Relapse Prevention of Panic Disorder in Adult Outpatient Responders to Treatment With Venlafaxine Extended Release

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Objective: To compare the long-term efficacy of venlafaxine extended release (ER) with placebo in preventing panic disorder relapse in outpatient treatment responders.

Method: Outpatients aged ≥ 18 years who met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, criteria for panic disorder with or without agoraphobia for at least the previous 3 months, with ≥ 6 full symptom panic attacks in the 2 weeks prior to screening and ≥ 3 in the 2 weeks before baseline and a Clinical Global Impressions-Severity of Illness rating ≥ 4 at screen were eligible to participate. Outpatients received flexible-dose (75–225 mg/day) venlafaxine ER for 12 weeks. Treatment responders were randomly assigned to venlafaxine ER or placebo for 26 weeks. Criteria for response were ≤ 1 panic attack per week during the last 2 weeks of open-label treatment and a Clinical Global Impressions-Improvement score of 1 or 2. The primary endpoint, time to relapse during double-blind treatment, defined as ≥ 2 full symptom panic attacks per week for 2 consecutive weeks or discontinuation due to loss of effectiveness, was evaluated using Kaplan-Meier survival analysis. The study was conducted between December 2001 and August 2003.

Results: The intent-to-treat population had 291 patients in the open-label phase and 169 in the double-blind phase (placebo, N = 80; venlafaxine ER, N = 89; mean daily dose 165–171 mg). Time to relapse was significantly longer with venlafaxine ER than placebo ($p < .001$). All secondary measures of panic attack treatment efficacy, quality of life, and disability were significantly better with venlafaxine ER than placebo ($p \leq .005$).

Conclusion: Venlafaxine ER was safe, well tolerated, and effective in preventing relapse in outpatients with panic disorder.

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In the past 2 years, Dr. Ferguson has been a principal investigator on at least 1 CNS clinical trial for Amylin, Alkermes, Arena, Bristol-Myers Squibb, Cephalon, Eisai, Forest, Fujisawa, Eli Lilly, Merck, Mitsubishi, Myriad Genetics, Neurocrine, Novartis, Johnson & Johnson, Pfizer, Sanofi-Aventis, Sepracor, Shire, Solvay, Takeda, and Wyeth; has had consulting contracts with Wyeth, Merck, and Shire; and has been a shareholder in Forest, Sanofi-Aventis, and Dr. Reddy's Laboratories. Drs. Mangano and Entsuah and Mr. Tzanis are employees of Wyeth, and Mr. Tzanis is a shareholder in Wyeth. Dr. Khan reports no additional financial or other relationship relevant to the subject of this article.

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Panic disorder is a chronic, disabling illness associated with substantial psychiatric comorbidity and considerable cost to the individual and society.[1–3] Between one third and two thirds of patients with a history of panic disorder have experienced at least 1 episode of major depression.[4–8] Longitudinal studies lasting up to 20 years suggest that only 10% to 35% of treated patients with panic disorder achieve full remission[9–14] and that many patients who have achieved remission experience relapse.[10,15,16]

The tricyclic agent imipramine was the first antidepressant shown to be effective in the treatment of panic disorder, as reported by Klein in 1964.[17] Subsequent studies demonstrated the efficacy of imipramine[18,19] and clomipramine,[20,21] both of which inhibit serotonin and norepinephrine reuptake. Desipramine, which primarily inhibits the reuptake of norepinephrine, was only modestly effective in the treatment of patients with panic disorder.[22] A small maintenance study by Mavissakalian and Perel[23] and a much larger relapse prevention study by the same investigators[24] demonstrated the efficacy of maintenance therapy with imipramine in preventing relapse of panic disorder.

The selective serotonin reuptake inhibitors (SSRIs) are comparable in efficacy to tricyclic antidepressants but

demonstrate better safety and tolerability, making them the treatment of choice for panic disorder.[2,25,26] Although alprazolam and clonazepam are also approved for the treatment of panic disorder, SSRIs are preferred to benzodiazepines as first-line treatment because they lack the sedating, cognitive, and motor effects; interactions with alcohol; and risk of dependency associated with benzodiazepines.[2,25,26]

The American Psychiatric Association Practice Guidelines for the Treatment of Patients With Panic Disorder[25] acknowledge the effectiveness of both pharmacologic treatment and cognitive-behavioral therapy for the treatment of panic disorder. Acute treatment using either form of therapy lasts for approximately 12 weeks. The guidelines recommend continuation of treatment for an additional 12 to 18 months or longer for patients with residual symptoms. Treatment discontinuation is recommended only for the patients who experience significant improvement or full resolution of their symptoms. The Consensus Statement on Panic Disorder from the International Consensus Group on Depression and Anxiety[26] and the World Council of Anxiety Recommendations for the Long-Term Treatment of Panic Disorder[2] advise 12 months of acute treatment for panic disorder, followed by 1 to 2 years of additional treatment or more when clinically indicated.

Evidence from double-blind, randomized clinical trials using SSRIs such as fluoxetine,[27,28] paroxetine,[29–31] sertraline,[31–34] or citalopram,[35] or the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine extended release (ER),[36–38] supports the use of these agents in the short-term treatment of panic disorder. To date, few randomized clinical trials have investigated the effects of longer term treatment with these agents in preventing relapse.[39–43]

In the first long-term study[39] of paroxetine for the treatment of panic disorder, after 12 weeks of acute-phase, double-blind treatment, relapse rates during the subsequent 36 weeks of continuation treatment were 10.8% (4 patients) for placebo compared with 8.3% (5 patients) for paroxetine, the study drug, and 6.0% (3 patients) for clomipramine, the active comparator. The discontinuation rate due to adverse events was 19% for clomipramine compared with 7% for paroxetine and 9% for placebo. In a second study[40] of paroxetine, patients received 10 weeks of acute-phase treatment followed by an additional 12 weeks of continuation treatment. In the placebo group, 29.7% (11 patients) relapsed, compared with 4.7% (2 patients) who relapsed in the paroxetine group ($p < .002$).

In a study[41] in which panic disorder patients received 10 weeks of acute-phase treatment with fluoxetine followed by 24 weeks of continuation-phase treatment with fluoxetine or placebo, 3% (1 patient) in the fluoxetine continuation group relapsed (defined as worsening of Clinical Global Impressions-Improvement [CGI-I] score ≥ 4 for 2 consecutive visits) compared with 8% (4 patients) in the placebo group, a difference that was not statistically significant. Additionally, 2 patients who continued taking fluoxetine discontinued treatment because of lack of efficacy compared with 7 patients taking placebo.

In a study by Rapaport and colleagues,[42] 398 patients with panic disorder received 52 weeks of open-label treatment with flexible-dose sertraline. Responders received an additional 28 weeks of double-blind treatment with sertraline (N = 90) or placebo (N = 90). Roughly 69% of the patients in the sertraline group completed the double-blind phase compared with 49.4% of patients in the placebo group. Twelve percent of those receiving active drug withdrew due to relapse or insufficient response compared with 23.6% of patients in the placebo group ($p = .040$). Thirteen percent of patients treated with sertraline had an exacerbation of their panic disorder symptoms compared with 33% in the placebo treatment group ($p = .013$).[42]

In another long-term study,[43] 475 patients with panic disorder were randomly assigned to 8 weeks of double-blind acute treatment with fixed dosage ranges of citalopram (10 or 15 mg/day, 20 or 30 mg/day, or 40 or 60 mg/day), 1 dosage range of clomipramine (60 or 90 mg/day), or placebo, with 279 patients agreeing to continue treatment up to 1 year (including the acute phase) at their assigned doses. In this study, however, eligible patients were those who were expected to benefit from continued treatment rather than those who had achieved acute treatment response, the criterion used in the above drug efficacy trials for panic disorder. The proportion of patients who withdrew prior to the 12-month endpoint because of reported ineffectiveness was significantly greater in the placebo group than in the groups treated with citalopram ($p = .04$). Cumulative response rates were also significantly higher in all citalopram groups and in the clomipramine group compared with the placebo group for patients who completed the 1-year treatment period.

Naturalistic studies of patient populations treated with a variety of antipanic medications and psychotherapies provide another method of assessing the tendency for patients with panic disorder to relapse after achieving remission. A study conducted by the Harvard-Brown Anxiety Disorders Research Program of 78 patients who achieved a 2-month period of sustained remission on benzodiazepines, antidepressants, or a combination found that 46.2% relapsed within 2 years of follow-up. Fifty percent of patients who continued to receive "inadequate" or "possibly adequate" pharmacologic treatment relapsed, compared with 40% or fewer patients who continued to receive "adequate" or "intensive" pharmacotherapy.[16] Only 27% of patients received SSRIs, however, in part because the data were collected from 1991 to 1994.

Toni and associates[15] conducted a prospective, naturalistic study of 326 patients with panic disorder and agoraphobia who received pharmacologic treatment (39.0%

received imipramine, 28.5% clomipramine, and 23.3% other antidepressants). They found that the probability of a patient achieving at least 1 remission was 96.5% for panic disorder and 95.9% for agoraphobia over the course of 3 years of follow-up. Roughly 67% of patients experienced a relapse of panic disorder during the 3-year follow-up period.

Although naturalistic studies more closely approximate the conditions of clinical practice than controlled efficacy trials, they must be interpreted with caution, since randomization is not used in assigning pharmacologic or other treatment modalities, such as cognitive-behavioral therapy. Nevertheless, results of naturalistic studies suggest that panic disorder is a chronic, relapsing illness, even in patients who achieve sustained acute-phase remission and continue to receive adequate treatment.[16]

Recently, antidepressants with mechanisms of action other than selective serotonergic reuptake inhibition have been investigated for the treatment of panic disorder. The noradrenergic agent reboxetine has shown efficacy in the treatment of panic disorder in a randomized, double-blind, placebo-controlled trial.[44] A randomized single-blind study comparing paroxetine and reboxetine found that paroxetine was more effective than reboxetine in reducing the frequency of panic attacks, but not in reducing anticipatory anxiety or avoidance,[45] suggesting that norepinephrine and serotonin may play different roles in the pathophysiology and treatment of panic disorder.

The combined effect of serotonin and norepinephrine reuptake inhibition has been investigated in studies of the SNRI venlafaxine ER. In randomized, double-blind, placebo-controlled trials, venlafaxine ER has demonstrated efficacy in the treatment of depression,[46,47] generalized anxiety disorder,[48–50] social anxiety disorder,[51–55] and panic disorder[36–38] and is approved by the U.S. Food and Drug Administration for all 4 indications. Venlafaxine ER also has demonstrated efficacy in the treatment of major depressive disorder with comorbid generalized anxiety disorder.[56]

The primary objective of the current study was to investigate the efficacy of continuation treatment in relapse prevention with venlafaxine ER versus placebo in outpatients who had responded to open-label venlafaxine ER treatment for panic disorder.

METHOD

A total of 52 research sites in Australia, Canada, Denmark, France, Hungary, Italy, Poland, and the United States participated in this randomized, double-blind, placebo-controlled trial conducted between December 2001 and August 2003. The institutional review boards of all participating centers approved the study protocol, research sites, and consent documents. Written informed consent was provided by all subjects.

Patient Population

Open-label phase (12 weeks). Inclusion criteria were as follows. Outpatients aged ≥ 18 years who met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) criteria for panic disorder with or without agoraphobia for at least 3 months before study day 1 (the first day of treatment) were eligible for the study. Participants had to have a score ≥ 4 on the Clinical Global Impressions-Severity of Illness (CGI-S)[57] subscale and ≥ 6 full-symptom panic attacks during the 2 weeks before the screening visit. In the 2 weeks between screen and baseline, they had to experience ≥ 3 full-symptom panic attacks per week. Patients had to have a Covi Anxiety Scale[58] total score greater than their Raskin Depression Scale[58] total score at the baseline visit. Women of childbearing potential had to have a negative serum pregnancy test result at screening, and sexually active women participating in the study had to use a medically acceptable form of contraception.

Patients were excluded if they had any clinically important medical condition that could compromise the study or be detrimental to the patient; any clinically significant current or predominant Axis I or II diagnosis other than panic disorder (with or without agoraphobia) within 6 months of study day 1; drug or alcohol dependence or abuse as defined in the DSM-IV within 1 year of study day 1; a history or presence of any psychotic illness, bipolar disorder, organic brain disease, clinically important head trauma, or seizure disorder; acute suicidality; positive urine drug screen for illicit drugs; cognitive-behavioral therapy within 30 days preceding study day 1; introduction or change in intensity of formal psychotherapy within 60 days of study day 1; or a screening or baseline Montgomery-Asberg Depression Rating Scale (MADRS)[59] score ≥ 22.

Patients were also excluded if they had used investigational drugs, investigational procedures, electroconvulsive therapy, antipsychotics, fluoxetine, or triptans within 30 days of study day 1; had used antidepressants (other than fluoxetine), monoamine oxidase inhibitors, lithium, sedative hypnotics other than zaleplon or zolpidem, stimulants, or any herbal or homeopathic products intended to treat anxiety, depression, or insomnia within 14 days of study day 1; or had used benzodiazepines or similar anxiolytics or nonpsychopharmacologic drugs with psychotropic effects within 7 days of study day 1 (except nonpsychopharmacologic drugs taken at a stable dose for at least 3 months before study day 1). Treatments that were prohibited during study participation included any treatment prohibited before study day 1.

Double-blind phase (26 weeks). Patients who completed the 12-week open-label treatment phase were considered responders and therefore eligible for the double-blind continuation phase if they had ≤ 1 full-symptom panic attack per week during the last 2 weeks of open-

label treatment and a Clinical Global Impressions-Improvement (CGI-I)[57] score of 1 or 2 relative to their baseline score.

Study Design

This study was designed to show that successful short-term treatment of panic disorder (12 weeks) can be maintained with continued treatment, that there were benefits to the patient beyond the reduction in frequency of panic attacks, and that the treatment was safe and tolerable. The study included a 2-week baseline phase, a 12-week open-label efficacy and safety phase, and a 26-week double-blind continuation phase for patients who responded during the open-label phase, experienced no significant adverse effects, and were willing to continue in the double-blind phase. Patients eligible to participate in the double-blind continuation phase were randomly assigned to receive either venlafaxine ER or placebo. During the transition from the open-label to double-blind phase of the study, patients took the same number of capsules per day of study medication as they had taken during the open-label phase of the study to preserve blinding. Patients assigned to continuation treatment with placebo had their open-label dosage tapered down for 2 weeks or longer if medically indicated. Those assigned to treatment with venlafaxine ER continued to receive their open-label dosage for up to 6 months of double-blind treatment, followed by a poststudy taper off medication of 14 ± 3 days.

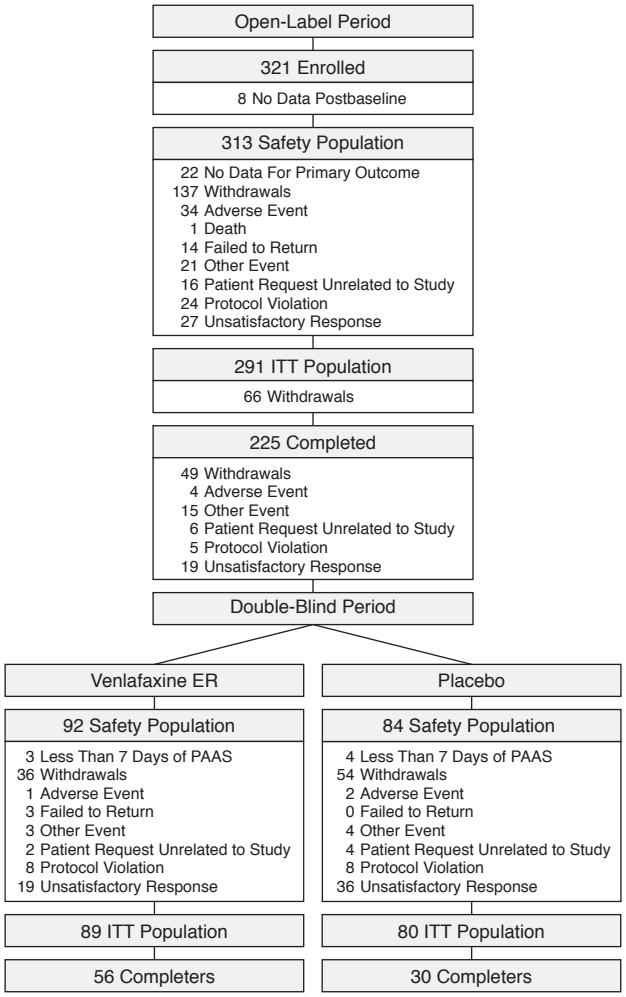
For the first week of the open-label phase, patients received 37.5 mg of venlafaxine ER, which was increased to 75 mg at day 8. Patients were required to maintain a minimum daily dose of 75 mg during the trial. Investigators could increase a patient's dosage by 75 mg on days 15 and 22, up to a maximum of 225 mg/day if clinically indicated. Patients who could not tolerate the minimum daily dose were withdrawn from the study. Dose changes were not allowed after week 8.

The study flowchart is shown in Figure 1. During the open-label phase, patients were required to have at least 1 on-therapy evaluation on the primary efficacy variable during visits 3 through 10. Twenty-two patients did not have a sufficient number of on-therapy primary efficacy evaluations during the open-label phase to qualify for inclusion in the intent-to-treat population.

During the double-blind phase, patients were required to have at least 1 on-therapy evaluation on the primary efficacy variable during study visits 11 through 18. Seven patients had some efficacy data, but did not have a sufficient number of on-therapy primary efficacy evaluations during the double-blind phase to qualify for inclusion in the intent-to-treat population.

Patients who had a recurrence of panic attacks during the double-blind continuation phase were instructed to contact the investigator, who determined whether the panic attacks met the criteria for relapse. Relapse of panic disorder was defined as having ≥ 2 full-symptom unexpected or situational panic attacks per week for 2 consecutive weeks or having been discontinued from the double-blind phase because of loss of effectiveness, as determined by the investigators.

Figure 1. Study Flowchart



Abbreviations: ER = extended release, ITT = intent to treat, PAAS = Panic and Anticipatory Anxiety Scale.

Efficacy Measures

The primary efficacy endpoint was the time to relapse for patients who entered the double-blind continuation phase of the study. A number of secondary measures were used to further evaluate efficacy, psychiatric disability, and improvement in quality of life during the open-label and double-blind phases. The secondary efficacy measures included (1) the percentage of patients having no full-symptom panic attacks in the previous 2-week period; (2) Panic Disorder Severity Scale (PDSS)[60] total score; (3) the number of full-symptom panic attacks

during the 2-week period; (4) CGI-S; (5) Phobia Scale[61] (fear and avoidance); (6) anticipatory anxiety; and (7) the percentage of patients with Panic and Anticipatory Anxiety Scale (PAAS)[61] limited panic attack symptoms. Full- and limited-symptom panic attacks during each 2-week period and the percentage of time patients experienced anticipatory anxiety were measured using the PAAS. Other analyses for the double-blind phase included the Hamilton Rating Scale for Anxiety (HAM-A)[62] and the MADRS scores. Health outcomes assessments included the Sheehan Disability Scale,[61] the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q),[63] and the Resource Utilization in Panic Disorder revised assessment (unpublished; available from the authors on request).

Statistical Analysis

Statistical analyses were based on pooling of data from individual study sites. Because of the large number of sites in this study, the data were grouped by geographic regions (North America, Eastern Europe, Western Europe, and Australia for pooled statistical analysis). The primary and secondary efficacy endpoints for the double-blind continuation phase were measured from the day of randomization (study day 85). Time to relapse was measured from the beginning of the double-blind phase (study day 1) until initial relapse and was analyzed using the Kaplan-Meier method. Multiple logistic regression was applied to secondary outcome measures that were proportions (e.g., the percentage of patients with no panic attacks and the response rates). The change from baseline in the number of full-symptom panic attacks was analyzed with Mann-Whitney U tests. The number of full-symptom panic attacks and the PDSS, Phobia Scale, CGI-S, HAM-A, and MADRS scores were analyzed using ranked score at baseline as a covariate.

Analysis of variance was used for the CGI-I based on ranks. One-way analysis of variance was used to test for comparability of treatment groups at baseline with respect to continuous variables like age and duration of panic disorder. A χ^2 test was used to compare treatment groups with respect to baseline nominal variables such as sex. Final efficacy ratings were conducted on the last day the patient took a full dose of medication or at the time of early discontinuation. In the double-blind phase, the final efficacy measurements were made prior to dose tapering or as soon as possible thereafter. A patient had to complete all visits up to and including day 266 to be considered an efficacy completer during the study. Statistical significance in this study was defined as $p \leq .05$, 2-tailed.

RESULTS

Patient Characteristics

Of the 321 patients who received study medication, 8 had no data collected and were excluded from the data analysis. Of the 225 patients who completed the open-label treatment phase, 176 continued into the double-blind treatment phase: 84 were blindly assigned to placebo and 92 to venlafaxine ER treatment. During the double-blind phase, all 176 patients were included in the safety analysis. There were no significant differences between the venlafaxine ER and placebo groups in baseline or demographic characteristics among patients who entered the double-blind phase (Table 1). Mean CGI-S scores at baseline for the double-blind phase were 2.21 for the placebo group compared with 2.08 for the venlafaxine ER group. Of the 86 patients who completed this phase of the study, 35% were in the placebo group and 65% were in the venlafaxine ER group.

During the open-label phase, 44% of patients in the safety population discontinued treatment. Adverse events

Table 1. Baseline and Demographic Characteristics, Safety Population

Characteristic	Open-Label Baseline Venlafaxine ER (N = 313)	Double-Blind Baseline Placebo (N = 84)	Double-Blind Baseline Venlafaxine ER (N = 92)
Age, mean ± SD, y	37.2 ± 11.3	39.5 ± 10.7	37.3 ± 10.9
Sex, N (%)			
Female	212 (68)	54 (64)	69 (75)
Male	101 (32)	30 (36)	23 (25)
Ethnic origin, N (%)			
Arabic	1 (< 1)	N/A	N/A
Black	12 (4)	2 (2)	1 (1)
Hispanic	25 (8)	9 (11)	6 (7)
Native American	1 (< 1)	N/A	1 (1)
Asian	3 (< 1)	1 (1)	N/A
Other	3 (< 1)	1 (1)	N/A
White	268 (86)	71 (85)	84 (91)
Weight[a], mean ± SD, kg	76.7 ± 19.9	76.9 ± 18.9	74.9 ± 18.2
Height, mean ± SD, cm	169.7 ± 9.3	169 ± 9.8	169 ± 8.9
Current panic disorder episode duration, mean, y	4.8 ± 7.5	5.3 ± 8.4	4.3 ± 7.1
Current panic disorder episode duration groups, N (%)			
0 to < 5 y	232 (74)	59 (70)	71 (77)
5 to < 13 y	46 (15)	15 (18)	11 (12)
13 to < 25 y	22 (7)	5 (6)	8 (9)
25 to < 49 y	12 (4)	5 (6)	2 (2)
Global severity rating, N (%)			
1	NA	17 (20)	24 (26)
2	NA	38 (45)	43 (47)
3	NA	25 (30)	21 (23)
4	NA	4 (5)	4 (4)
Full-symptom panic attacks from PAAS, mean ± SD[b]	NA	0.37 ± 0.64	0.34 ± 0.62
No. of full-symptom panic attacks, N (%)[b]			
0	NA	60 (71)	67 (74)
1	NA	17 (20)	17 (19)
2	NA	7 (8)	7 (8)

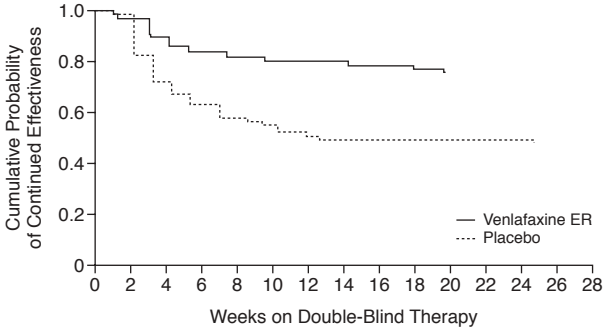
[a]Placebo, N = 77; venlafaxine ER, N = 87.
[b]In the 2 weeks before baseline.
Abbreviations: ER = extended release, NA = not applicable, PAAS = Panic and Anticipatory Anxiety Scale.

Table 2. Discontinuations by Primary Reason, Safety Population, N (%)

Reason	Open-Label Treatment (12 wk) Venlafaxine ER (N = 313)	Double-Blind Treatment (26 wk) Placebo (N = 84)	Double-Blind Treatment (26 wk) Venlafaxine ER (N = 92)	p Value[a]
Total	137 (44)	54 (64)	36 (39)	< .001
Adverse event	34 (11)	2 (2)	1 (1)	.606
Death	1 (< 1)	0	0	…
Failed to return	14 (4)	0 (0)	3 (3)	.247
Other event	21 (7)	4 (5)	3 (3)	.710
Patient request unrelated to study	16 (5)	4 (5)	2 (2)	.426
Protocol violation	24 (8)	8 (10)	8 (9)	1.000
Unsatisfactory response	27 (9)	36 (43)	19 (21)	.001

[a]Comparison of venlafaxine ER versus placebo during the double-blind phase using the Fisher exact test.
Abbreviation: ER = extended release.

Figure 2. Kaplan-Meier Survival Function Estimates (ITT population)



Abbreviations: ER = extended release, ITT = intent to treat.

were the most common reason for discontinuation (11%), followed by unsatisfactory response to treatment (9%).

During the double-blind phase, 51% of patients discontinued treatment. As shown in Table 2, discontinuations for any reason were significantly ($p < .001$) more common in the placebo group (64%) than in the venlafaxine ER group (39%). Unsatisfactory response was the most common reason for discontinuation during the double-blind phase. Significantly ($p = .001$) more patients in the placebo group (43%) than in the venlafaxine ER group (21%) discontinued treatment for lack of efficacy.

Efficacy

Open-label phase. The percentage of patients who were free of full-symptom panic attacks, as measured by the PAAS during the open-label phase, increased over time from no subjects at baseline to 69.1% at the 12-week endpoint in patients who completed the study, whereas mean PDSS total scores declined from 16.77 to 4.81, a mean decrease of 12.1 points from baseline. The percentage of CGI-I responders (CGI-I score = 1 or 2) was 95.4% by the end of the open-label phase.

Double-blind phase. The Kaplan-Meier survival analysis of time to relapse (Figure 2) indicates that venlafaxine ER showed significantly ($p < .001$) greater efficacy than placebo in preventing relapse in responders to open-label treatment during the double-blind phase. The relapse rate for the placebo-treated patients was 50.0% compared with a 22.5% relapse rate for venlafaxine ER–treated patients (Table 3). The cumulative probability of relapse for placebo-treated patients was 0.523 compared with 0.239 for venlafaxine ER–treated patients. In addition to preventing relapse, the overall efficacy of venlafaxine ER was maintained during the double-blind phase relative to placebo, with 76.4% of venlafaxine ER–treated patients remaining free of full-symptom panic attacks at the end of the double-blind phase compared with 55.0% of placebo-treated patients ($p = .004$; adjusted hazard ratio = 2.653; last observation carried forward). An observed-cases analysis showed 52.8% of venlafaxine ER–treated patients free of full-symptom panic attacks compared with 31.3% of placebo-treated patients ($p = .005$; adjusted hazard ratio = 2.475).

Venlafaxine ER–treated patients also had a statistically significant advantage over placebo-treated patients on all secondary efficacy measures at the final on-therapy evaluation (Tables 3 and 4), with the exception of the school and coursework item of the Q-LES-Q and the items included in the Resource Utilization in Panic Disorder revised assessment. Table 5 shows the effect sizes for selected final on-therapy outcomes, which ranged from 0.43 on the PAAS anticipatory anxiety item (percentage of time spent worrying about having another attack) to 0.77 on the HAM-A psychic anxiety subscale.

Beginning at week 2 of the double-blind continuation treatment phase, the mean change from baseline in PDSS total score was significantly greater for the group of patients treated with placebo than for those treated with venlafaxine ER, indicating a worsening of their panic disorder over time (Figure 3). The mean CGI-S score change from baseline was significantly greater for the placebo group than for the venlafaxine ER group beginning during this same time period, indicating a worsening of this group's overall disease severity (Figure 4). The mean change from baseline in Phobia Scale fear factor rating shows an increase (worsening) for placebo, which differed significantly from the relatively steep decline (improvement) for venlafaxine ER (Figure 5A). The mean increase in score from baseline in the Phobia Scale avoidance factor rating for the placebo group differed significantly from the decline in scores for the venlafaxine ER group, beginning at week 10 (Figure 5B).

Table 3. Selected Final On-Therapy Outcomes (double-blind phase)[a]

Outcome Measure	Placebo (N = 80)	Venlafaxine ER (N = 89)	p Value
Relapse rate,[b] N (%)	40 (50.0)	20 (22.5)	< .001
Free of full-symptom panic attacks,[c] N (%)	25 (31.3)	47 (52.8)	.005
Free of full-symptom panic attacks (week 26, LOCF)[c], N (%)	44 (55.0)	68 (76.4)	.004
Frequency of full-symptom panic attacks, mean[d]	3.42	1.26	< .001
Free of limited-symptom panic attacks (LOCF), N (%)	34 (42.5)	70 (78.7)	< .001
PDSS total score, mean	8.56	4.54	< .001
CGI-S score, mean	3.14	2.16	< .001
Phobia Scale score, mean			
Fear	22.11	11.65	< .001
Avoidance	9.08	5.49	< .001
Overall phobia state	3.55	1.89	< .001
Anticipatory anxiety (PAAS), mean[e]	14.09	7.65	.002
HAM-A score, mean			
Total	13.77	7.44	< .001
Somatic subscale	6.23	3.65	< .001
Psychic subscale	7.55	3.80	< .001
MADRS total score, mean	11.11	6.06	< .001

[a]Unless otherwise indicated, all values other than relapse rate are scores from the final on-therapy evaluation, and mean scores are unadjusted. P values are based on adjusted means, obtained using ranked analysis of covariance model: rank score = ranked baseline + treatment + center.
[b]p values obtained using log-rank statistics of Kaplan-Meier survival model.
[c]p values obtained using logistic regression model logit (response) = treatment + center.
[d]Number of attacks per 2-week period.
[e]Percentage of waking time spent worrying about future attacks.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, ER = extended release, HAM-A = Hamilton Rating Scale for Anxiety, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, PAAS = Panic and Anticipatory Anxiety Scale, PDSS = Panic Disorder Severity Scale.

Table 4. Sheehan Disability Scale and Quality of Life Enjoyment and Satisfaction Questionnaire Scores at Endpoint for the Double-Blind Phase (LOCF data, ITT population)[a]

Scale	Placebo (N = 71)	Venlafaxine ER (N = 79)	p Value
Sheehan Disability Scale			
Work	3.33	1.61	< .001
Social life and leisure activities	3.42	1.65	< .001
Family life and home responsibilities	1.39	1.64	< .001
Work and social disability	2.93	2.05	< .001
Quality of Life Enjoyment and Satisfaction Questionnaire			
Physical health and activities	3.31	3.70	.001
Subjective feelings of well-being	3.56	4.00	< .001
Work	3.70	4.09	.002
Household duties	3.66	4.05	< .001
School and coursework	3.79	3.33	.877
General activities	3.36	3.79	< .001
Satisfaction with medication	3.21	4.09	< .001
Leisure time activities	3.30	3.84	< .001
Social relations	3.55	3.96	< .001
Overall life satisfaction	3.30	3.80	.003

[a]Comparisons are for venlafaxine ER versus placebo, with p values obtained from ranked analysis of covariance model: ranked score = ranked baseline + treatment + center.
Abbreviations: ER = extended release, ITT = intent to treat, LOCF = last observation carried forward.

Safety

Venlafaxine dosing during the final on-therapy evaluation for the open-label and double-blind treatment phases is shown in Table 6. After the initial 7-day titration period during the open-label phase, mean daily doses of venlafaxine ER over the course of the subsequent 11 weeks ranged from 75.5 (SD ± 6.6) to 172.1 mg (SD ± 53.2). The mean daily dose of venlafaxine ER during the last 2 weeks of the open-label phase was 172.1 (SD ± 56.2). Over the course of the entire double-blind phase, mean daily doses of venlafaxine ER ranged from 164.9 (SD ± 56.9) to 170.8 (SD ± 56.4) mg.

Open-label phase. Adverse events were the most common reason for withdrawal during the open-label phase. Eleven percent of the patients in the safety population treated with venlafaxine ER discontinued treatment due to an adverse event. Nausea and anxiety (3% each) were the adverse events most frequently cited as the cause for withdrawal. The most common treatment-emergent adverse events reported by venlafaxine ER–treated patients (Table 7) were headache (38%), nausea (31%), dizziness (18%), and dry mouth (18%). One patient died during the study: a 43-year-old woman who was treated with venlafaxine ER in the open-label phase who was subsequently diagnosed as having lung cancer with liver metastases. In the investigator's opinion, this death was not related to the study drug. Two patients treated with venlafaxine ER during the open-label phase experienced clinically important increases in blood pressure, as judged by the medical monitor.

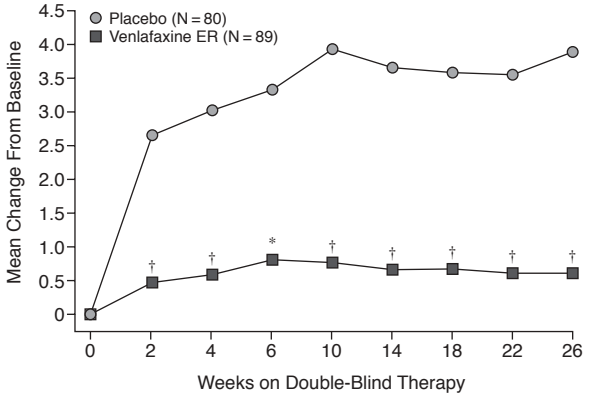
Double-blind phase. Unsatisfactory response (lack of efficacy) was the most common reason for discontinuation during the double-blind phase (placebo group, 43%; venlafaxine ER group, 21%). Patients treated with placebo were also more likely to withdraw from the study for any reason than patients treated with venlafaxine ER. Two percent of the patients in the placebo group and 1% of patients in the venlafaxine ER group discontinued treatment because of an adverse event. The adverse events that most frequently caused discontinuation in the placebo group during double-blind treatment were anxiety (5%) and dizziness (4%). The most common treatment-emergent adverse events are listed in Table 7. One patient treated with venlafaxine ER during the double-blind phase experienced a clinically important increase in blood pressure. No clinically important mean changes were observed in quantitative laboratory tests, vital signs, or electrocardiographic data.

Table 5. Effect Sizes for Selected Final On-Therapy Outcomes (unadjusted means)

Outcome Measure	Mean Score: Placebo	Mean Score: Venlafaxine ER	Pooled SD	Effect Size (venlafaxine ER – placebo)	95% CL of Effect Size
PDSS	8.56	4.54	5.95	0.67	0.36, 0.99
CGI-S	3.14	2.16	1.33	0.73	0.42, 1.05
Phobia Scale					
Fear	22.11	11.65	17.52	0.60	0.28, 0.91
Avoidance	9.08	5.49	7.54	0.48	0.17, 0.79
Overall phobia state	3.55	1.89	2.31	0.72	0.40, 1.04
Anticipatory anxiety (PAAS)[a]	14.09	7.65	15.14	0.43	0.12, 0.73
HAM-A					
Total	13.77	7.44	8.56	0.74	0.41, 1.07
Somatic subscale	6.23	3.65	4.09	0.63	0.30, 0.96
Psychic subscale	7.55	3.80	4.87	0.77	0.44, 1.10
MADRS	11.11	6.06	8.22	0.61	0.29, 0.94

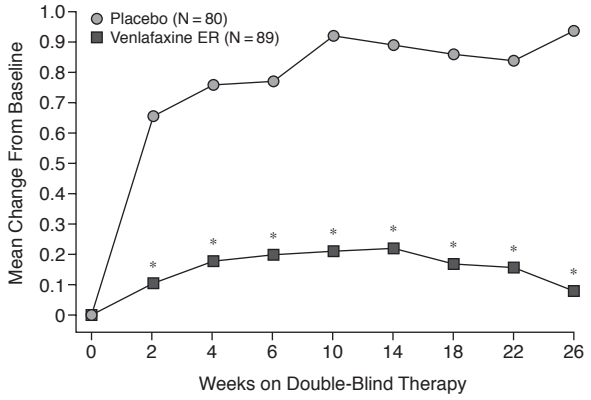
[a]Percentage of waking time spent worrying about future attacks.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, CL = confidence limits, ER = extended release, HAM-A = Hamilton Rating Scale for Anxiety, MADRS = Montgomery-Asberg Depression Rating Scale, PAAS = Panic and Anticipatory Anxiety Scale, PDSS = Panic Disorder Severity Scale.

Figure 3. Change in Panic Disorder Severity Scale Total Score (ITT population, LOCF)



*p < .01 venlafaxine ER vs. placebo.
†p < .001 venlafaxine ER vs. placebo.
Abbreviations: ER = extended release, ITT = intent to treat, LOCF = last observation carried forward.

Figure 4. Change in CGI-S Total Score (ITT population, LOCF)



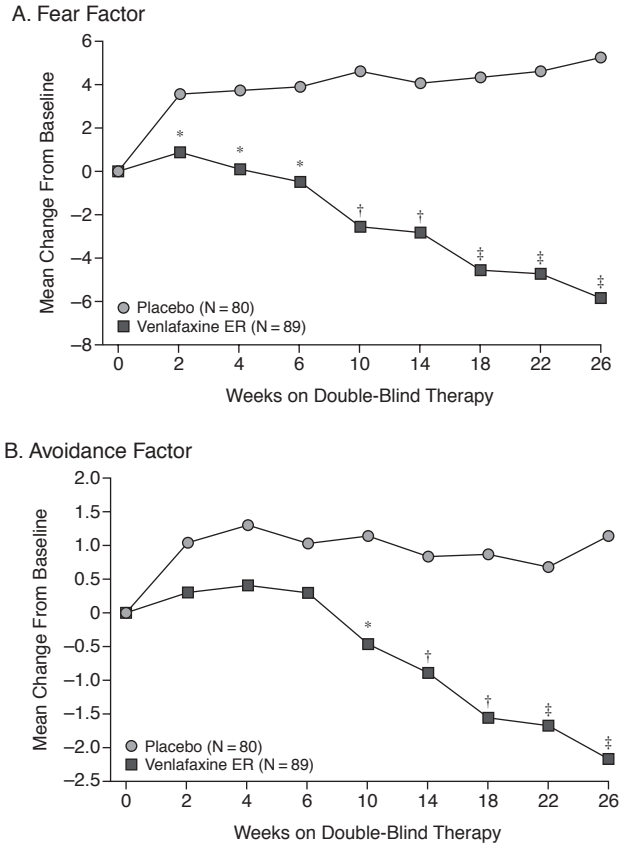
*p < .001 venlafaxine ER vs. placebo.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, ER = extended release, ITT = intent to treat, LOCF = last observation carried forward.

DISCUSSION

The results of this study showed that venlafaxine ER had significantly greater efficacy than placebo in preventing relapse in patients who had responded to open-label, acute treatment. Differences between the venlafaxine ER and placebo groups were statistically significant on the primary efficacy outcome measure and all secondary efficacy outcome measures, with the exception of 1 Q-LES-Q item (school and coursework) and the items comprising the Resource Utilization in Panic Disorder revised assessment. It should be noted that patients who were not students may not have understood the conventions for completing the school/coursework item, which may account for the lack of a significant between-group difference on this item.

The time to relapse was significantly longer and the cumulative relapse rate was significantly lower for venlafaxine ER–treated patients during the double-blind continuation phase. The proportion of patients who were free of full- and limited-symptom panic attacks was significantly higher and the frequency of each type of panic attack was significantly lower in the venlafaxine ER group than in the placebo group. Venlafaxine ER also showed a significant advantage over placebo on the PDSS, CGI-S, Phobia Scale fear and avoidance factors and overall phobia state, percentage of time patients spent experiencing anticipatory anxiety, HAM-A total and somatic and psychic subscales, MADRS, Sheehan Disability Scale, and Q-LES-Q. Large effect sizes (≥ 0.6) were observed for scores on the PDSS, CGI-S, Phobia Scale fear factor and

Figure 5. Change in Phobia Scale Scores (ITT population, LOCF)



*p < .05 venlafaxine ER vs. placebo.
†p < .01 venlafaxine ER vs. placebo.
‡p < .001 venlafaxine ER vs. placebo.
Abbreviations: ER = extended release, ITT = intent to treat, LOCF = last observation carried forward.

Table 6. Venlafaxine ER Dose Level During the Last 2-Week Phase of Each Study Phase[a]

Days on Therapy	N	Daily Dose (mg), Mean ± SD
Open-label phase (days 71–84)	231	172.1 ± 53.2
Double-blind phase (days 85–266)	59	165.6 ± 54.2

[a]After the initial 7-day titration phase during the open-label phase, mean daily doses of venlafaxine ER ranged from 75.5 to 172.1 mg. During the double-blind phase, mean daily doses of venlafaxine ER ranged from 164.9 to 170.8 mg. The mean daily dose was 164.9 mg for patients who continued venlafaxine ER treatment during the initial 2-week phase of the double-blind phase.
Abbreviation: ER = extended release.

Table 7. Commonly Reported (≥ 5% in any treatment group) Double-Blind Treatment-Emergent Adverse Events: Number (%) of Patients

	Open-Label Phase (12 wk), Venlafaxine ER	Double-Blind Phase	
Adverse Event	(N = 313)	Placebo (N = 84)	Venlafaxine ER (N = 92)
Any adverse event	267 (85)	60 (71)	71 (77)
Body as a whole			
Abdominal pain	23 (7)	3 (4)	4 (4)
Accidental injury	8 (3)	3 (4)	7 (8)
Asthenia	38 (12)	6 (7)	7 (8)
Back pain	12 (4)	5 (6)	3 (3)
Headache	119 (38)	16 (19)	26 (28)
Infection	26 (8)	9 (11)	15 (16)
Pain	11 (4)	2 (2)	5 (5)
Cardiovascular system			
Hypertension	13 (4)	0 (0)	5 (5)
Digestive system			
Anorexia	30 (10)	2 (2)	0
Constipation	27 (9)	0	4 (4)
Diarrhea	25 (8)	5 (6)	9 (10)
Dry mouth	55 (18)	0	2 (2)
Nausea	98 (31)	12 (14)	8 (9)
Nervous system			
Anxiety	26 (8)	9 (11)	1 (1)
Depression	3 (< 1)	5 (6)	2 (2)
Dizziness	56 (18)	15 (18)	9 (10)
Insomnia	59 (19)	11 (13)	4 (4)
Nervousness	26 (8)	6 (7)	5 (5)
Somnolence	41 (13)	1 (1)	4 (4)
Tremor	19 (6)	2 (2)	3 (3)
Respiratory system			
Pharyngitis	13 (4)	7 (8)	8 (9)
Sinusitis	6 (2)	3 (4)	5 (5)
Sweating	38 (12)	1 (1)	1 (1)

Abbreviation: ER = extended release.

overall phobia state, HAM-A total and somatic and psychic anxiety subscales, and MADRS. Moderate effect sizes (0.4 to < 0.6) were found on the Phobia Scale avoidance factor and PAAS anticipatory anxiety items.

Adverse events and the results of laboratory tests, vital signs, and electrocardiographic data observed with venlafaxine ER in this study were similar to those observed in premarketing studies for depression, generalized anxiety disorder, and social anxiety disorder.[64] In general, the incidence and severity of treatment-emergent adverse events were similar between treatment groups. Venlafaxine ER–treated patients were significantly less likely to withdraw from the study for any reason than patients treated with placebo ($p < .001$).

This study demonstrates the robust efficacy of venlafaxine ER in preventing relapse using a randomization-after-treatment design in the absence of adjunctive pharmacologic or psychosocial treatment, while reaffirming the need for continuation therapy in patients with panic disorder noted by Klein[17] and later clinical investigators.[2,25,26] Conclusions regarding the efficacy of continuation treatment over a longer time period and the efficacy to be expected when treating a general clinical population also cannot be made on the basis of our findings. In the absence of a head-to-head comparison, we cannot compare these outcome data for venlafaxine ER, a drug with a dual mechanism of action, with the efficacy of SSRIs, a class of drugs with a single mechanism of action. Considerable evidence, however, suggests the involvement of norepinephrine, as well as serotonin, in the pathophysiol-

ogy of panic disorder, although the roles of the 2 neurotransmitters in this illness are not well understood.[65–68]

Of the studies published to date, our findings most closely resemble those obtained in the long-term sertraline discontinuation trial by Rapaport and colleagues,[42] which found that the rate of withdrawals due to relapse or insufficient response was roughly twice as high in the placebo-substitution group as in the active treatment group during the double-blind continuation phase. Our study found a relapse rate of 22.5% for the group that continued treatment with venlafaxine ER compared with 50.0% for the group that continued treatment with placebo and a withdrawal rate due to insufficient response of 21% for the venlafaxine ER group compared with 43% for the placebo group. It should be noted, however, that the duration of the open-label phase of the sertraline study[42] (52 weeks, followed by a 28-week discontinuation trial) was much longer than that of the present study (12 weeks) and that the 2 studies differed in other important respects.

To address the possibility that the higher relapse rate in the placebo group than in the venlafaxine ER group might be attributable to withdrawal effects in patients switched to placebo, we performed an additional analysis comparing the 2 groups, excluding the first 2 weeks of the double-blind continuation phase, when such effects would be most likely. The relapse rate was 14.6% for the group that continued to receive venlafaxine ER compared with 35.0% for the group that continued to receive placebo ($p < .001$), suggesting that withdrawal effects in the placebo group could not account for the greater efficacy of venlafaxine ER in preventing relapse of panic disorder.

Overall, the results of this study demonstrate that venlafaxine ER is safe, well tolerated, and effective in the long-term treatment and prevention of relapse in patients with panic disorder. Further studies of the efficacy of SNRIs in the long-term treatment and prevention of relapse of panic disorder are warranted.

Drug names: alprazolam (Xanax and others), citalopram (Celexa and others), clomipramine (Anafranil and others), clonazepam (Klonopin and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others), zaleplon (Sonata), zolpidem (Ambien).

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