Efficacy, Safety, and Tolerability of Venlafaxine Extended Release and Buspirone in Outpatients With Generalized Anxiety Disorder

Jonathan R. T. Davidson, M.D.; Robert L. DuPont, M.D.; Dawson Hedges, M.D.; and J. Thomas Haskins, Ph.D.

Background: The objective of this randomized, double-blind study was to compare the efficacy and safety of venlafaxine extended release (XR) and buspirone in outpatients with generalized anxiety disorder (GAD) but without concomitant major depressive disorder.

Method: Male and female outpatients at least 18 years old who met the DSM-IV criteria for GAD and had scores of 18 or higher on the Hamilton Rating Scale for Anxiety (HAM-A) were randomly assigned to treatment with either venlafaxine XR (75 or 150 mg/day), buspirone (30 mg/day in 3 divided doses), or placebo for 8 weeks. The primary efficacy variables were changes in anxiety as determined by final on-therapy HAM-A total and psychic anxiety scores and Clinical Global Impressions scale (CGI) scores. Other key efficacy variables were HAM-A anxious mood and tension scores and the anxiety subscale scores of the patient-rated Hospital Anxiety and Depression scale (HAD).

Results: The efficacy analysis included 365 patients and the safety analysis, 405. At week 8, adjusted mean HAM-A psychic anxiety, anxious mood, and tension scores were significantly lower for venlafaxine XR–treated patients than for placebo-treated patients. On the HAD anxiety subscale, venlafaxine XR, 75 or 150 mg/day, was significantly more efficacious than placebo at all time points except weeks 1 (both dosages) and 2 (150-mg/day dosage only) and significantly more efficacious than buspirone at all time points except week 1. On the CGI-Improvement scale, scores for venlafaxine XR (both dosages) and buspirone were numerically superior to those for placebo at all time points, and statistical significance was observed at weeks 3, 4, 6, and 8 for venlafaxine XR and at weeks 6 and 8 for buspirone. The adverse events were not essentially different between treatment groups.

Conclusion: Venlafaxine XR is an effective, safe, and well-tolerated once-daily anxiolytic agent in patients with GAD without comorbid major depressive disorder. This agent was significantly superior to buspirone on the HAD anxiety subscale. Buspirone demonstrated statistical significance versus placebo on a measure of anxiolytic response.

(J Clin Psychiatry 1999;60:528–535)

Received March 9, 1999; accepted June 16, 1999. *From the Department of Psychiatry, Duke University Medical Center, Durham, N.C. (Dr. Davidson); the Institute for Behavior and Health, Rockville, Md. (Dr. DuPont); the Department of Psychiatry, University of Utah Health Sciences Center, Salt Lake City (Dr. Hedges); and Wyeth-Ayerst Research, Philadelphia, Pa. (Dr. Haskins).*

Supported by Wyeth-Ayerst Research, Philadelphia, Pa.

The authors extend their appreciation to the following members of the 214-U.S. Study Group: J. T. Apter, M.D. (Princeton Biomedical Research, Princeton, N.J.); J. S. Carman, M.D. (Carman Research, Smyrna, Ga.); M. Drehobl, M.D. (Clinical Research, San Diego, Calif.); E. A. DuBoff, M.D. (Denver, Colo.); A. M. Freeman III, M.D. (Department of Psychiatry, Louisiana State University Medical Center, Shreveport); R. W. Gibson, M.D. (Piedmont Research Associates, Inc., Winston-Salem, N.C.); S. Goldstein, M.D. (Medical and Behavioral Health Research, New York, N.Y.); A. Khan, M.D. (Bellevue, Wash.); R. Landbloom, M.D. (St. Paul-Ramsey Medical Center, St. Paul, Minn.); L. Charles, M.D. (Southern NJ Medical Center, Stratford, N.J.); G. Post, M.D. (Denver Drug Research Associates, Englewood, Colo.); F. W. Reimherr, M.D. (Department of Psychiatry, University of Utah, Salt Lake City); R. A. Reisenberg, M.D. (Bio Behavioral Research Center, Decatur, Ga.); J. Santo, Ph.D. (Center for Research in Anxiety, Inc., New York, N.Y.); S. K. Strawn, M.D. (Freedom Research, Inc., College Station, Tex.).

Reprint requests to: Jonathan R. T. Davidson, M.D., Department of Psychiatry, Duke University Medical Center, Box 3812, Durham, NC 27710.

Generalized anxiety disorder (GAD) is one of the most commonly diagnosed psychiatric illnesses in the United States, with an estimated lifetime prevalence of 5.1%.[1] The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), describes the primary feature of GAD as a 6-month or longer history of excessive and unrealistic anxiety or worry about typical events or activities of daily life. A diagnosis of GAD includes the presence of a constellation of somatic or psychic complaints (e.g., restlessness, fatigue, difficulty concentrating, irritability, muscle tension, tremor, sweating, gastrointestinal problems, sleep disturbances), but the absence of panic or phobic symptoms.[2,3] GAD can interfere significantly with the patient's life, leading to the need for professional intervention and administration of medications to combat symptoms.[4]

GAD, like other anxiety disorders, is associated with overuse of health care services and both higher morbidity and mortality, either as a result of the primary anxiety disorder or a coexisting condition.[5] Patients with GAD have higher rates of comorbid psychiatric and medical illnesses such as depression, cardiovascular disease, and irritable

bowel syndrome. Furthermore, the potential for worsened outcomes of these illnesses is higher in these patients if GAD is not treated.[5–7]

The economic costs of anxiety are also substantial. In the period 1985–1990, the estimated direct and indirect costs of anxiety disorders in the United States (including care, treatment, rehabilitation, and diminished or lost work productivity[8]) increased from $33.7 billion to $46.6 billion.[9] In 1994, the total cost further increased to $65 billion, confirming anxiety disorders as among the most costly of mental illnesses. The majority of these costs ($49.6 billion) were related to reduced or lost productivity, whereas direct treatment accounted for only $14.9 billion.[10]

The options for pharmacologic treatment of patients with GAD have generally been limited to the benzodiazepines, buspirone, and imipramine.[11–20] However, benzodiazepines are typically recommended only for short periods of time because of the significant risk of dependence and a well-characterized withdrawal syndrome.[11–14] Buspirone is often used as an alternative to the benzodiazepines because of its relative safety. However, its delayed onset of activity, the need for careful dose titration, and daily multiple-dose requirements make it a less-than-ideal agent for use in chronic therapy.[17]

Antidepressants, including the tricyclic agents, selective serotonin reuptake inhibitors (SSRIs), trazodone, and nefazodone, may be effective in treating GAD.[19,21–23] However, as with buspirone, they have a delayed onset of activity, and as with benzodiazepines, abrupt withdrawal of some of these drugs may precipitate a discontinuation syndrome characterized by nausea, vomiting, anxiety, sleep disturbances, movement disorders, panic attacks, and delirium. Although these symptoms may be mild and short-lived, they can reduce productivity and contribute to missed work days.[24,25]

No published placebo-controlled comparator trials have addressed the use of either the more recently available or older antidepressants in patients strictly meeting the DSM-IV criteria for GAD. The current study was undertaken to compare the efficacy, safety, and tolerability of venlafaxine extended release (XR) versus buspirone and placebo in patients with GAD but without comorbid major depressive disorder.

METHOD

Study Design

This multicenter, randomized, double-blind, placebo-controlled study compared the efficacy and safety of fixed doses of venlafaxine XR (75 mg or 150 mg/day) with those of divided doses of buspirone (30 mg/day) or matching placebo during 8 weeks of treatment for GAD. The protocol was approved by the institutional review boards at all study centers.

During the double-blind treatment phase, efficacy was assessed by the Hamilton Rating Scale for Anxiety (HAM-A),[26] the Clinical Global Impressions-Severity of Illness scale (CGI-S) and CGI Improvement scale (CGI-I),[27] the Hospital Anxiety and Depression (HAD) scale (anxiety subscale only),[28] the Covi Anxiety Scale,[29] and the Raskin Depression Scale.[30] The principal investigators, subinvestigators, and study coordinators were trained to evaluate study candidates by viewing a videotape of a patient interview and rating the patient's degree of anxiety on the HAM-A and CGI-S scales. Discussions of the ratings were led by an expert in psychiatry, and reliability between raters was established by generally good rating agreement for most items on the efficacy scales.

Patient Selection

Male and female outpatients aged 18 years or older from 17 centers in the United States (18–28 patients per center) were eligible if they met the DSM-IV criteria for GAD and were sufficiently symptomatic as to require treatment. Patients were also required to have screening and baseline HAM-A total scores of at least 18 and both HAM-A anxious mood and tension scores of 2 or more.

Patients were excluded if they met diagnostic criteria for major depressive disorder at the time of screening or within the 6 months preceding study day 1. Investigators were also instructed to use specific modules from the Structured Clinical Interview for DSM-III-R[31] to reinforce patient inclusion or exclusion based on the diagnostic criteria for major depressive disorder. Additionally, patients were excluded if their total Raskin depression score was greater than 9 or was greater than the Covi anxiety score or if any single item score on the Raskin Depression Scale was greater than 3. Also excluded were those with a recent history or current diagnosis of drug or alcohol dependence, current suicidal ideation and/or a history of suicide attempt, or 2 or more panic attacks in the 4 weeks before proposed study entry. Other exclusion criteria included a history of a mental disorder due to general medical conditions; a history or presence of medical disease that might compromise the study or be detrimental to the patient (e.g., hepatic or renal disease); the use of any investigational drug or procedure, any antipsychotic drug, fluoxetine, sumatriptan, or a benzodiazepine within 30 days of study day 1; the use of paroxetine, nefazodone, sertraline, or any other antidepressants or any monoamine oxidase inhibitor within 14 days of study day 1; and the presence of a clinically significant psychiatric disorder (other than GAD), antisocial personality disorder, or other severe Axis II disorders. Signed informed consent was obtained from each patient before study enrollment, and the protocol was approved by the institutional review boards of all study centers.

Measurements

At the screening visit, study candidates underwent a complete evaluation of medical and psychiatric history, a diagnostic evaluation for GAD, a physical examination, laboratory determinations including prestudy urine screens for benzodiazepines and drugs of abuse, 12-lead electrocardiogram (ECG), and assessment with the HAM-A, Covi anxiety, and Raskin depression scales. A single-blind placebo run-in phase of 7 ± 3 days followed, after which patients returned for a baseline visit that included assessment with the HAM-A, CGI, HAD anxiety subscale, and Covi and Raskin scales.

Patients satisfying the selection criteria were then randomly assigned to treatment with venlafaxine XR (75 or 150 mg/day), buspirone (15–25 mg/day during week 1 and 30 mg/day during weeks 2–8), or matching placebo. Buspirone was administered daily in 3 divided doses and was titrated according to the following schedule: 15 mg/day on study days 1 and 2, 20 mg/day on days 3 and 4, 25 mg/day on days 5–7, and 30 mg/day on days 8–56.[16] During week 1, patients in the 150-mg/day venlafaxine group received 75 mg/day; in week 2, the dosage was increased to 150 mg/day and maintained for the remainder of the study.

All efficacy measures were chosen before study and analysis. The primary and key efficacy measures were the final HAM-A total, psychic anxiety factor, anxious mood, and tension scores and CGI scores, obtained after 8 weeks of double-blind treatment or at the last on-therapy ratings for patients who discontinued prematurely before week 8. The secondary efficacy measures included the HAM-A somatic anxiety factor, HAD anxiety subscale, and Covi anxiety scores. Two separate criteria were used to identify responders: a decrease of at least 50% from baseline in HAM-A total score or a CGI-I score of 1 (very much improved) or 2 (much improved). If a patient's results met either criterion, the patient was considered responsive to treatment.

Study medications were provided in blister packs, with double-dummy techniques for blinding purposes. Venlafaxine XR and matching placebo were supplied in identical peach-colored capsules and buspirone and matching placebo in identical gray capsules. At the end of the double-blind treatment period, medications were tapered over 1 week. Patients were allowed to take chloral hydrate (up to 1000 mg at bedtime no more than 4 times per week through study day 21), but other psychotropic drugs were prohibited.

Patients were seen at the screening and baseline visits; at days 8, 15, 22, 29, 43, and 57 during the double-blind phase; and then 4 to 10 days after drug taper. Efficacy, adverse events, vital signs, and compliance were evaluated at each visit. Compliance with study regimen was assessed by checking pill counts, with those who took less than 80% of a prescribed dosage considered noncompliant and discontinued from the study. Physical examination and laboratory determinations were performed and ECGs obtained at screening and at the final study visit. Final efficacy ratings were obtained on the last day the patients took a full dose of study medication (i.e., before taper) or as soon as possible thereafter, but not more than 3 days after the last full dose.

Patients were examined for and questioned about adverse symptoms. Safety evaluations were based on reports of study events and the results of scheduled physical examinations, laboratory determinations, and ECGs. An adverse event was defined as any negative event that a patient experienced during the study. A treatment-emergent adverse event was defined as an adverse event not present at baseline or an event present at baseline that worsened during treatment, regardless of whether the investigator considered it to be unrelated to treatment.

Data Analysis

Efficacy analyses were done on an intent-to-treat basis; these analyses included all patients who had a baseline evaluation and at least one evaluation of at least one primary efficacy variable within 3 days of discontinuation of study drug during double-blind treatment. The last observation for a patient who discontinued the study was carried forward to all subsequent assessment periods. The study was designed to enroll a sufficient number of patients to allow for the completion of 90 intent-to-treat patients per group. The sample size estimate was set to attain a power of 90% to detect a 4-point difference in the HAM-A total scores between any 2 treatment groups by a 2-sided test with an alpha level set at .05.

Changes from baseline in HAM-A total, psychic anxiety, somatic anxiety, anxious mood, and tension scores and HAD anxiety subscale scores were analyzed by 2-way analysis of covariance (ANCOVA), with treatment and investigator as main effects and baseline scores as covariates. Changes from baseline in CGI-I scores were analyzed by analysis of variance (ANOVA). A Fisher protected F test was used to provide an overall test of efficacy. When the overall p value was ≤ .05, a pairwise comparison between treatment groups was performed, and for these tests, an alpha level was set at .05 (2-sided).

RESULTS

Patients

The safety analysis included the 405 patients who completed the placebo run-in period and received study drug during the double-blind treatment phase. In 36 of these patients, no primary efficacy evaluations on therapy or within 3 days of discontinuation of study drug were recorded, and they were not included in the efficacy analysis. In addition, 4 patients randomized at one site were excluded for administrative reasons. The baseline demographics and clinical characteristics of the remaining 365

© Copyright 1999 Physicians Postgraduate Press, Inc.

Table 1. Baseline Demographics and Clinical Characteristics of Intent-to-Treat Patients[a]

Characteristic	Placebo (N = 98)	Venlafaxine XR 75 mg/d (N = 87)	Venlafaxine XR 150 mg/d (N = 87)	Buspirone 30 mg/d (N = 93)	p Value
Age, y	39 ± 11	38 ± 10	37 ± 11	37 ± 10	.57
Sex (female:male)	61:37	52:35	60:27	51:42	.27
Race, N (%)					.69
White	89 (91)	80 (92)	74 (85)	79 (85)	
Black	3 (3)	4 (5)	5 (6)	7 (8)	
Hispanic	4 (4)	2 (2)	3 (3)	5 (5)	
Asian	1 (1)	1 (1)	3 (3)	2 (2)	
Other	1 (1)	0 (0)	2 (2)	0 (0)	
Duration, current episode (wk)	355 ± 577	433 ± 556	297 ± 417	403 ± 628	.66
HAM-A score					
Total	23.7 ± 4.2	23.7 ± 4.1	23.0 ± 4.0	23.8 ± 4.6	.62
Psychic anxiety factor	13.7 ± 2.5	13.6 ± 2.6	13.1 ± 2.4	14.1 ± 2.3	.06
CGI-S score, N (%)					.46
≤ 4	70 (71)	70 (80)	69 (79)	72 (77)	
> 4	28 (29)	17 (20)	18 (21)	21 (23)	

[a]Data presented as mean ± SD unless specified otherwise.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-A = Hamilton Rating Scale for Anxiety, XR = extended release.

patients are shown in Table 1. No significant differences between the groups were apparent, although mean HAM-A psychic anxiety score was slightly higher in the buspirone group. Chloral hydrate was taken by 7 patients receiving placebo, 2 receiving venlafaxine XR 75 mg, 7 receiving venlafaxine XR 150 mg, and 2 receiving buspirone. The number of patients who completed 8 weeks of treatment was 68 of those receiving placebo, 64 of those receiving venlafaxine XR 75 mg, 55 of those receiving venlafaxine XR 150 mg, and 69 of those receiving buspirone.

Efficacy

Adjusted changes from baseline in HAM-A total scores in all treatment groups were greater than those in the placebo group at all timepoints. These differences, however, failed to reach statistical significance (Table 2). HAM-A psychic anxiety scores in the venlafaxine XR groups were significantly lower relative to placebo at week 8 ($p \leq .05$) (see Table 2). The adjusted mean HAM-A anxious mood scores in the venlafaxine XR groups were significantly lower than in the placebo group at weeks 2, 4, 6, and 8 ($p < .05$) (Figure 1A). The adjusted mean HAM-A tension scores were also significantly lower, relative to placebo, in the venlafaxine XR 75-mg/day group at weeks 2, 3, 4, and 8 ($p \leq .005$) and in the 150-mg/day group at weeks 3 and 8 ($p < .05$; Figure 1B). Venlafaxine XR 75 mg/day was superior to placebo at all timepoints after week 2 ($p \leq .01$) and to buspirone at weeks 3, 4, and 8 ($p \leq .05$) as assessed by CGI-S scores (Figure 2A). CGI-I scores showed that venlafaxine XR 75 mg/day was more effective than placebo at weeks 4 and 8 ($p \leq .01$) and than buspirone at week 4 ($p \leq .05$; Figure 2B). Venlafaxine XR 150 mg/day was also better than placebo at week 8 by this efficacy measure ($p = .05$; Figure 2B). No significant differences between buspirone and placebo were seen in HAM-A total and psychic anxiety scores (see Table 2), CGI-S scores, or CGI-I scores at any timepoint (see Figure 2B).

The proportion of responders (as defined by a decrease of at least 50% from baseline in HAM-A total scores) was not significantly different in the treatment groups at any timepoint (Table 3). For response based on CGI-I scores of 1 (very much improved) or 2 (much improved), venlafaxine XR 75 mg/day was better than placebo at all timepoints after week 2 ($p \leq .03$), and buspirone was better than placebo at weeks 6 and 8 ($p \leq .04$) (see Table 3). Both venlafaxine XR groups were more effective than placebo on the patient-rated HAD anxiety subscale at weeks 3 through 8 ($p < .05$); the 75-mg/day dose was also more effective than placebo at week 2 ($p < .05$) (Figure 3). By this same efficacy measure, both venlafaxine XR groups were superior to buspirone at all timepoints after week 1 ($p \leq .05$) (see Figure 3).

Safety and Tolerability

Venlafaxine XR and buspirone were both well tolerated, and adverse events were consistent with those reported in the literature for these agents.[18,32] Adverse events led to study withdrawal in 10% (10/104) of the placebo group, 22% (22/102) of the venlafaxine XR 75-mg/day group, 28% (28/101) of the venlafaxine XR 150-mg/day group, and 15% (15/98) of the buspirone group.

The most common adverse events are listed in Table 4. Events related to active treatment were generally mild to moderate in severity, occurred early in the course of treatment, and tended to resolve with continued treatment. Few clinically significant serious adverse events or changes in laboratory test results, vital signs, weight, or ECG assessments were noted.

DISCUSSION

Venlafaxine, in both the immediate- and extended-release formulations, is a well-established treatment for depression[32–35] and is also effective in depression with associated anxiety symptoms. In a meta-analysis of 6 studies, Rudolph et al.[36] found that such symptoms were significantly improved in anxious depressed patients who received venlafaxine compared with those who received placebo. The ability of venlafaxine to inhibit the reuptake of both norepinephrine and serotonin may represent a particular advantage in GAD, because evidence suggests that both of these neurotransmitters are dysregulated in GAD.[37]

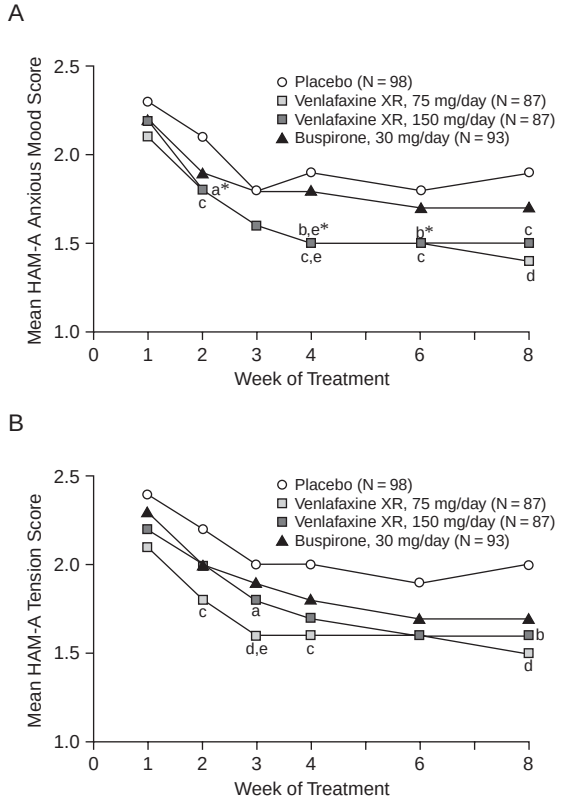
The currently available anxiolytic drugs are not ideally suited for the treatment of patients with GAD. For ex-

Table 2. Adjusted Mean Scores for HAM-A Total and HAM-A Psychic Anxiety Factor[a]

	Placebo (N = 98)		Venlafaxine XR 75 mg/d (N = 87)		Venlafaxine XR 150 mg/d (N = 87)		Buspirone 30 mg/d (N = 93)		F
HAM-A	Mean (95% CI)	SE	Mean (95% CI)	SE	Mean (95% CI)	SE	Mean (95% CI)	SE	Value
Total									
Week 1	19.9 (19.0 to 20.9)	0.63	18.9 (17.9 to 19.9)	0.64	19.2 (18.2 to 20.3)	0.72	19.2 (18.2 to 20.1)	0.57	.51
Week 2	17.8 (16.8 to 18.9)	0.58	16.2 (15.1 to 17.3)	0.68	16.8 (15.7 to 17.9)	0.69	17.0 (15.9 to 18.0)	0.62	.22
Week 3	16.4 (15.2 to 17.6)	0.68	14.8 (13.6 to 16.1)	0.77	15.3 (14.0 to 16.5)	0.74	15.6 (14.4 to 16.8)	0.71	.32
Week 4	15.8 (14.6 to 17.1)	0.70	14.2 (12.8 to 15.5)	0.75	14.8 (13.5 to 16.2)	0.78	14.8 (13.5 to 16.1)	0.68	.36
Week 6	15.7 (14.4 to 17.1)	0.75	13.7 (12.3 to 15.1)	0.78	14.0 (12.6 to 15.4)	0.81	14.1 (12.7 to 15.5)	0.71	.15
Week 8	15.6 (14.1 to 17.0)	0.73	13.0 (11.5 to 14.5)	0.82	13.8 (12.3 to 15.3)	0.86	14.1 (12.6 to 15.5)	0.76	.10
Psychic anxiety factor									
Week 1	11.8 (11.2 to 12.4)	0.36	10.7 (10.0 to 11.3)	0.39	11.1 (10.4 to 11.7)	0.39	11.3 (10.7 to 11.9)	0.33	.09
Week 2	10.5 (9.8 to 11.1)	0.34	9.33 (8.6 to 10.0)	0.40	9.5 (8.8 to 10.2)	0.41	9.8 (9.2 to 10.5)	0.35	.07
Week 3	9.7 (8.9 to 10.4)	0.42	8.4 (7.6 to 9.2)	0.46	8.6 (7.8 to 9.4)	0.41	9.2 (8.5 to 10.0)	0.41	.08
Week 4	9.4 (8.7 to 10.2)	0.44	8.0 (7.2 to 8.9)	0.45	8.4 (7.5 to 9.2)	0.42	8.8 (8.0 to 9.6)	0.41	.08
Week 6	9.3 (8.4 to 10.1)	0.47	7.8 (6.9 to 8.7)	0.46	7.9 (7.1 to 8.8)	0.45	8.3 (7.5 to 9.2)	0.42	.07
Week 8	9.3 (8.5 to 10.2)	0.48	7.4[b] (6.5 to 8.4)	0.47	7.9[c] (6.9 to 8.8)	0.49	8.4 (7.5 to 9.3)	0.45	.02

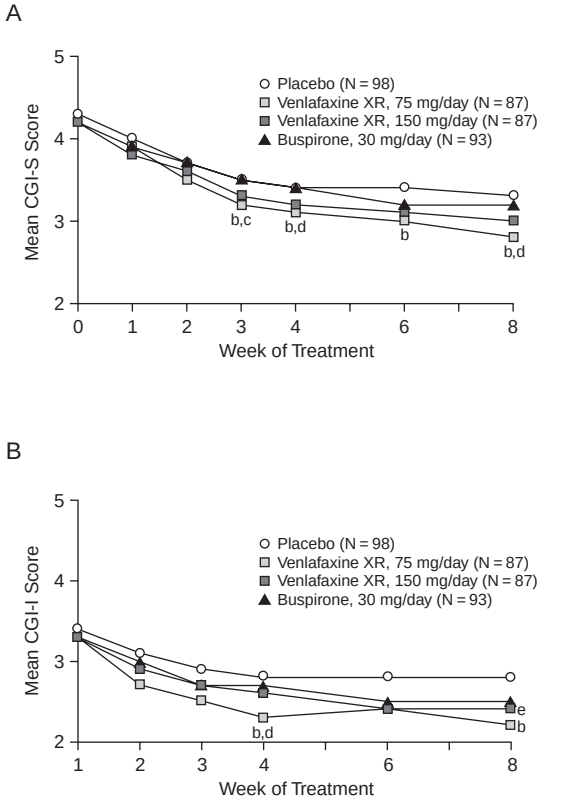
[a]Intent-to-treat patients and last-observation-carried-forward analysis. Data presented as adjusted mean (95% CI) and adjusted change SE.
Abbreviation: CI = confidence interval.
[b]p ≤ .01 vs. placebo.
[c]p ≤ .05 vs. placebo.

Figure 1. Mean Hamilton Rating Scale for Anxiety (HAM-A) Anxious Mood (A) and Tension (B) Scores



*75-mg/day group.
[a]p < .05 vs. placebo.
[b]p < .01 vs. placebo.
[c]p ≤ .005 vs. placebo.
[d]p < .001 vs. placebo.
[e]p ≤ .05 vs. buspirone for A and p <.01 vs. buspirone for B.

Figure 2. Mean in CGI-S (A) and CGI-I (B) Scores[a]



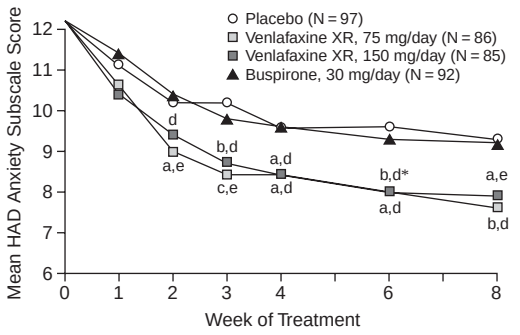
[a]Abbreviation: CGI-I = CGI-Improvement scale.
[b]p < .01 vs. placebo.
[c]p < .01 vs. buspirone.
[d]p ≤ .05 vs. buspirone.
[e]p ≤ .05 vs. placebo.

Table 3. Evaluation of Responders[a]

Scale	Placebo	Venlafaxine XR 75 mg/d	Venlafaxine XR 150 mg/d	Buspirone 30 mg/d
HAM-A total				
Week 1	6/93 (6)	10/85 (12)	10/88 (11)	8/95 (8)
Week 2	14/98 (14)	19/87 (22)	20/89 (22)	17/95 (18)
Week 3	24/98 (24)	29/87 (33)	33/89 (37)	28/95 (29)
Week 4	31/98 (32)	36/87 (41)	35/89 (39)	34/95 (36)
Week 6	33/98 (34)	42/87 (48)	40/89 (45)	38/95 (40)
Week 8	35/98 (36)	43/87 (49)	44/89 (49)	43/95 (45)
CGI-I				
Week 1	12/93 (13)	15/85 (18)	19/88 (22)	15/95 (16)
Week 2	26/98 (27)	31/87 (36)	30/89 (34)	33/95 (35)
Week 3	34/98 (35)	45/87 (52)[b]	42/89 (47)	40/95 (42)
Week 4	41/98 (42)	54/87 (62)[c]	46/89 (52)	47/95 (49)
Week 6	41/98 (42)	53/87 (61)[d]	46/89 (52)	54/95 (57)[e]
Week 8	38/98 (39)	54/87 (62)[f]	44/89 (49)	52/95 (55)[b]

[a]Response is defined as a decrease of at least 50% from baseline in HAM-A total score or a CGI-I score of 1 (very much improved) or 2 (much improved). Data presented as N responders/N patients evaluated (%).
[b]p = .03 vs. placebo.
[c]p = .008 vs. placebo.
[d]p = .01 vs. placebo.
[e]p = .04 vs. placebo.
[f]p = .002 vs. placebo.

Figure 3. Mean Hospital Anxiety and Depression (HAD) Anxiety Subscale Scores



*150-mg/day group.
[a]p < .05 vs. placebo.
[b]p ≤ .005 vs. placebo.
[c]p < .001 vs. placebo.
[d]p ≤ .05 vs. buspirone.
[e]p ≤ .01 vs. buspirone.

Table 4. Most Common Treatment-Emergent Adverse Events During Double-Blind Treatment[a]

Adverse Event	Placebo (N = 104)	Venlafaxine XR 75 mg/d (N = 102)	Venlafaxine XR 150 mg/d (N = 101)	Buspirone 30 mg/d (N = 98)
Nausea	14 (13)	34 (33)	44 (44)	29 (30)
Dizziness	13 (13)	17 (17)	21 (21)	46 (47)
Asthenia	10 (10)	14 (14)	22 (22)	15 (15)
Dry mouth	5 (5)	15 (15)	25 (25)	5 (5)

[a]Most common events are defined as those occurring at an incidence of 20% or more and at least twice the incidence with placebo treatment. Data presented as N (%).

ample, benzodiazepines are limited by their potential for abuse, possible cognitive and psychomotor impairment, and the withdrawal syndrome that can follow discontinuation of treatment.[11,13] In addition, the drug interaction profile of benzodiazepine agents may require careful patient management.[38] The most significant interactions are with other agents that depress the central nervous system (e.g., alcohol, sedatives, some antidepressants, barbiturates) and drugs that undergo hepatic metabolism. In some instances, the clearance of benzodiazepine drugs may be increased (e.g., as with cigarette smoking) or decreased (e.g., as with oral contraceptive use), possibly leading to the need for dosage adjustments.[38]

The only nonbenzodiazepine anxiolytic agent available in the United States is buspirone, which may be safer and better tolerated by patients than benzodiazepines.[17] However, it has a relatively slow onset of action, and an initial response to therapy may not occur for several weeks.[17] Titration to an effective dose may also take several weeks, and the thrice-daily regimen can be a disadvantage. These factors may hinder patient compliance and create difficulties for primary care physicians when monitoring patients during the titration period.

Antidepressants such as the tricyclic agents, SSRIs, nefazodone, and trazodone are also used to treat GAD, but data on their role in this indication are scarce.[12,19] In some studies, patients with coexisting depression were included, so conclusions about the efficacy of these agents in a pure anxiety disorder are limited.[19,39]

In the current trial, it is unknown to what extent inhibition of norepinephrine and serotonin reuptake occurred, especially at the lower dose. It would be of considerable interest, therefore, to evaluate the relative importance of these mechanisms for the control of GAD. Both are probably involved, but in different ways.[37] For example, norepinephrine may mediate nonrewarded behaviors, whereas serotonin may mediate fear-induced inhibition of movement and also punishment, as originally proposed by Gray,[40] who postulated that the locus ceruleus and septohippocampal systems are respectively involved in these behaviors.[41]

Another placebo-controlled study of venlafaxine XR was recently conducted in outpatients meeting the DSM-IV criteria for GAD in whom no other major psychiatric diagnosis, including depression, was present.[42] Results of this study indicated that once-daily administration of venlafaxine XR (75 or 150 mg/day) provided safe and effective treatment of GAD. Adjusted mean HAM-A total and psychic anxiety factor scores were significantly lower in one or both of the venlafaxine XR groups than in the placebo group beginning as early as week 1.

The present study is the first to compare the efficacy of the recently available antidepressant venlafaxine XR with an established anxiolytic agent, buspirone, in patients with GAD, as defined by the new criteria of DSM-IV,

without comorbid major depressive disorder. Our results confirm the beneficial effects of venlafaxine XR in these patients, especially on the psychic symptoms. Venlafaxine XR–treated patients had significantly lower adjusted mean HAM-A psychic anxiety factor, CGI-I, and CGI-S scores than placebo-treated patients, although no effect was found on the HAM-A total scores. The HAD anxiety subscale scores for both doses of venlafaxine XR (75 and 150 mg/day) were also significantly better than those for buspirone (30 mg/day) starting at week 2 and continuing through the end of study. Buspirone, the active control, demonstrated superiority over placebo at each week on the CGI-I, a measure of response to treatment; statistically significant differences were observed at weeks 6 ($p = .04$) and 8 ($p = .03$). Failure of buspirone to show more convincingly greater efficacy than placebo on other measures calls for comment. Higher doses might have been more effective, and it is unknown whether the drug is generally as effective in the DSM-IV form of GAD as in the older definitions of the disorder. Finally, a higher frequency of some adverse events with buspirone may have limited its differentiation from placebo.

The safety and tolerability of venlafaxine XR compare favorably with those of both placebo and buspirone. Venlafaxine XR has a low affinity for muscarinic, histaminergic, and adrenergic receptors, suggesting that, unlike tricyclic antidepressants, it lacks many of the adverse effects associated with binding to these receptors.[33,43] This agent also has a favorable drug interaction profile.[43–47] In general, the adverse events associated with venlafaxine XR in the current study were mild to moderate in severity, occurred early in the study, and tended to subside with continued therapy. Nevertheless, the aggressive dose titration schedule used in this study may explain the higher incidence of adverse events associated with the 150-mg/day versus the 75-mg/day dosage. A slower dose titration schedule, such as that described in the approved labeling for venlafaxine XR, may improve tolerability and reduce the rate of discontinuation that occurred in this study.

Once-daily administration of venlafaxine XR, 75 mg or 150 mg, is an effective, safe, and well-tolerated treatment for patients with DSM-IV-defined GAD without coexisting major depressive disorder. It was significantly superior to placebo and comparable to, or slightly better than, buspirone. The once-daily dosing of venlafaxine XR also facilitates administration and enhances compliance. This newer agent's role in the anxiolytic armamentarium requires further exploration, including long-term evaluation in GAD. Because it is also an established treatment for depression, venlafaxine XR may potentially provide therapeutic benefit for the significant proportion of patients with GAD and comorbid depression.

Drug names: buspirone (BuSpar), fluoxetine (Prozac), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft), sumatriptan (Imitrex), trazodone (Desyrel and others), venlafaxine (Effexor).

REFERENCES

1. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Arch Gen Psychiatry 1994;51:8–19
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994:435–436
3. Kirkwood CK, Hayes PE. Anxiety disorders. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy. 3rd ed. Stamford, Conn: Appleton & Lange; 1991:1443–1462
4. Wittchen HU, Zhao S, Kessler RC, et al. DSM-III-R generalized anxiety disorder in the National Comorbidity Survey. Arch Gen Psychiatry 1994; 51:355–364
5. Zajecka J. Importance of establishing the diagnosis of persistent anxiety. J Clin Psychiatry 1997;58(suppl 3):9–13
6. Flint AJ. Epidemiology and comorbidity of anxiety disorders in the elderly. Am J Psychiatry 1994;151:640–649
7. Stoudemire A. Epidemiology and psychopharmacology of anxiety in medical patients. J Clin Psychiatry 1996;57(suppl 7):64–72
8. Hofmann SG, Barlow DH. The costs of anxiety disorders: implications for psychosocial interventions. In: Miller NE, Magruder KM, eds. Psychotherapy: Costs and Benefits. A Guide for Practitioners, Researchers and Policymakers. New York, NY: John Wiley & Sons. In press
9. DuPont RL, Rice DP, Miller LS, et al. Economic costs of anxiety disorders. Anxiety 1996;2:167–172
10. DuPont RL, DuPont CM, Rice DP. The economic costs of anxiety disorders. In: Stein DJ, Hollander E, eds. Textbook of Anxiety Disorders. Washington, DC: American Psychiatric Press. In press
11. Dubovsky SL. Generalized anxiety disorder: new concepts and psychopharmacologic therapies. J Clin Psychiatry 1990;51(1, suppl):3–10
12. Roy-Byrne P, Wingerson D, Cowley D, et al. Psychopharmacologic treatment of panic, generalized anxiety disorder, and social phobia. Psychiatr Clin North Am 1993;16:719–735
13. Shader RI, Greenblatt DJ. Use of benzodiazepines in anxiety disorders. N Engl J Med 1993;328:1398–1405
14. Rickels K, Schweizer E. The clinical course and long-term management of generalized anxiety disorder. J Clin Psychopharmacol 1990;10: 101S–110S
15. Schweizer E, Rickels K. Strategies for treatment of generalized anxiety in the primary care setting. J Clin Psychiatry 1997;58(suppl 3):27–31
16. Buspirone HCl. In: Drug Facts and Comparisons. 1998 edition. St. Louis, Mo: Facts and Comparisons; 1998:1593–1596
17. Ninan PT, Cole JO, Yonkers KA. Nonbenzodiazepine anxiolytics. In: Schatzberg AF, Nemeroff CB, eds. The American Psychiatric Press Textbook of Psychopharmacology. Washington, DC: American Psychiatric Press; 1998:287–306
18. Buspirone hydrochloride. In: McEvoy GK, ed. AHFS 98 Drug Information. Bethesda, Md: American Society of Health-System Pharmacists; 1998:1960–1966
19. Rickels K, Downing R, Schweizer E, et al. Antidepressants for the treatment of generalized anxiety disorder: a placebo-controlled comparison of imipramine, trazodone, and diazepam. Arch Gen Psychiatry 1993;50: 884–895
20. DuPont RL, DuPont CM. The treatment of anxiety: realistic expectations and risks posed by controlled substances. J Law Med Ethics 1994;22: 206–214
21. Rocca P, Fonzo V, Scotta M, et al. Paroxetine efficacy in the treatment of generalized anxiety disorder. Acta Psychiatr Scand 1997;95:444–450
22. Hedges DW, Reimherr FW, Strong RE, et al. An open trial of nefazodone in adult patients with generalized anxiety disorder. Psychopharmacol Bull 1996;32:671–676
23. Hoehn-Saric R, McLeod DR, Zimmerli WD. Differential effects of alprazolam and imipramine in generalized anxiety disorder: somatic versus psychic symptoms. J Clin Psychiatry 1988;49:293–301
24. Lejoyeux M, Ades J. Antidepressant discontinuation: a review of the literature. J Clin Psychiatry 1997;58(suppl 7):11–16
25. Wolfe RM. Antidepressant withdrawal reactions. Am Fam Physician 1997;56:455–462
26. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55
27. National Institute of Mental Health. Special feature: rating scales and assessment instruments for use in pediatric psychopharmacology research.

Psychopharmacol Bull 1985;21:839–843
28. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression scale. Acta Psychiatr Scand 1983;67:361–370
29. Lipman RS. Differentiating anxiety and depression in anxiety disorders: use of rating scales. Psychopharmacol Bull 1982;18:69–77
30. Raskin A, Schulterbrandt J, Reatig N, et al. Replication of factors of psychopathology in interview, ward behavior, and self-report ratings of hospitalized depressives. J Nerv Ment Dis 1969;148:87–98
31. Spitzer RL, Williams JB, Gibbon M, et al. The structured clinical interview for DSM-III-R (SCID), I: history, rationale, and description. Arch Gen Psychiatry 1992;49:624–629
32. Thase ME. Efficacy and tolerability of once-daily venlafaxine extended-release (XR) in outpatients with major depression. J Clin Psychiatry 1997; 58:393–398
33. Holliday SM, Benfield P. Venlafaxine: a review of its pharmacology and therapeutic potential in depression. Drugs 1995;49:280–294
34. Cunningham LA. Efficacy and tolerability of once daily venlafaxine extended release (XR) in outpatients with major depression. Ann Clin Psychiatry 1997;9:157–164
35. Guelfi JD, White C, Hackett D, et al. Effectiveness of venlafaxine in patients hospitalized for major depression and melancholia. J Clin Psychiatry 1995;56:450–458
36. Rudolph RL, Entsuah R, Chitra R. A meta-analysis of the effects of venlafaxine on anxiety associated with depression. J Clin Psychopharmacol 1998;18:136–144
37. Connor KM, Davidson JRT. The neurobiology of generalized anxiety disorder. Biol Psychiatry 1998;44:1284–1294
38. Grimsley SR. Anxiety disorders. In: Young LY, Koda-Kimble MA, Kradjan WA, et al, eds. Applied Therapeutics: The Clinical Use of Drugs. 6th ed. Vancouver, British Columbia: Applied Therapeutics; 1995: 73-1–73-31
39. Feighner JP, Entsuah AR, McPherson MK. Efficacy of once-daily venlafaxine extended-release (XR) for symptoms of anxiety in depressed outpatients. J Affect Disord 1998;47:55–62
40. Gray JA. A conceptual nervous system for avoidance behaviour. In: Gray JA, ed. The Psychology of Fear and Stress. 2nd ed. New York, NY: Cambridge University Press; 1991:241–271
41. Gray JA. Fear and the central nervous system. In: Gray JA, ed. The Psychology of Fear and Stress. 2nd ed. New York, NY: Cambridge University Press; 1991:272–330
42. Haskins T, Rudolph R, Pallay A, et al, for the Venlafaxine XR 210 Study Group. Double-blind, placebo-controlled study of once daily venlafaxine XR in outpatients with generalized anxiety disorder (GAD) [poster]. Presented at the 21st meeting of the Collegium Internationale Neuro-Psychopharmacologicum; July 12–16, 1998; Glasgow, Scotland
43. DeVane CL. Pharmacokinetics of the newer antidepressants: clinical relevance. Am J Med 1994;97(suppl 6A):13S–23S
44. Ereshefsky L. Drug-drug interactions involving antidepressants: focus on venlafaxine. J Clin Psychopharmacol 1996;16(suppl 2):37S–53S
45. Amchin J, Zarycranski W, Taylor KP, et al. Effect of venlafaxine on the pharmacokinetics of alprazolam. Psychopharmacol Bull 1998;34:211–219
46. Amchin J, Zarycranski W, Taylor KP, et al. Effect of venlafaxine on CYP1A2-dependent pharmacokinetics and metabolism of caffeine. J Clin Pharmacol 1999;39:252–259
47. Amchin J, Zarycranski W, Taylor KP, et al. Effect of venlafaxine on the pharmacokinetics of terfenadine. Psychopharmacol Bull 1998;34:383–389