipatory anxiety time was not significantly different at end point for patients in the venlafaxine ER and placebo groups. At LOCF week 10, the median change in baseline percentage of time that patients had

Table 3. Rates of Improvement for Primary and Secondary Efficacy Outcome Measures at the LOCF End Point for the ITT Population by Treatment Group

Outcome Measure/Treatment Group	LOCF End-Point Analysis, % (n/n)	p Value vs Placebo
Primary efficacy measure		
Free of PAAS full-symptom panic attacks		
Placebo	43.2 (67/155)	
Venlafaxine ER	51.6 (80/155)	.108
Secondary efficacy measures		
Free of PAAS limited-symptom panic attacks		
Placebo	52.9 (82/155)	
Venlafaxine ER	54.8 (85/155)	.690
CGI-I responders[a]		
Placebo	58.8 (90/153)	
Venlafaxine ER	71.1 (108/152)	.031
PDSS responders[b]		
Placebo	58.0 (87/150)	
Venlafaxine ER	74.3 (104/140)	.004
Remission, PAAS and CGI-I[c]		
Placebo	27.5 (42/153)	
Venlafaxine ER	38.2 (58/152)	.051
Remission, PAAS and CGI-S[d]		
Placebo	29.4 (45/153)	
Venlafaxine ER	40.1 (61/152)	.055

[a]CGI-I response defined as a score of 1 or 2.
[b]PDSS response defined as a ≥ 40% reduction in PDSS total score from baseline.
[c]Remission defined as free of PAAS full-symptom panic attacks and a CGI-I score of 1.
[d]Remission defined as free of PAAS full-symptom panic attacks and a CGI-S score of 1 or 2.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, ER = extended release, ITT = intent to treat, LOCF = last observation carried forward, PAAS = Panic and Anticipatory Anxiety Scale, PDSS = Panic Disorder Severity Scale.

anticipatory anxiety was –8.4% for the venlafaxine ER group versus –5.8% for the placebo group (p = .118).

PDSS total scores over time are shown in Figure 2, and PDSS adjusted mean changes from baseline to end point and effect sizes are presented in Table 4. At the LOCF week 10 evaluation, a significant difference from placebo was observed in the adjusted mean change in PDSS total score for the venlafaxine ER group (difference in adjusted means: 1.78, p = .006; ES = 0.33). Significant differences versus placebo were observed starting at week 4 and were sustained through week 10. Similarly, in the OC analysis, significant differences versus placebo also were observed starting at week 4 and were maintained through week 10 (difference in adjusted means at week 10: 2.17; p = .003).

Mean changes from baseline to the LOCF week 10 evaluation and ES for additional secondary efficacy variables (except HAM-A, for which OC data were analyzed) are presented in Table 4. Significant differences for venlafaxine ER versus placebo were observed for the CGI-S scale (difference in adjusted means: 0.43; p = .003; ES = 0.35) and Phobia Scale fear (difference in adjusted means: 6.57; p = .006; ES = 0.31) and avoidance (difference in adjusted means: 2.09; p = .022; ES = 0.26). HAM-A total scores were not significantly different between groups, although the difference approached statistical significance (OC analysis, difference in adjusted means: 1.86; p = .058; ES = 0.27).

Response and remission. Rates of response and remission are presented in Table 3. CGI-I response rates (CGI-I score of 1 or 2) were significantly higher for venlafaxine ER than for placebo at weeks 4 (55.3% vs. 41.2%, respectively; p = .02) and 10 (71.1% vs. 58.8%, respectively; p = .03) in the LOCF analysis. In the OC analysis, CGI-I response rates were significantly higher for venlafaxine ER than for placebo at weeks 4 (60.6% vs. 43.9%, respectively; p = .007), 6 (71.8% vs. 59.7%, respectively; p = .047), and 10 (83.0% vs. 65.4%, respectively; p = .005).

PDSS response rates (≥ 40% reduction in PDSS total score from baseline) were significantly higher for venlafaxine ER than for placebo at LOCF weeks 4 (51.8% vs. 38.9%, respectively; p = .033), 8 (70.0% vs. 53.3%, respectively; p = .004), and 10 (74.3% vs. 58.0%, respectively; p = .004).

Rates of remission using the combination of PAAS full-symptom panic-free status and a CGI-I score of 1 approached statistical significance for venlafaxine ER, relative to placebo, at LOCF weeks 6 (19.1% vs. 11.1%, respectively; p = .056) and 10 (38.2% vs. 27.5%, respectively; p = .051).

Remission rates based on PAAS full-symptom panic-free status and a CGI-S score of 1 or 2 approached significance for venlafaxine ER, relative to placebo, in the LOCF analysis at week 10 (40.1% vs. 29.4%, respectively; p = .055).

Patient-reported health outcomes. Changes from baseline to LOCF end point for patient-reported health outcomes are presented in Table 5. Data were analyzed only in the OC analysis. Patients treated with venlafaxine ER were significantly improved at the observed week 10 evaluation on 3 of the 4 domains of the SDS, the work (p = .006), social life and leisure activities (p = .018), and work and social disability (p = .003) subscales. Venlafaxine ER treatment also was associated with significant improvement at the observed week 10 evaluation on the physical health and activities (p = .006), subjective feelings of well-being (p < .001), general activities (p = .006), satisfaction with medication (p = .01), leisure time activities (p = .037), social relations (p = .007), and overall life satisfaction (p = .018) subscales of the Q-LES-Q.

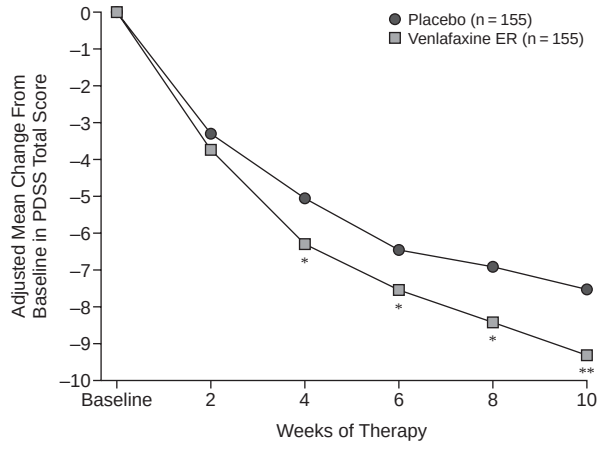
Agoraphobia and PAAS full-symptom panic attacks. A post hoc subanalysis was conducted to identify the number of patients in the study population who had comorbid agoraphobia and to determine if the presence of agoraphobia significantly influenced results on the primary efficacy outcome, the percentage of patients free of

Table 4. Changes From Baseline to LOCF End Point and Effect Sizes for Selected Secondary Efficacy Outcome Measures for the ITT Population by Treatment Group

Outcome Measure/Treatment Group	n	Baseline Raw Mean Score	Adjusted Mean Change From Baseline (SE)	Difference in Adjusted Means (95% CI)	p Value vs Placebo	Effect Size
PAAS[a]						
Full-symptom panic attacks[b]						
Placebo	154	2.13	–1.56 (0.11)			
Venlafaxine ER	154	2.23	–1.82 (0.11)	0.25 (–0.04 to 0.55)	.089	0.19
Limited-symptom panic attacks[c]						
Placebo	154	0.76	–0.61 (0.09)			
Venlafaxine ER	154	0.87	–0.67 (0.08)	0.06 (–0.18 to 0.29)	.629	0.06
PDSS total score						
Placebo	150	15.85	–7.50 (0.45)			
Venlafaxine ER	140	16.13	–9.28 (0.46)	1.78 (0.53 to 3.03)	.006	0.33
CGI-S						
Placebo	153	4.55	–1.46 (0.10)			
Venlafaxine ER	152	4.65	–1.89 (0.10)	0.43 (0.15 to 0.71)	.003	0.35
Phobia Scale						
Fear						
Placebo	154	45.07	–14.99 (1.71)			
Venlafaxine ER	152	49.84	–21.56 (1.71)	6.57 (1.86 to 11.29)	.006	0.31
Avoidance						
Placebo	154	15.89	–4.55 (0.65)			
Venlafaxine ER	152	17.41	–6.64 (0.65)	2.09 (0.30 to 3.87)	.022	0.26
HAM-A total score[d]						
Placebo	105	18.40	–7.65 (0.68)			
Venlafaxine ER	104	18.77	–9.51 (0.68)	1.86 (–0.06 to 3.78)	.058	0.27

[a]Log-transformed data shown for the PAAS.
[b]Full-symptom panic attacks defined as panic attacks with ≥ 4 symptoms.
[c]Limited-symptom panic attacks defined as panic attacks with < 4 symptoms.
[d]Week 10 observed-cases data were analyzed for HAM-A.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, ER = extended release, HAM-A = Hamilton Rating Scale for Anxiety, ITT = intent to treat, LOCF = last observation carried forward, PAAS = Panic and Anticipatory Anxiety Scale, PDSS = Panic Disorder Severity Scale.

Figure 2. Secondary Efficacy Outcome: PDSS Total Score Over Time (adjusted mean change from baseline for ITT population; LOCF)



*p < .05 vs. placebo.
**p < .01 vs. placebo.
Abbreviations: ER = extended release, ITT = intent to treat, LOCF = last observation carried forward, PDSS = Panic Disorder Severity Scale.

PAAS full-symptom panic attacks, at week 10 (LOCF). Overall, 222 patients (72%) in the trial had panic disorder with agoraphobia and 88 patients (28%) had panic disorder without agoraphobia. Logistic regression analyses showed that the interaction between therapy and agoraphobia was not significant (p = .141), indicating that the treatment effect (venlafaxine ER versus placebo) on PAAS full-symptom panic attacks was not significantly different for patient groups with or without agoraphobia. In the subgroup of patients with agoraphobia, 113 were in the placebo group and 44% (50 of 113) were panic-free; 109 patients were in the venlafaxine ER group and 49% (53 of 109) were panic-free. In the subgroup of patients without agoraphobia, 42 patients were in the placebo group and 40% (17 of 42) were panic-free; 46 patients were in the venlafaxine ER group and 59% (27 of 46) were panic-free.

Safety

Overall, treatment-emergent adverse events (TEAEs) were reported by 125 patients (79%) receiving placebo and 144 (88%; p < .05) receiving venlafaxine ER (Table 6). The most common TEAEs (i.e., those reported by

Table 5. Changes From Baseline to Week 10 (observed-cases analysis) for Patient-Reported Health Outcome Measures for the ITT Population by Treatment Group

Outcome Measure/Treatment Group	n	Baseline Raw Mean Score	Adjusted Mean Change From Baseline	Difference in Adjusted Means (95% CI)	p Value vs Placebo
Sheehan Disability Scale					
Work					
Placebo	104	4.45	–1.39		
Venlafaxine ER	100	4.78	–2.36	0.96 (0.29 to 1.64)	.006
Social life and leisure activities					
Placebo	106	5.39	–1.81		
Venlafaxine ER	103	5.68	–2.69	0.88 (0.15 to 1.60)	.018
Family life and home responsibilities					
Placebo	106	4.38	–1.64		
Venlafaxine ER	103	4.55	–2.17	0.53 (–0.14 to 1.20)	.118
Work and social disability					
Placebo	103	3.66	–0.85		
Venlafaxine ER	101	3.69	–1.31	0.47 (0.16 to 0.78)	.003
Q-LES-Q					
Physical health and activities					
Placebo	105	2.95	0.27		
Venlafaxine ER	102	2.88	0.57	–0.30 (–0.50 to –0.09)	.006
Subjective feelings of well-being					
Placebo	106	3.33	0.29		
Venlafaxine ER	103	3.27	0.61	–0.32 (–0.48 to –0.15)	< .001
General activities					
Placebo	106	3.15	0.38		
Venlafaxine ER	100	3.19	0.64	–0.26 (–0.44 to –0.08)	.006
Satisfaction with medication					
Placebo	80	3.04	0.54		
Venlafaxine ER	83	3.09	0.93	–0.39 (–0.68 to –0.09)	.010
Leisure time activities					
Placebo	102	3.21	0.35		
Venlafaxine ER	101	3.18	0.56	–0.21 (–0.41 to –0.01)	.037
Social relations					
Placebo	106	3.36	0.26		
Venlafaxine ER	102	3.35	0.51	–0.25 (–0.43 to –0.07)	.007
Overall life satisfaction					
Placebo	106	3.06	0.50		
Venlafaxine ER	100	3.10	0.78	–0.28 (–0.51 to –0.05)	.018

Abbreviations: ER = extended release, ITT = intent to treat, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire.

≥ 5% of the venlafaxine-treated patients and at a frequency at least twice the rate for placebo-treated patients during double-blind treatment) were hypertension, anorexia, constipation, dry mouth, nausea, insomnia, somnolence, abnormal ejaculation, sweating, and impotence. The following specific TEAEs were reported at a significantly higher rate for venlafaxine ER than placebo during double-blind treatment: anorexia, constipation, dry mouth, nausea, insomnia, somnolence, and sweating (Table 6). Most TEAEs were generally mild or moderate in severity. AEs were the primary or secondary cause for withdrawal for 7 placebo patients (4%) and 12 venlafaxine ER patients (7%).

Taper/poststudy–emergent AEs were reported by 46 placebo patients (29%) and 70 venlafaxine ER patients (43%; p = .01). Events reported by ≥ 5% of venlafaxine ER–treated patients were headache, dizziness, and nausea. Headache was reported by ≥ 5% of placebo patients during the same period. Taper/poststudy–emergent AEs that were significantly greater with venlafaxine ER than placebo were nausea (7% vs. 1%, respectively; p = .01) and dizziness (15% vs. 3%, respectively; p < .001).

No deaths occurred during or immediately after the study, nor were there any new, unexpected serious events in the venlafaxine ER group that were considered to be drug-related on the basis of comparison with the U.S. venlafaxine ER package insert[42] and the opinion of the investigators reporting the AEs. Of the 13 patients (6 placebo, 7 venlafaxine ER) considered to have serious AEs, 6 discontinued treatment: 3 placebo patients (1 with depression, 2 with unintended pregnancies) and 3 venlafaxine ER patients (1 each with suicide attempt, depression, and convulsion). The remaining 7 patients did not discontinue treatment: 3 placebo patients (1 each with chest pain, basal cell carcinoma, and false-positive urine pregnancy test) and 4 venlafaxine ER patients (3 with unintended pregnancies, 1 with gastroenteritis).

Individual, clinically important laboratory results were reported in 5 patients: increased triglycerides (1 placebo, 2 venlafaxine ER), increased aspartate aminotransferase

Table 6. Treatment-Emergent Adverse Events by Treatment Group in the Safety Population[a]

Adverse Event	Placebo (n = 159), n (%)	Venlafaxine ER (n = 164), n (%)
Any adverse event	125 (79)	144 (88)*
Nausea	16 (10)	34 (21)**
Insomnia	9 (6)	26 (16)**
Dry mouth	10 (6)	24 (15)***
Constipation	6 (4)	19 (12)**
Somnolence	9 (6)	25 (15)**
Anorexia	3 (2)	15 (9)**
Impotence[b]	2 (3)	4 (8)
Sweating	1 (< 1)	12 (7)**
Hypertension	5 (3)	10 (6)
Abnormal ejaculation[b]	1 (2)	3 (6)

[a]Incidence ≥ 5% and twice that of placebo.
[b]Based on the number of male patients: placebo, n = 64; venlafaxine ER, n = 49.
*p < .05 for venlafaxine ER vs. placebo.
**p ≤ .01 for venlafaxine ER vs. placebo.
***p < .001 for venlafaxine ER vs. placebo.
Abbreviation: ER = extended release.

and alanine aminotransferase (1 venlafaxine ER), and increased total cholesterol (1 venlafaxine ER). Between-group comparisons were significant for total cholesterol (p = .001).

Two patients, 1 each in the placebo and venlafaxine ER groups, experienced clinically important increases in blood pressure. Between-group comparisons were significant for supine systolic blood pressure (p = .001) and supine diastolic blood pressure (p = .002).

Weight in the venlafaxine ER group was significantly decreased from baseline at week 10 (–0.83 kg; p ≤ .001); the decrease was significantly different (p = .039) from the week 10 decrease in the placebo group (–0.16 kg).

ECG data showed that 2 patients experienced clinically important changes in U waves (1 each for placebo and venlafaxine ER) and 1 venlafaxine ER patient experienced premature ventricular contractions. Mean heart rate at week 10 showed significant increases from baseline in both the venlafaxine ER (7.29 beats/min, p < .001) and placebo (2.93 beats/min, p < .01) groups; the increase in the venlafaxine ER group was significantly different from that in the placebo group (p < .001). Mean PR interval at week 10 in the venlafaxine ER group showed significant decreases from baseline (–2.53, p < .05), whereas the placebo group showed a nonsignificant, numerical increase (0.83); the change in the venlafaxine ER group was significantly different from that in the placebo group (p = .02). Mean QT interval at week 10 showed significant decreases from baseline in both the venlafaxine ER (–19.41, p < .001) and placebo (–9.21, p < .001) groups; the decrease in the venlafaxine ER group was significantly different from that in the placebo group (p = .002). No patient had any clinically important changes in physical findings other than those reported as AEs.

DISCUSSION

In this multicenter, randomized, double-blind, placebo-controlled trial of flexible-dose venlafaxine ER (75–225 mg/d) for the treatment of panic disorder in patients with or without agoraphobia, the primary efficacy end point, the percentage of patients free of PAAS full-symptom panic attacks at LOCF week 10, did not show significant differences between the venlafaxine ER and placebo groups. However, in the OC analysis for this variable, statistical significance was attained at weeks 8 and 10. Results of the primary outcome measure were not influenced by the presence of agoraphobia; logistic regression analyses showed that the treatment effect for venlafaxine ER versus placebo on the PAAS panic-free rate was not significantly different for patient groups with or without agoraphobia. On related panic attack frequency measures, median reductions from baseline in PAAS full-symptom and limited-symptom panic attacks were not significantly different for the venlafaxine ER and placebo groups at end point.

Several secondary outcomes resulted in statistically stronger separation of drug and placebo than the PAAS ratings of panic attack frequency. Although the secondary efficacy results should be considered exploratory because the primary end point in this study was not significant, the outcomes are suggestive of the efficacy of venlafaxine ER for reducing panic attack frequency. Patients treated with venlafaxine ER achieved significantly greater improvements than placebo patients on the PDSS, which is a highly sensitive outcome measure that integrates several clinically relevant domains of panic disorder, including panic attacks, anticipatory anxiety, and agoraphobic avoidance. A significantly greater reduction in PDSS total score and a significantly greater percentage of PDSS responders were observed in the LOCF analysis beginning at week 4. Rates of PDSS response (74%) associated with venlafaxine ER treatment in this study were generally consistent with those previously observed in short-term pharmacotherapy trials for panic disorder.[43,44] In retrospect, the PDSS, which reflects the integrated disorder, may have been a superior primary efficacy measure than the PAAS, which is highly variable and placebo responsive. Global measures of response on the CGI-I and CGI-S assessments also showed statistically significant separation of drug from placebo. Rates of CGI-I response (71%) for venlafaxine ER in this study were generally similar to those previously reported in acute pharmacotherapy trials for panic disorder.[5,7,45] A significantly greater decrease in the level of both phobic avoidance and fear were observed for venlafaxine ER compared with placebo. Furthermore, the majority of patient-rated quality-of-life outcomes significantly favored venlafaxine ER treatment over placebo, strengthening the evidence of efficacy for venlafaxine ER in panic disorder. Rapaport et

al.[10] have suggested that quality-of-life outcomes may be the best indication of placebo-versus-drug response, as placebo responders may demonstrate a reduction of symptoms but no clinically meaningful improvement in quality of life.

Results of the current trial are consistent with those of the similarly designed, 10-week, double-blind, randomized, placebo-controlled trial by Bradwejn et al.,[29] in which flexible-dose venlafaxine ER (75–225 mg/d) was not significantly different from placebo on the primary outcome measure, the percentage of patients free from PAAS full-symptom panic attacks at end point. Venlafaxine ER was significantly superior to placebo on several secondary efficacy measures, including rates of CGI response, improvement in symptoms of anxiety, fear, and avoidance, as well as improvement in a majority of domains representing quality of life and functionality.[29]

Two recent, similarly-designed, fixed-dose venlafaxine ER trials by Pollack and colleagues[27,28] showed significant differences between the venlafaxine ER and placebo groups on the primary efficacy outcome, percentage of patients free of PAAS full-symptom panic attacks, as well as on almost all secondary efficacy outcomes. Although the design of the fixed-dose trials was similar to the design of the present flexible-dose study, there were several differences. Both trials by Pollack and colleagues[27,28] used 2 fixed doses of venlafaxine ER (75 mg/d and either 150 or 225 mg/d), included an active comparator (paroxetine), and were slightly longer in duration than the current study (12 weeks vs. 10 weeks). Furthermore, the panic disorder episode durations were shorter in both fixed-dose trials (approximately 3.6 years) compared with the present study (about 6.2 years), which may have influenced treatment outcomes.[46]

The nonsignificant findings for the primary outcome measure in this study may be related to methodological challenges in conducting clinical trials of panic disorder. Such trials commonly use frequency of full-symptom panic attacks as a primary outcome because panic attacks are a core feature of panic disorder; however, the intermittent, variable nature of panic attacks can lead to inherent problems with measurement,[47] and panic attack frequency in antidepressant clinical trials has been shown to correlate poorly with global and functional efficacy measures.[10,11,29] In line with this observation, our study found a statistically nonsignificant difference for venlafaxine ER versus placebo in the PAAS panic-free rate (approximately 52% vs. 43%, respectively; p = .11), a significant between-group difference in CGI-I response rate (approximately 71% vs. 59%, respectively; p = .03), and poor correlation between the 2 measures. These results are consistent with the Bradwejn et al. study,[29] which found a statistically nonsignificant difference for venlafaxine ER versus placebo in panic-free rate (approximately 55% vs. 52%, respectively), a significant between-group difference in CGI-I response rate (approximately 68% vs. 55%, respectively; p = .02), and poor correlation between the 2 measures. CGI-I response rate may be a better reflection of overall clinical response and a more sensitive detector of drug-placebo difference compared with the PAAS panic-free rate.

Treatment with venlafaxine ER was generally safe and well tolerated in this study. In most cases, AEs were mild to moderate in severity and venlafaxine ER was associated with few clinically important changes in laboratory tests, vital sign results, or ECG assessments. The AEs observed with venlafaxine ER in this study were similar in type and frequency to those observed in studies for MDD, GAD, and SAD. No new, unexpected, drug-related, serious AEs occurred with venlafaxine ER, and the incidence of discontinuation due to AEs was low in the venlafaxine ER group, indicating that there is no evidence of an increased risk in patients with panic disorder.

Strengths of this study include the randomized, placebo-controlled trial design and the broad range of efficacy and safety measures employed. Furthermore, patients with a primary diagnosis of major depression were excluded from the trial, so the improvements associated with venlafaxine ER treatment may not be attributable to an improvement in depressive symptoms.

Certain limitations related to the study design merit consideration. First, although patient selection criteria included not having CBT within 30 days of baseline, as well as no initiation or change in formal psychotherapy within 60 days of baseline, self-employed CBT techniques were not monitored, and ongoing psychotherapy without a change in intensity was permitted; both can be considered treatment methods that may have decreased the reliability of the results. Additional studies are needed to determine the impact of CBT in particular on treatment outcomes.

Second, assessments with the PAAS, including the primary outcome measure, were based on patient recall and recording of panic attack frequency and anticipatory anxiety in diary cards. Few steps were taken in the study to enhance the reliability of and adherence to the PAAS scale, which may have consequently weakened the results. Future studies should explore the use of more reliable efficacy assessments, such as the PDSS, for the primary outcome measure.

Third, this study was short-term (10 weeks). Like treatment for MDD,[48] panic disorder treatment for some patients may require extended treatment time to improve outcomes and prevent the return of symptoms. In a 26-week, relapse-prevention clinical trial of outpatients with panic disorder who were responders to acute treatment with venlafaxine ER (75–225 mg/d), Ferguson and colleagues[49] found that time to relapse was significantly longer and the cumulative relapse rate was significantly lower with venlafaxine ER than with placebo.

Venlafaxine ER also was associated with significant improvements in the PAAS panic-free rate, PDSS, anticipatory anxiety, fear and avoidance, CGI-S, and quality-of-life measures.[49] Additional long-term studies are warranted to examine the treatment benefits of venlafaxine ER over longer durations as well as at higher doses.

In summary, venlafaxine ER (75–225 mg/d) did not differ from placebo on the primary efficacy end point, although significant improvements compared with placebo were demonstrated on several secondary efficacy measures, including CGI-defined and PDSS-defined response rates and patient-rated quality-of-life outcomes. Venlafaxine ER was generally safe and well tolerated for the treatment of panic disorder, and, when considered in the context of other venlafaxine ER trials, the overall results are suggestive of the efficacy of venlafaxine ER for panic disorder and warrant additional study.

Drug names: fluoxetine (Prozac and others), lithium (Eskalith, Lithobid, and others), naratriptan (Amerge), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), sumatriptan (Imitrex), venlafaxine (Effexor and others), zaleplon (Sonata and others), zolmitriptan (Zomig), zolpidem (Ambien and others).

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