A Randomized Controlled Trial of Venlafaxine Extended Release in Generalized Social Anxiety Disorder

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Background: Generalized social anxiety disorder is a debilitating psychiatric illness characterized by maladaptive thoughts about social situations. This double-blind study evaluated the anxiolytic efficacy, safety, and tolerability of venlafaxine extended release (ER) in adult outpatients with generalized social anxiety disorder.

Method: Patients were randomly assigned to receive 12 weeks of treatment with a flexible dose of venlafaxine ER (75 to 225 mg/day) or placebo. The Liebowitz Social Anxiety Scale (LSAS) total score was the primary efficacy variable. Secondary efficacy variables included scores on the Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales, Social Phobia Inventory (SPIN), and LSAS subscales. Response was defined as a CGI-I score of 1 or 2. Two definitions of remission were used: LSAS total score ≤ 30 and CGI-I score of 1.

Results: Data from 271 patients (intent-to-treat population) were analyzed for efficacy; 279 patients were analyzed for safety. Overall, 173 patients completed the study. Improvement on the LSAS was significantly greater with venlafaxine ER treatment than with placebo at weeks 6 through 12 ($p < .05$, weeks 6 and 8; $p < .01$, week 10; and $p < .001$, week 12) and at weeks 8 through 12 based on CGI-S and SPIN scores. Week 12 response and remission (LSAS score ≤ 30) rates were significantly greater in the venlafaxine ER group than in the placebo group (response: 44% vs. 30%, respectively, $p = .018$; remission: 20% vs. 7%, respectively, $p < .01$). Patients experienced no unexpected or serious adverse events.

Conclusion: Venlafaxine ER is safe, well tolerated, and efficacious in the short-term treatment of generalized social anxiety disorder.

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Generalized social anxiety disorder is a chronic and insidious psychiatric disorder that first received widespread attention during the 1980s.[1] Social anxiety disorder has an early onset, typically between 14 and 16 years of age,[2,3] and subsequently follows a chronic course that persists well into adulthood. Spontaneous recovery is possible, but it occurs gradually and only in about half of all sufferers.[4]

Social anxiety disorder is characterized by a persistent fear of public performance, social situations that may expose the individual to scrutiny, or social interactions with unfamiliar people.[5] Individuals with social anxiety disorder fear that, in these situations, they may be evaluated negatively by others, which frequently will cause them to avoid social interaction. In addition to psychological symptoms, social anxiety disorder is associated with multiple physical symptoms (e.g., trembling, sweating) that are commonly observed in other anxiety disorders.[6] However, the primary physical symptom, blushing, is unique to social anxiety disorder.[6]

The consequences of social anxiety disorder include a substantial impact on psychosocial functioning and quality of life, as well as an economic impact. Individuals afflicted with social anxiety disorder consistently report greater levels of impairment on psychosocial functioning and life satisfaction scales compared with persons without social anxiety disorder.[7–9] The degree to which quality

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of life is affected appears to vary with the severity of symptoms and functional impairment.[8] Because patients with social anxiety disorder are more likely to be unemployed,[10,11] miss days of work or have decreased work productivity,[10,11] have lower household incomes,[11] and have different patterns of health care utilization compared with the general population,[11] the economic burden of social anxiety disorder is substantial.

Social anxiety disorder often goes undiagnosed by primary physicians, despite its impact on multiple functional domains and the heavy burden it places on the health care system.[3,12,13] A number of studies have outlined the prevalence of social anxiety disorder—2% to 16% of the general population experience social anxiety disorder at some time in their lives[6,9,12,14,15]—and its comorbidity with other psychiatric disorders[16] such as major depressive disorder (58.3% of social anxiety disorder patients), panic disorder, generalized anxiety disorder (27.8% and 30.6% of social anxiety disorder patients, respectively),[13,17] suicide attempts or ideation, and substance abuse (32% of social anxiety disorder patients).[2,3,18–20] In addition, social anxiety disorder may be a risk factor for the development of comorbid psychiatric disorders, particularly major depression.[3] Therefore, early recognition and treatment of social anxiety disorder have the potential to reduce the risk of other psychiatric disorders later in life.

Although the impact of social anxiety disorder on quality of life and the importance of successful treatment of symptoms have been recognized, there has been disagreement on how to define outcomes such as response and remission.[6] It has been proposed that response be defined as a stable, clinically meaningful improvement in which the patient no longer experiences the full range of symptoms, but continues to experience more than minimal symptoms, and that remission be defined as an almost complete resolution of symptoms for at least 3 months across all domains of social anxiety disorder.[6] However, specific criteria for these outcomes have not yet been firmly established. Response has been evaluated in many clinical trials and has been defined as a specified decrease in score on a rating scale for social anxiety disorder symptoms (e.g., the Liebowitz Social Anxiety Scale [LSAS])[21–23] or as a Clinical Global Impressions-Improvement scale (CGI-I) score of 1 (very much improved) or 2 (much improved).[24–27] Remission has not commonly been assessed or reported in antidepressant treatment studies for social anxiety disorder. Proposed criteria have included LSAS score ≤ 30 and/or CGI-I score of 1, which are correlated with minimal symptomatology and significant improvement, respectively.[28,29] Additionally, receiver operating curve analyses find an LSAS score of 30 to be the best cut point for distinguishing between individuals with and without social anxiety disorder.[29]

Serotonin reuptake inhibition with subsequent serotonin potentiation or postsynaptic stimulation is hypothesized to be a key mechanism in reducing the symptoms of generalized social anxiety disorder. For this reason, selective serotonin reuptake inhibitors (SSRIs) are successfully used in the treatment of symptoms of anxiety related to social anxiety disorder.[26,30–33] Venlafaxine extended release (ER), which exerts its effect via serotonergic and noradrenergic pathways,[34,35] has been shown to be effective and well tolerated in patients with symptoms of anxiety, including depressed patients with comorbid anxiety,[36] and in patients with generalized anxiety disorder.[37–39]

This study was undertaken to determine the anxiolytic efficacy, safety, and tolerability of venlafaxine ER in the treatment of generalized social anxiety disorder.

METHOD

Study Design

This was a randomized, double-blind, 12-week, placebo-controlled, parallel-group, flexible-dose study of treatment with venlafaxine ER (75 to 225 mg/day) in 279 outpatients at 13 sites in the United States and 6 in Canada who met the DSM-IV[5] criteria for generalized social anxiety disorder. The institutional review board independent ethics committee at each site preapproved the protocol used in this study. The study was conducted according to the Declaration of Helsinki, with written informed consent obtained from all patients prior to enrollment.

Prestudy Procedures

Patients were recruited from the principal investigator's medical practice or from advertising. Prospective study candidates were prescreened by interview to determine eligibility and willingness to participate. Screening included obtaining a medical, psychiatric, and employment history; confirming a primary diagnosis of generalized social anxiety disorder using the Mini-International Neuropsychiatric Interview[40]; completing a physical examination; and obtaining a standard 12-lead electrocardiogram (ECG). In addition, the LSAS,[41] Clinical Global Impressions-Severity of Illness scale (CGI-S),[42] Covi Anxiety Scale[43] and Raskin Depression Scale[44] (used together as a battery), and Hamilton Rating Scale for Depression (HAM-D)[45] scores were obtained during the prestudy visit. After a single-blind placebo lead-in period of 7 ± 3 days, eligible patients were randomly assigned to receive either venlafaxine ER (75 to 225 mg/day) or placebo for up to 12 weeks, with an optional dose-tapering period of up to 2 weeks.

Patient Selection

Inclusion criteria. Outpatients at least 18 years of age who met DSM-IV criteria for generalized social anxiety disorder for at least 6 months before study initiation were eligible for screening. Inclusion was dependent on a CGI-S (item 1) baseline score ≥ 4, LSAS baseline score ≥ 50 with a decrease of ≤ 30% between prestudy and baseline, and a

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Covi Anxiety Scale score greater than Raskin Depression Scale score (when Raskin Depression total score was ≤ 9 at prestudy with a score ≤ 3 on any single item).

Exclusion criteria. Individuals with a history of hepatic or medical disease (e.g., raised intraocular pressure, narrow angle glaucoma, cardiac arrhythmia, uncontrolled diabetes or hypertension, myocardial infarction within 6 months of prestudy), mental disorder due to a general medical condition, psychotic disorder or organic brain disease, seizure disorder, or head trauma were excluded from enrollment. Patients with clinically important Axis I or Axis II comorbidities were excluded from study participation if the disorder was current or was predominant within 6 months of the start of the study. Also excluded were patients with a history of alcohol abuse within 1 year of the study, those who regularly used alcohol, and those with a urine drug screen positive for drugs of abuse. Those with multiple drug allergies (including hypersensitivity to venlafaxine immediate release [IR] or venlafaxine ER) or a clinically meaningful abnormality in vital signs and findings from physical examination, ECG, laboratory tests, or urine drug screen were not included. Individuals who used the investigational drugs (venlafaxine IR or ER), antipsychotics, sedative hypnotic drugs, antidepressants, anxiolytics (including herbal products), or migraine medication (within 30 days of study initiation) or received electroconvulsive therapy within 6 months before the study or formal psychotherapy within 30 days of study day 1 were excluded, as were women of childbearing potential who were pregnant or breastfeeding or who did not utilize a medically acceptable form of contraception.

Drug Dosage

The amount of venlafaxine ER used in this study was based on safe and effective dosages used in earlier studies of major depression and generalized anxiety disorder. To optimize tolerability, study medication was taken once daily with food in either the morning or evening.

The venlafaxine ER regimen was a potentially 3-step dose-escalation process with an initial 75-mg/day dose during the first week ± 3 days. During the second week, the dose was increased to 150 mg/day (2 capsules) if clinically indicated to enhance response. The dose was increased to 225 mg/day (3 capsules) if clinically indicated on study day 15 ± 3 days. Although medication was not increased to more than 3 capsules daily, dose reduction to 75 mg/day (1 capsule) was allowed if necessary to improve tolerability. Patients receiving venlafaxine ER and placebo were given the same number of capsules. At study completion (or early termination), patients who had been taking more than 1 capsule daily for more than 1 week had their dose tapered. A patient was considered eligible for study termination if medication was missed for more than 3 consecutive days at a time or if the patient was < 80% compliant over a 2-week period.

Efficacy Evaluation

The primary efficacy variable was the LSAS total score, which was assessed at weeks 1, 2, 3, 4, 6, 8, 10, and 12. The intent-to-treat (ITT; patients who began the double-blind treatment phase, had at least 1 dose of study medication, and had at least 1 LSAS evaluation) population was the primary patient population (venlafaxine ER N = 133 and placebo N = 138). Secondary variables were scores on the CGI-S, CGI-I, Social Phobia Inventory (SPIN),[46] Sheehan Disability Scale (SDS),[47] and LSAS fear/anxiety and avoidance subscales and responder status (i.e., CGI-I rating of very much improved [score = 1] or much improved [score = 2]). The LSAS, CGI-S, CGI-I, and SPIN assessments were performed at baseline and on study days 7, 14, 21, 28, 42, 56, 70, and 84; the SDS was administered at baseline and on study days 28 and 84; and the HAM-D and Covi-Raskin scales were administered at the prestudy visit and on study days 42 and 84 as ancillary evaluations. Final ratings for efficacy were obtained on the last day of full dose administration before tapering or within 3 days of the last full dose. Day 84 measurements, for patients who discontinued before day 84, were obtained on the last day of full dose administration or within 3 days of the last full dose.

A post hoc analysis was performed to evaluate remission rates. Consistent with remission criteria proposed by Ballenger[28] and Mennin et al.,[29] 2 definitions of remission were used: LSAS score ≤ 30 and CGI-I score of 1.

Safety

Safety assessments were based on reports of adverse events, results of routine physical examinations, measurements of vital signs and weight, laboratory determinations, and ECGs. The information recorded was based on the signs or symptoms detected during the physical examination and clinical evaluation of the patient, and the patient's response to the question "How have you been feeling since your last visit?" If a patient discontinued from the study before 84 ± 3 days, safety assessments were obtained on the last day of full dose administration or as soon as possible thereafter. Patients were required to have fasted for at least 12 hours before testing. Two hundred seventy-nine patients were included in the safety evaluation.

Statistical Methods

Primary statistical models were changes from baseline on the LSAS total, LSAS fear and avoidance, SPIN, and SDS scores. Scores were analyzed using an analysis of covariance, with treatment and investigator as the main effects and the baseline score as the covariate. Changes from baseline on the CGI-S were analyzed using the analysis of variance (ANOVA) with treatment, investigator, and baseline CGI-S score as main effects. For comparisons of baseline characteristics between treatment

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groups, the baseline CGI-S scores were split into 2 categories (i.e., a score of 4 or ≥ 5) because only 17% of the patients had scores ≥ 6. CGI-I results were analyzed using the same model as the CGI-S, except there was no baseline CGI-I score to enter into the model. Scores were calculated on a last-observation-carried-forward (LOCF) basis on ITT patients. Finally, investigator-by-treatment interaction terms were not included in the models because the p values for this term were above .10. This criterion was specified in the protocol. The investigator-by-treatment interaction term was not significant for the LSAS total, SPIN, or CGI-S (week 12 LOCF).

Secondary statistical models were also used. The first model was a mixed-effects ANOVA with the LSAS total score as the outcome variable. The null hypothesis was that the average slope of the LSAS-by-time would be the same in the 2 treatment groups, in which time was expressed as the relative day with baseline included (time = 0). The slopes and intercepts for the LSAS-by-time regression line were fit for individual patients and treated as random effects with an unstructured covariance matrix (the investigator was included as a categorical variable). The second model using the LSAS score was the Entsuah Endpoint Ranking Procedure with the equal-spaced scoring system.[48] The final secondary statistical model was an ANOVA using the ranks of the scores, in which both the baseline and outcome scores were ranked without regard to any covariate. In this case, the statistical model was the same as the primary model.

RESULTS

Of the 280 patients randomly assigned into the double-blind study, 271 patients were included in the ITT efficacy analyses and 279 were included in the safety population. One hundred thirty-nine patients were randomly assigned to receive venlafaxine and 140 patients to placebo.

A comparable number of patients in each treatment group completed the study, i.e., 88 in the venlafaxine group and 85 in the placebo group. Significantly more patients in the placebo group (15%) than in the venlafaxine group (2%) discontinued treatment because of unsatisfactory response ($p < .001$), while significantly more patients in the venlafaxine group discontinued treatment because of adverse events (17% vs. 6%; $p < .004$). The adverse events that most frequently caused discontinuation of treatment were nausea (5%), dizziness (4%), and insomnia (4%).

There were no significant differences between treatment groups for any of the demographic or baseline characteristics (Table 1), nor did the demographic and baseline characteristics of the ITT patient population differ appreciably from those of the safety population. Mean baseline LSAS total scores were relatively high (> 85) in both treatment groups.

Table 1. Demographic and Baseline Characteristics of Intent-to-Treat Population

Characteristic	Placebo (N = 138)	Venlafaxine ER (N = 133)
Age, mean ± SD (range), y	35.9 ± 11.4 (18–70)	34.9 ± 11.7 (18–65)
Sex, N (%)		
Women	64 (46)	59 (44)
Men	74 (54)	74 (56)
Ethnic origin, N (%)		
White	112 (81)	106 (80)
Black	7 (5)	9 (7)
Hispanic	8 (6)	7 (5)
Asian	5 (4)	8 (6)
Other	6 (4)	3 (2)
Weight, mean ± SD (range), kg	78.7 ± 20.0 (47–156)	77.7 ± 17.2 (45–136)
Duration of current illness, mean ± SD (range), y	22.4 ± 13.5 (0–61)	21.0 ± 14.1 (0–60)
Baseline scores		
LSAS total, mean ± SD (range)	86.75 ± 19.74 (50–140)	91.07 ± 19.01 (50–133)
CGI-S score, N (%)		
4	69 (50.0)	52 (39.1)
5	49 (35.5)	56 (42.1)
6	20 (14.5)	23 (17.3)
7	0 (0)	2 (1.5)

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, ER = extended release, LSAS = Liebowitz Social Anxiety Scale.

Efficacy Outcomes

Liebowitz Social Anxiety Scale. Venlafaxine-treated patients had significantly lower adjusted mean LSAS total scores than placebo-treated patients at weeks 6 through 12 ($p < .05$ at weeks 6 and 8, $p < .01$ at week 10, and $p < .001$ at week 12) (Figure 1). An analysis of scores on the fear/anxiety subscale of the LSAS indicated that venlafaxine was significantly more effective than placebo at weeks 6 through 12 ($p < .05$ at weeks 6 and 8, $p < .01$ at week 10, and $p < .001$ at week 12). The LSAS avoidance analyses showed similar results, except that a significant difference ($p < .05$) was also seen at week 1.

Clinical Global Impressions scale. Venlafaxine-treated patients had significantly lower adjusted mean CGI-S scores at weeks 8 through 12 ($p < .05$ at week 8 and $p < .001$ at weeks 10 and 12) (Figure 2) and significantly lower CGI-I scores at weeks 6 through 12 ($p < .05$ at weeks 6 and 8, $p < .01$ at week 10, and $p < .001$ at week 12) than placebo patients.

Social Phobia Inventory. Adjusted mean SPIN scores were significantly lower for venlafaxine-treated patients compared with placebo-treated patients at weeks 8 through 12 ($p < .05$ at weeks 8 and 10 and $p < .01$ at week 12). The adjusted mean change from baseline was –8.5 in the placebo group and –13.3 in the venlafaxine ER group at week 12.

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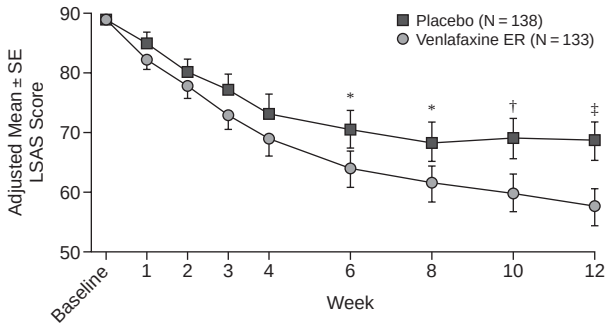
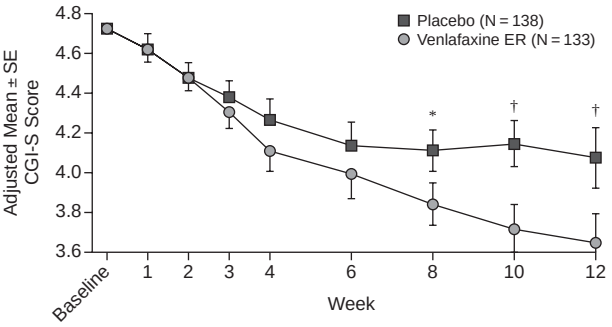
Figure 1. Adjusted Mean ± SE Total LSAS Scores for Venlafaxine ER vs. Placebo Over the 12-Week Treatment Period[a]



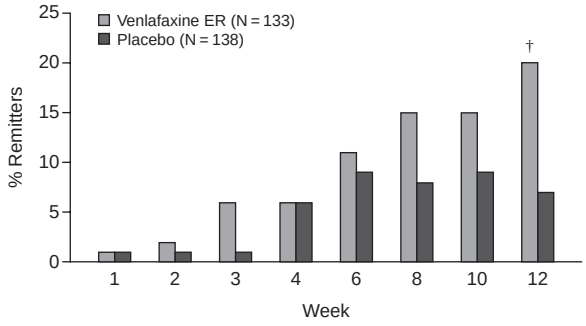
[a]Intent-to-treat population, last-observation-carried-forward analysis.
*p < .05, venlafaxine score significantly less than placebo score.
†p < .01, venlafaxine score significantly less than placebo score.
‡p < .001, venlafaxine score significantly less than placebo score.
Abbreviations: ER = extended release, LSAS = Liebowitz Social Anxiety Scale.

Figure 2. Adjusted Mean ± SE CGI-S Scores for Venlafaxine ER vs. Placebo Over the 12-Week Treatment Period[a]



[a]Intent-to-treat population, last-observation-carried-forward analysis.
*p < .05, venlafaxine score significantly less than placebo score.
†p < .001, venlafaxine score significantly less than placebo score.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, ER = extended release.

Figure 3. Percentage of Remitters (LSAS score ≤ 30) for Venlafaxine ER vs. Placebo Over the 12-Week Treatment Period[a]



[a]Last-observation-carried-forward analysis.
†p < .01, venlafaxine versus placebo.
Abbreviations: ER = extended release, LSAS = Liebowitz Social Anxiety Scale.

Response

Response to treatment was defined as a CGI-I rating of very much improved (score = 1) or much improved (score = 2). Significantly more venlafaxine-treated patients were classified as responders compared with placebo-treated patients at weeks 10 (41% vs. 28%; p < .05) and 12 (44% vs. 30%; p = .018).

Sheehan Disability Scale

In assessing health outcomes, the SDS results after venlafaxine treatment were significantly better than placebo for the categories of work (weeks 4 and 12), social life/leisure activities (week 12), family life/home responsibilities (week 12), and the global work/social disability scale (week 12).

Ancillary Variables

Venlafaxine-treated patients showed significant improvement compared with placebo patients on the Covi Anxiety Scale total score at week 12 (p < .01). There were no significant differences between treatment groups for the Raskin Depression Scale total or the HAM-D total scores. Mean HAM-D total scores decreased from 6.52 in the placebo group and 6.34 in the venlafaxine ER group at baseline to 5.57 and 4.86, respectively, at week 12 (p = NS).

Remission

Remission rates were analyzed using both LOCF and observed-cases (OC) data. Based on LSAS total scores, remission rates were significantly greater in the venlafaxine ER group than in the placebo group at weeks 3 (OC analysis; p = .05), 8 (OC analysis; p = .048), and 12 (20% vs. 7% LOCF analysis; p < .01; 27% vs. 9% OC analysis; p < .01) (Figure 3). When remission was defined as a CGI-I score of 1, a significantly greater percentage of venlafaxine ER–treated patients than placebo-treated patients had achieved remission at weeks 10 and 12 (OC and LOCF analysis; not shown).

Scores of Responders and Remitters on Efficacy Measures

Table 2 presents the adjusted mean LSAS total, SPIN, and CGI-S scores at the week 12 evaluation for the following groups of patients: the placebo treatment group, the venlafaxine ER treatment group, all responders (i.e., CGI-I score of 1 or 2), all remitters based on CGI-I score of 1, and all remitters based on LSAS total score ≤ 30. The group of patients who achieved LSAS remission consistently had the lowest adjusted mean scores on these efficacy variables, as well as on the LSAS subscales and all

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Table 2. Scores of Intent-to-Treat Population, Responders and Remitters (week 12 evaluation)

Group	LSAS Total	SPIN	CGI-S
Placebo, mean (SE)	68.9 (2.22)	34.6 (1.17)	4.1 (0.10)
Venlafaxine ER, mean (SE)	60.9 (2.22)	31.5 (1.17)	3.7 (0.10)
Responders, mean (SD)	40.02 (22.32)	21.58 (12.84)	2.84 (0.94)
CGI-I remitters, mean (SD)	23.53 (16.87)	12.65 (9.76)	2.15 (0.95)
LSAS remitters, mean (SD)	16.50 (8.26)	9.86 (6.33)	1.97 (0.81)

Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, ER = extended release, LSAS = Liebowitz Social Anxiety Scale, SPIN = Social Phobia Inventory.

domains of the SDS, suggesting that LSAS total score may be a more rigorous indicator of a remitted state for patients with social anxiety disorder compared with a measure of global improvement alone.

Safety

The mean dose of venlafaxine ER during the double-blind treatment period was 165 mg/day (189 mg/day among patients who were evaluated during the last week of treatment), and the majority of patients were treated with doses of venlafaxine ER in the 150 to 225 mg/day range. No unexpected adverse events or serious adverse events occurred. Most of the treatment-emergent adverse events reported during the study were mild to moderate in severity. Table 3 lists the most commonly reported treatment-emergent adverse events, i.e., reported by at least 5% of the venlafaxine-treated patients and at least twice the rate for placebo-treated patients. A total of 6 patients were considered to have had serious adverse events of clinical importance: 2 in each group during the study (venlafaxine ER: drug abuse, hypertension; placebo: hypertension, intraoperative bladder perforation), and 1 in each group during the poststudy period (venlafaxine ER: skin neoplasm; placebo: pregnancy).

The administration of venlafaxine ER was associated with few clinically important changes in laboratory test results, vital signs and body weights, or ECGs. The incidence of potentially clinically important changes in laboratory results was comparable in both groups, with the exception of elevated (nonnegative) urine protein/albumin levels in venlafaxine ER patients, the clinical significance of which is unknown. Venlafaxine ER was also associated with small but statistically significant mean increases from baseline at week 12 and final on-therapy evaluation in cholesterol (0.33 mmol/L and 0.31 mmol/L, respectively; $p \leq .001$), high-density lipoprotein (0.07 mmol/L and 0.07 mmol/L, respectively; $p \leq .01$), low-density lipoprotein (0.19 mmol/L and 0.18 mmol/L, respectively; $p \leq .05$), and aspartate aminotransferase (SGOT) (3.3 U/L and 2.8 U/L, respectively; $p \leq .01$). The mean increases in cholesterol ($p \leq .01$) and lipids ($p \leq .05$) among venlafaxine ER patients were significantly greater than the decreases noted among placebo patients.

Table 3. Most Common Treatment-Emergent Adverse Events (at least 5% of venlafaxine patients and ≥ 2 times placebo), N (%)

Adverse Event	Venlafaxine ER (N = 139)	Placebo (N = 140)
Nausea	47 (34)	17 (12)
Insomnia	35 (25)	9 (7)
Anorexia	32 (23)	4 (3)
Asthenia	30 (21)	9 (7)
Dizziness	22 (16)	11 (8)
Sweating	20 (14)	3 (2)
Dry mouth	20 (14)	2 (1)
Somnolence	19 (14)	9 (7)
Libido decreased	18 (13)	0 (0)
Impotence[a]	10 (13)	1 (1)
Abnormal ejaculation/orgasm[a]	8 (10)	0 (0)
Nervousness	13 (9)	5 (4)
Accidental injury	11 (8)	4 (3)
Anorgasmia		
Men[a]	6 (8)	0 (0)
Women[b]	4 (7)	0 (0)
Yawning	9 (6)	1 (1)
Agitation	8 (6)	3 (2)

[a]Based on the number of men: venlafaxine ER N = 79; placebo N = 75.
[b]Based on the number of women: venlafaxine ER N = 61; placebo N = 64.
Abbreviation: ER = extended release.

The only mean baseline-to-endpoint change in vital signs in the placebo group that was statistically significant was a decrease of 2.86 mm Hg in supine systolic blood pressure observed at the final on-therapy evaluation. The venlafaxine ER group showed statistically significant ($p \leq .001$) mean baseline-to-endpoint increases in supine pulse rate at week 12 and at the final on-therapy evaluation (3.70 bpm and 3.95 bpm, respectively), which differed significantly from the baseline-to-endpoint changes observed for placebo (–0.05 bpm, $p = .005$; and –0.01 bpm, $p < .001$, respectively). Venlafaxine ER also showed a statistically significant ($p \leq .05$) mean baseline-to-endpoint increase in supine systolic blood pressure at the week 12 evaluation and a nonsignificant increase at the final on-therapy evaluation (2.31 mm Hg and 1.63 mm Hg, respectively), both of which, statistically, differed significantly from the baseline-to-endpoint changes observed for placebo (–2.07 mm Hg, $p = .007$; and –2.86 mm Hg, $p < .001$, respectively). Additionally, the venlafaxine ER group showed statistically significant ($p \leq .01$) mean baseline-to-endpoint increases in supine diastolic blood pressure at week 12 and at the final on-therapy evaluation (2.57 mm Hg and 1.86 mm Hg, respectively), which statistically, differed significantly from the baseline-to-endpoint change for placebo at week 12 (–0.88 mm Hg, $p = .003$), but not at the final on-therapy evaluation (–1.12 mm Hg, NS). The venlafaxine ER group showed statistically significant ($p \leq .001$) mean baseline-to-endpoint decreases in body weight at the week 12 and final on-therapy evaluations (–0.90 kg and –0.95 kg, respectively), which, statistically, differed significantly from the placebo group (0.03 kg,

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$p = .006$ at week 12 and 0.04 kg, $p < .001$ at the final on-therapy evaluation). None of the changes in vital signs or weight was considered clinically significant.

DISCUSSION

This study's results demonstrate that venlafaxine ER is significantly more effective than placebo in the treatment of generalized social anxiety disorder. This study is one of the first to document the effectiveness of venlafaxine ER as a short-term treatment for social anxiety disorder. Significant differences in LSAS total, CGI-I, and LSAS fear/anxiety scores were seen beginning at week 6 and continued through week 12. LSAS avoidance scores also improved significantly, suggesting that subjects improved not only on subjective levels of distress, but also in terms of avoidance behavior.

Although no direct comparisons were made, response rates suggest that venlafaxine ER may be as effective as paroxetine,[49] sertraline,[33] and fluvoxamine[31] and more effective than fluoxetine[50] and buspirone.[22]

The improvement in social anxiety disorder symptoms with venlafaxine ER treatment is consistent with a role for serotonin in social anxiety disorder pathophysiology,[51] which has been suggested based on the efficacy of SSRIs in this disorder.[52–54] The putative role of norepinephrine in mechanisms underlying social anxiety disorder remains unclear.[51,55] There is also evidence of dopaminergic dysregulation in social anxiety disorder, as demonstrated by the efficacy of monoamine oxidase inhibitors[56] but not tricyclic antidepressants[57] in the treatment of social anxiety disorder and by more recent brain imaging findings of reduced striatal dopamine transporter[58] and postsynaptic D_2 receptors.[59] This evidence is not inconsistent with SSRI efficacy, as serotonergic agents have been shown to have effects on dopaminergic as well as serotonergic systems.[60]

There were no unexpected adverse events in this study—i.e., reported adverse events were similar to those observed in previous studies of venlafaxine ER.[39,61,62] In addition, the adverse events associated with venlafaxine ER treatment are similar to those experienced by patients treated with SSRIs.[24,30,31,33] Nausea was the most commonly reported adverse event (at least 5% and ≥ 2 times placebo) and one of the adverse events leading to discontinuation among venlafaxine ER–treated patients in this study. This is not surprising, considering nausea is typically one of the most frequently reported adverse events among SSRI-treated patients in studies of social anxiety disorder, with rates ranging from approximately 25% to 30%,[24,30,31] and has been reported among the most common adverse events leading to discontinuation of treatment.[24,33] Another finding of interest is the differences in the rates of sexual adverse events reported by venlafaxine ER–treated patients compared with placebo-treated patients. While up to 13% of male or female patients receiving venlafaxine ER reported 1 or more sexual adverse events, this was true for only 1% of male patients receiving placebo. Although a significantly greater proportion of venlafaxine ER–treated patients discontinued due to adverse events compared with placebo-treated patients, the discontinuation rate of 17% associated with venlafaxine ER is comparable to those reported in studies with SSRIs.[24,30,31,33]

As is the case with most newer antidepressants, the safety and tolerability profile of venlafaxine ER is better than that of first-generation antidepressants,[63,64] giving this dual reuptake inhibitor a high benefit-risk ratio.[65] The potentially clinically important changes observed in laboratory assessments and vital signs were determined to be isolated or transient occurrences associated with nonfasting, unrelated to adverse events or discontinuations, and generally inconsistent with the rest of the clinical picture. The increases in cholesterol and lipid levels are most likely of little clinical significance in otherwise healthy patients, but may be clinically relevant for patients with comorbid cardiovascular disorders. Nevertheless, the potential for increases in cholesterol levels and blood pressure associated with venlafaxine ER treatment suggests that monitoring of these parameters would be warranted, particularly in patients who receive long-term therapy.

Symptoms (LSAS), functionality or impairment (SDS), and well-being or overall improvement (CGI-S and CGI-I) were the 3 principal domains in which improvement was observed, indicating that the beneficial effects of venlafaxine ER were global and not limited to a symptom reduction. Proposed criteria for remission generally require that improvement in multiple domains be achieved.[6,28,49] In measuring core symptoms, however, a total score of ≤ 30 on the LSAS has been recommended[28,29] as a reliable marker of remission. Thus, the LSAS total score ≤ 30 was selected as one of the remission criteria for this short-term study.

It has been suggested that long-term treatment (i.e., beyond 6 to 12 weeks) is necessary to achieve remission.[26] The early age at onset[2,3] and long duration of illness associated with generalized social anxiety disorder[66,67] may be factors that contribute to the difficulty in bringing patients to remission with short-term treatment. Given that the mean duration of illness in this study was more than 20 years, it is notable that about 20% of venlafaxine ER–treated patients achieved remission by week 12 and that significant reductions in LSAS scores were apparent as early as week 6. A long-term study of venlafaxine XR in generalized social anxiety disorder demonstrated that remission rates increased from about 24% at week 12 to about 30% at week 28 of treatment.[68]

No significant differences were observed between the placebo group and the venlafaxine ER group in terms of demographics or baseline characteristics, which indicates that it is unlikely that these factors contributed to the sig-

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nificantly greater proportion of remitters in the venlafaxine ER group. In addition, analysis of these factors revealed no significant differences between remitters and nonremitters, suggesting that demographic characteristics and baseline severity of illness did not influence the likelihood of achieving remission.

While mean week 12 scores on most measures were similar among LSAS remitters and CGI-I remitters, those for LSAS remitters were consistently lower than those for CGI-I remitters. This may suggest that the LSAS score ≤ 30 criterion, which has been correlated with minimal symptomatology[28] and has been shown to best distinguish between individuals with and without social anxiety disorder,[29] might be a more rigorous indicator of remission. Nevertheless, it should be noted that the mean LSAS total score for CGI-I remitters was approximately 24, indicating that both criteria are able to reliably identify those patients who have improved significantly and whose symptoms have reached a subclinical level. Among responders, the mean LSAS total score at the final on-therapy visit was approximately 40, indicating, as expected, a significant improvement of symptoms, albeit not to a subclinical level.[29]

The significant symptom improvement associated with venlafaxine ER treatment over placebo shown in this study indicates the therapeutic potential of this agent. However, long-term studies in patients with social anxiety disorder are needed to assess the utility of venlafaxine ER in achieving and maintaining remission. In addition, given that psychotherapeutic approaches have been efficacious in reducing social anxiety disorder symptoms,[69,70] future studies to evaluate the efficacy of a combination of pharmacotherapy and behavior modification approaches would be useful in determining optimal clinical management for social anxiety disorder.

This study had several limitations that should be considered in evaluating the overall findings. First, although the study sample showed high baseline LSAS scores and a long mean duration of illness, it might not be representative of usual clinical populations, which often include patients with comorbidities including substance abuse, or of populations with different demographic characteristics. Second, although flexible dosing more closely approximates clinical practice and allows optimization of dosing for each patient, a flexible-dose paradigm does not allow for a determination of the optimal treatment dosage for the disorder. Additionally, the remission analysis is limited by the lack of an a priori definition in the original study protocol. Further, the lack of standard remission criteria for social anxiety disorder complicates comparisons of the results with those of other studies. Moreover, the lack of an active comparator does not allow for truly accurate comparisons of efficacy or tolerability with other agents.

In conclusion, venlafaxine ER is efficacious in the short-term treatment of generalized social anxiety disorder. This serotonin-norepinephrine reuptake inhibitor has already been established as an effective treatment for depression and generalized anxiety disorder and has demonstrated efficacy in treating a broad range of other psychiatric disorders, including social anxiety disorder. Additional investigations will help to more specifically determine the ability of venlafaxine ER to reduce or eliminate the symptoms of social anxiety disorder and to prevent the further development of other psychiatric disturbances and somatic complaints.

Drug names: buspirone (BuSpar and others), fluoxetine (Prozac and others), paroxetine (Paxil and others), sertraline (Zoloft), venlafaxine extended release (Effexor XR).

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