Once-Daily Venlafaxine Extended Release (XR) Compared With Fluoxetine in Outpatients With Depression and Anxiety

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Background: We conducted a randomized, double-blind, placebo-controlled study of the efficacy and safety of once-daily venlafaxine extended release (XR) and fluoxetine in outpatients with major depression and concomitant anxiety.

Method: Patients who met DSM-IV criteria for major depressive disorder and satisfied eligibility criteria were randomly assigned to once-daily venlafaxine XR, fluoxetine, or placebo for 12 weeks. Efficacy was assessed with the Hamilton Rating Scale for Depression (HAM-D), Hamilton Rating Scale for Anxiety (HAM-A), and Clinical Global Impressions scale.

Results: Among 359 outpatients, venlafaxine XR and fluoxetine were significantly superior ($p < .05$) to placebo on the HAM-D total score beginning at week 2 and continuing to the end of the study. Venlafaxine XR but not fluoxetine was significantly better than placebo at week 2 on the HAM-D depressed mood item. At week 12, the HAM-D response rate was 43% on placebo, 67% on venlafaxine XR, and 62% on fluoxetine ($p < .05$). The HAM-D remission rate was significantly higher ($p < .05$) at weeks 3, 4, 6, 8, 12, and final evaluation with venlafaxine XR and at weeks 8, 12, and final evaluation with fluoxetine than with placebo. The HAM-A response rate was significantly higher ($p < .05$) with venlafaxine XR than with fluoxetine at week 12. The incidence of discontinuation for adverse events was 5% with placebo, 10% with venlafaxine XR, and 7% with fluoxetine.

Conclusion: Once-daily venlafaxine XR is effective and well tolerated for the treatment of major depression and concomitant anxiety and provides evidence for superiority over fluoxetine.

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Moderate anxiety occurs concomitantly in at least 65% of patients who have major depression.[1] Depression with anxiety is associated with a more chronic course, poorer outcome, and a higher incidence of relapse and suicide than depression alone.[2,3] Patients with anxiety and depression represent the majority of psychiatric illness treated by primary care physicians and account for approximately 13% of patients seen in the primary care setting.[4–6] In this setting, simplicity of the dosage regimen and acceptable drug tolerability are important factors in patient compliance and effectiveness.

Venlafaxine, an antidepressant that selectively blocks reuptake of both serotonin and norepinephrine, is effective in patients with major depression and associated symptoms of anxiety.[7,8] Immediate release venlafaxine has a relatively short half-life of 5 hours and must be administered 2 or 3 times daily.[9] Venlafaxine extended release (XR), a recently developed microsphere encapsulated formulation, provides the same total extent of absorption of venlafaxine with once-daily administration, while maintaining constant plasma levels over the dosing interval and providing increased tolerability.[10,11] Results from placebo-controlled studies have demonstrated the efficacy of once-daily venlafaxine XR in patients with major depression,[12,13] and the results of an analysis of pooled data demonstrated efficacy in the cohort of patients with symptoms of anxiety.[14] The present study was conducted to compare the efficacy and tolerability of once-daily venlafaxine XR, fluoxetine, and placebo in outpatients with major depression and concomitant anxiety.

METHOD

Study Design

This study was a prospective, multicenter, double-blind, randomized, placebo-controlled comparison of the efficacy and safety of once-daily venlafaxine XR and fluoxetine in outpatients with major depression and concomitant anxiety. The protocol was approved by the ethics committees at each clinical site, and written informed consent was obtained from patients before enrollment.

Patient Selection

Outpatients aged 18 years or older who met DSM-IV criteria[15] for major depressive disorder were eligible if they had a minimum baseline score of 20 on the first 17 items of the 21-item Hamilton Rating Scale for Depression (HAM-D)[16] with not more than a 20% decrease in score between screening and baseline. They also had a minimum score of 8 on the Covi scale[17] and symptoms of depression for at least 1 month before study entry.

Women who were pregnant, lactating, or of childbearing potential and had a positive beta-human chorionic gonadotropin (β-hCG) pregnancy test result were not included. Also excluded were patients who had a history of clinically significant medical disease or clinically significant abnormalities on a screening physical examination, electrocardiogram (ECG), or laboratory tests. Those who had acute suicidal tendencies, a history of a seizure disorder, an organic mental disorder, bipolar disorder, or history of mania or any psychotic disorder not associated with depression were also excluded. Other reasons for exclusion were use of any investigational drug or electroconvulsive therapy within 30 days, fluoxetine within 28 days, or a monoamine oxidase inhibitor or paroxetine within 14 days of double-blind treatment. Patients could not have taken any other antidepressant, antipsychotic, anxiolytic, sedative-hypnotic drug, or psychotropic drug or substance within 7 days of the start of double-blind treatment; any nonpsychopharmacologic drug with psychotropic effects (e.g., β-adrenergic blockers) within 7 days of baseline unless the dosage had been stable for a minimum of 1 month before double-blind treatment. Patients with a history of drug or alcohol dependence within 2 years or a history of drug abuse within 6 months of the start of double-blind treatment were excluded.

Study Procedure

Eligible outpatients underwent a single-blind, placebo-controlled prestudy evaluation within 7 to 10 days before entering the double-blind treatment period. The prestudy assessments included a complete medical and psychiatric history including administration of HAM-D and Covi scales, a complete physical examination, vital signs, standard clinical laboratory testing, serum β-hCG pregnancy test for women, and a 12-lead ECG. After the single-blind phase, patients were assessed with the HAM-D, the Hamilton Rating Scale for Anxiety (HAM-A),[18] the Covi scale, the Hospital Anxiety and Depression Scale (HAD),[19] and the Clinical Global Impressions (CGI) scale.[20] These assessments were repeated on days 7, 14, 21, 28, 42, 56, and 84.

Patients who satisfied the selection criteria were randomly assigned to venlafaxine XR 75 mg, fluoxetine 20 mg, or placebo once daily for 13 days. The investigator could increase the doses of venlafaxine XR and fluoxetine, if clinically indicated for an improved response, to 150 mg and 40 mg, respectively, on day 14 and to 225 mg and 60 mg, respectively, on day 28. From day 28, dosages were maintained within the range of 75 to 225 mg/day for venlafaxine XR and 20 to 60 mg/day for fluoxetine. At the end of the double-blind treatment period, the dosage of venlafaxine XR was tapered over 4 to 8 days for patients receiving 150 to 225 mg/day. All study medications, including placebo, were supplied in matching capsules and were administered with food in the morning. Patients were permitted to take chloral hydrate up to 1000 mg or zopiclone 7.5 mg at bedtime for sleep, but other psychotropic medications were prohibited. Cisapride, up to 30 mg/day, was recommended for nausea.

Study Assessments

Patients were examined and questioned regarding any adverse symptoms. Safety evaluation was based on reports of adverse events, concomitant medication records, vital signs, weight, ECG, and laboratory tests. Adverse events included treatment-emergent signs or symptoms (i.e., those that were new or that worsened during treatment), new intercurrent illnesses, or clinically significant changes in any laboratory test, vital signs, weight, or ECG.

Statistical Analysis

The primary efficacy variables were the final scores during therapy for the 21-item HAM-D, the HAM-A total, and the CGI improvement rating scales. Secondary variables were scores on the Covi, HAM-D depressed mood item, HAD scale, and CGI severity scale and HAM-D and HAM-A response rates. A response was defined as a decrease in total score of at least 50% from baseline for the HAM-D and HAM-A or a score of 1 (very much improved) or 2 (much improved) on the CGI improvement scale. A remission was defined as a final score less than 8 on the first 17 items of the HAM-D among patients classified as responders. Patients who withdrew before study completion had efficacy assessments performed on the last day of study medication. A poststudy evaluation also was done 4 to 7 days after the last dose of study medication.

Efficacy analyses were performed on an intent-to-treat basis, which included all patients who were randomly assigned to double-blind therapy, had at least 1 baseline evaluation on the HAM-D or HAM-A scale, received at least 1 dose of drug, and had at least 1 efficacy evaluation while on treatment. A last-observation-carried-forward (LOCF) analysis was used whereby the last observation for a patient who withdrew was carried forward to all subsequent assessment time periods. All tests were 2-sided at an α level of .05 with 90% power.

Analysis of variance (ANOVA) was used to test for comparability of treatment groups for continuous variables such as age, weight, clinical characteristics, and baseline scores for the HAM-D total and factors, HAM-A, and CGI severity. The Fisher exact test was used

Table 1. Baseline Demographics and Clinical Characteristics of Study Population[a]

Characteristic	Placebo (N = 118)	Venlafaxine XR (N = 122)	Fluoxetine (N = 119)
Sex, female:male	68:50	78:44	71:48
Age, y[b]	41.6 ± 10.8	41.1 ± 12.0	43.2 ± 10.9
Age range, y	19–69	19–71	18–65
Weight, kg[b]	80.1 ± 18.4	78.1 ± 18.2	76.9 ± 17.6
Duration of depression (wk), no. (%)			
0–4	1 (1)	2 (2)	1 (1)
5–12	11 (9)	13 (11)	15 (13)
13–26	24 (21)	26 (21)	22 (18)
27–52	23 (19)	22 (18)	24 (20)
53–104	17 (14)	21 (17)	23 (19)
> 104	42 (36)	38 (31)	34 (29)
No. of previous episodes[b]	2.1 ± 4.1	1.7 ± 3.5	2.5 ± 6.6
HAM-D total[b]	27.1 ± 4.5	27.6 ± 5.1	27.0 ± 4.6
HAM-A total[b]	25.4 ± 7.0	25.7 ± 8.1	24.5 ± 7.0
CGI severity of illness[b]	4.3 ± 0.7	4.3 ± 0.6	4.2 ± 0.6
Not assessed (0)[c]	1 (1)	0 (0)	0 (0)
Mildly ill (3)[c]	4 (3)	7 (5)	7 (6)
Moderately ill (4)[c]	76 (64)	80 (66)	82 (69)
Markedly ill (5)[c]	31 (26)	31 (25)	24 (20)
Severely ill (6)[c]	6 (5)	5 (4)	6 (5)

[a]Abbreviations: CGI = Clinical Global Impressions, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression.
[b]Mean ± standard deviation.
[c]Severity classification followed by numerical score in parentheses; expressed as number (%) of patients with that score.

Table 2. Reasons for Premature Withdrawal From the Study

Reason	No. (%) of Patients: Placebo (N = 119)	Venlafaxine XR (N = 128)	Fluoxetine (N = 121)	p Value[a]
Any reason	48 (40)	37 (29)	32 (26)	.051
Adverse reaction	6 (5)	13 (10)	8 (7)	.31
Failed to return	6 (5)	3 (2)	5 (4)	.52
Patient/subject request	4 (3)	3 (2)	1 (1)	.41
Unsatisfactory response/ lack of efficacy	29 (24)	6 (5)	6 (5)	< .001
Protocol violation	1 (1)	7 (5)	6 (5)	.10
Other medical event	0 (0)	2 (2)	4 (3)	.13
Other nonmedical event	2 (2)	3 (2)	2 (2)	1.00

[a]Between-group comparisons; Fisher exact test.

to compare nominal variables at baseline, such as sex, concurrent diagnoses, and concomitant medications, and for comparison of the proportion of patients who discontinued therapy. Scores for the HAM-D total and factors, HAM-A, HAD, CGI improvement and severity, and Covi were assessed at each visit by using a 2-way analysis of covariance (ANCOVA) with treatment, center, and the treatment by center interaction as factors and the baseline score as a covariate. Response and remission rates were compared by using the Fisher exact test, as were changes within groups in mean laboratory values, vital signs, weight, or ECG data over time. Comparisons between groups were made with a 2-way ANCOVA.

RESULTS

Three hundred sixty-eight patients were randomly assigned to study medication and were included in the safety analyses. Data from 9 patients were excluded from the efficacy analyses because no assessments were recorded during treatment. Baseline demographic and clinical characteristics of the 359 patients included in the intent-to-treat analyses were comparable between groups (Table 1). The mean duration of depression was 117 weeks with placebo, 109 weeks with venlafaxine XR, and 128 weeks with fluoxetine. A total of 117 (32%) patients withdrew before the end of the study (Table 2). Significantly ($p < .001$) more patients in the placebo group than in either active treatment group withdrew because of unsatisfactory response/lack of efficacy. The mean daily dose during week 2 was 74.8 mg for venlafaxine XR and 20.1 mg for fluoxetine, during week 4 was 111.2 mg for venlafaxine XR and 30.7 mg for fluoxetine, and during week 12 was 140.8 mg for venlafaxine XR and 39.9 mg for fluoxetine. Chloral hydrate or zopiclone were taken by 39%, 52%, and 40% of patients in the placebo, venlafaxine XR, and fluoxetine groups, respectively. Between 11% and 13% of patients took antacids or other drugs for the treatment of peptic ulcer disease.

Efficacy

From week 2 through week 12 and the final on-therapy assessment, mean HAM-D total scores decreased significantly ($p < .05$) with venlafaxine XR and fluoxetine compared with placebo (Table 3). On the HAM-A, mean scores decreased significantly ($p \leq .05$) with venlafaxine XR compared with placebo at weeks 8, 12, and the final on-therapy evaluation, but fluoxetine was significantly better than placebo only at the final on-therapy evaluation. Mean CGI improvement scores decreased significantly ($p < .05$) with venlafaxine XR and fluoxetine compared with placebo from week 2 through week 12 and the final on-therapy evaluation. Significant ($p < .05$) improvement was noted at weeks 8, 12, and the final on-therapy evaluation with venlafaxine XR and fluoxetine compared with placebo in HAM-D factor scores, except for the HAM-D sleep disturbance item. Significant ($p < .05$) improvement in the HAM-D cognitive disturbance item was noted with venlafaxine XR and fluoxetine compared with placebo as early as week 2. Venlafaxine XR but not fluoxetine was significantly better than placebo at week 2 on the HAM-D depressed mood item. HAD anxiety and depression factor scores and Covi anxiety scores were significantly ($p < .05$) improved with venlafaxine XR and fluoxetine compared with placebo at weeks 8, 12, and the final on-therapy evaluation.

On the HAM-D, the proportion of responders was significantly ($p < .05$) higher with venlafaxine XR and fluoxetine than with placebo at weeks 2, 8, 12, and the final

Table 3. Adjusted Mean Scores and Between Group Comparisons vs. Placebo (LOCF analysis)

Scale	Placebo (N = 118)	Venlafaxine XR (N = 122)	Fluoxetine (N = 119)	p Value vs Placebo[a] Venlafaxine XR	Fluoxetine
HAM-D Total					
Baseline	27.2	27.2	27.2	...	...
Week 1	23.7	23.1	22.7	.33	.12
2	21.7	19.3	20.1	.002	.043
3	19.5	17.2	17.6	.008	.027
4	18.0	15.9	16.0	.028	.038
6	16.9	14.5	14.7	.014	.026
8	16.4	13.0	13.4	< .001	.004
12	15.9	11.4	12.2	< .001	< .001
Final	16.1	11.3	12.0	< .001	< .001
HAM-A Total					
Baseline	25.2	25.2	25.2	...	...
Week 1	21.9	22.3	21.5	.51	.48
2	20.2	18.8	19.5	.076	.37
3	18.5	17.3	17.6	.17	.33
4	16.9	15.8	16.1	.29	.45
6	16.1	14.3	15.2	.07	.39
8	15.7	13.2	13.9	.017	.096
12	15.0	11.5	12.9	.002	.06
Final	15.0	11.5	12.8	.002	.042
CGI Improvement					
Week 1	3.6	3.3	3.3	.058	.036[b]
2	3.2	2.9	2.9	.018	.009
3	3.1	2.8	2.7	.014	.002
4	2.8	2.5	2.5	.018	.016
6	2.7	2.3	2.3	.015	.003
8	2.7	2.2	2.2	.004	.002
12	2.7	2.0	2.0	< .001	< .001
Final	2.7	2.0	2.0	< .001	< .001

[a]Difference between groups based on comparison of adjusted means.
[b]Comparison not significant because p value of F test not ≤ .05.

on-therapy evaluation (Figure 1). On the HAM-A, the proportion of responders was significantly ($p < .05$) higher with venlafaxine XR than with placebo at weeks 3, 8, 12, and the final on-therapy evaluation but was higher with fluoxetine than with placebo at week 3 only (Figure 2). At week 12, there were significantly ($p = .037$) more HAM-A responders with venlafaxine XR than with fluoxetine. The CGI improvement response rate was significantly ($p < .05$) higher than placebo from week 3 onward with fluoxetine and from week 4 onward with venlafaxine XR. The HAM-D remission rate was significantly ($p < .05$) higher at weeks 3, 4, 6, 8, 12, and the final on-therapy evaluation with venlafaxine XR and at weeks 8, 12, and the final on-therapy evaluation with fluoxetine compared with placebo (Figure 3).

When response rates on the HAM-D and HAM-A scales were combined, they were significantly ($p < .05$) higher with venlafaxine XR and fluoxetine than with placebo at weeks 2, 8, 12, and the final on-therapy evaluation. An analysis of response by the maximum prescribed dose was undertaken among patients who were not withdrawn before day 14. The proportion of patients whose dosage was increased was 81.0% for placebo, 74.4% for venlafaxine XR, and 79.7% for fluoxetine. The analysis on the combined HAM-D and HAM-A scales revealed a significantly ($p < .05$) higher response rate with venlafaxine XR than with placebo in the 2 higher dose groups (Figure 4). No differences were observed between fluoxetine and placebo on the combined HAM-D and HAM-A scales.

Safety

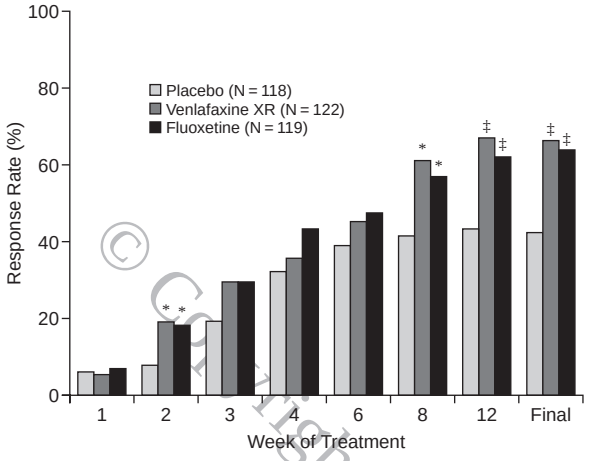
The incidence of adverse events with active drug occurring in more than 10% of patients and with at least twice the incidence of placebo is shown in Table 4. Significantly more dizziness ($p < .001$) and sweating ($p = .05$) occurred with venlafaxine XR than with fluoxetine. Dizziness, insomnia, sweating, nervousness, and anorexia occurred significantly ($p < .05$) more often with venlafaxine XR than with placebo. Insomnia occurred significantly ($p < .001$) more often with fluoxetine than placebo. The incidence of nausea was 28% with placebo, 41% with venlafaxine XR, and 32% with fluoxetine ($p = .094$ venlafaxine vs. placebo). Figure 5 shows the incidence of nausea over time by treatment. The highest incidence occurred during the first week; 28% experienced nausea with venlafaxine XR compared to 19% with fluoxetine, but the incidence of nausea with venlafaxine XR rapidly declined and was comparable to that with fluoxetine thereafter. Adverse events were the primary reason for discontinuation in 6 (5%) patients in the placebo group, 13 (10%) in the venlafaxine XR group, and 8 (7%) in the fluoxetine group. When primary and secondary reasons were considered, adverse events caused discontinuation in 6% of the placebo group, 13% of the venlafaxine XR group, and 11% of the fluoxetine group. Nausea, headache, anxiety, and dizziness were the most common adverse events, causing the withdrawal of 3% of venlafaxine XR and 4% of fluoxetine patients.

No unexpected clinically significant changes attributable to venlafaxine XR or fluoxetine occurred in laboratory test results, weight, or ECG results. Changes in blood pressure from baseline with venlafaxine XR or fluoxetine were slight and transient and not of clinical significance. Potentially clinically significant elevations in supine diastolic blood pressure were recorded in 2 patients (2%) in the placebo group, 4 (3%) in the venlafaxine group, and 2 (2%) in the fluoxetine group. The change from baseline in supine diastolic blood pressure ranged from –0.6 to 1.2 mm Hg with venlafaxine and from –2.4 to 0.8 mm Hg with fluoxetine. The only significant difference was at week 12 ($p = .042$, venlafaxine XR vs. fluoxetine) when supine diastolic blood pressure decreased 2.4 mm Hg from baseline with fluoxetine and increased 0.6 mm Hg with venlafaxine XR.

DISCUSSION

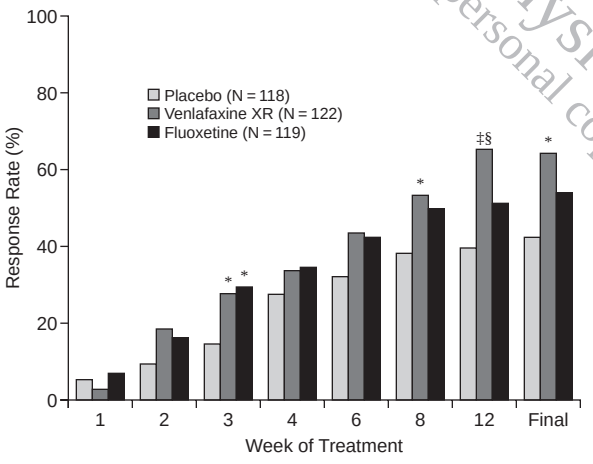
We report here the results from a double-blind, placebo-controlled trial comparing once-daily venlafaxine

Figure 1. HAM-D Response Rate (≥ 50% decrease from baseline) With Placebo, Venlafaxine XR, and Fluoxetine



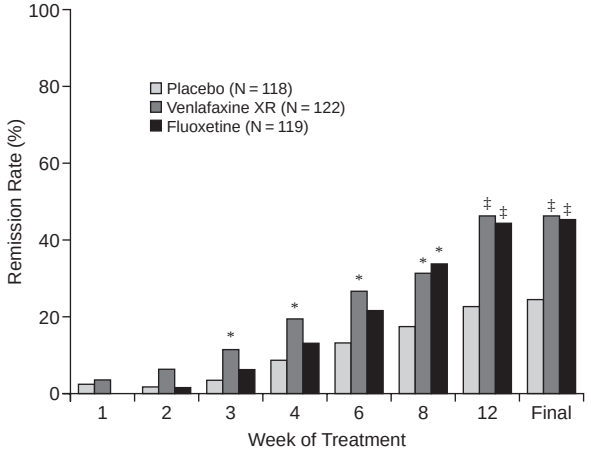
*p < .05 vs. placebo.
‡p < .001 vs. placebo.

Figure 2. HAM-A Response Rate (≥ 50% decrease from baseline) With Placebo, Venlafaxine XR, and Fluoxetine



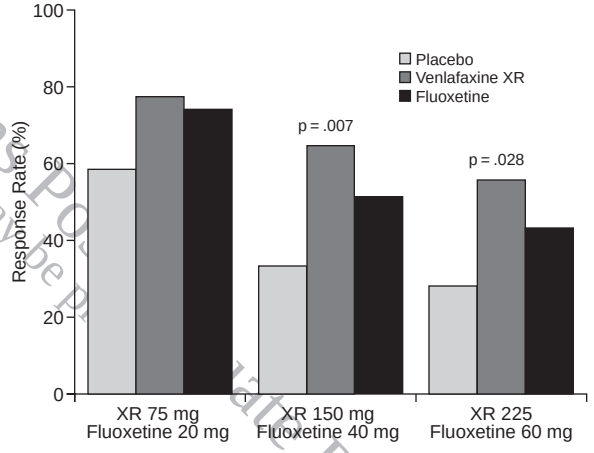
*p < .05 vs. placebo.
‡p < .001 vs. placebo.
§p = .037 vs. fluoxetine.

Figure 3. HAM-D Remission Rate (HAM-D score < 8) With Placebo, Venlafaxine XR, and Fluoxetine



*p < .05 vs. placebo.
‡p < .001 vs. placebo.

Figure 4. HAM-D + HAM-A Response Rate at Week 12 by Dosage Regimen for Venlafaxine XR and Fluoxetine[a]



[a]p Value represents difference between venlafaxine XR and placebo (Fisher exact test). [Number of patients for venlafaxine XR: 75 mg = 30, 150 mg = 55, 225 mg = 32; fluoxetine: 20 mg = 23, 40 mg = 55, 60 mg = 35; placebo = 22, 40, and 54.]

XR and fluoxetine in patients with major depression and concomitant anxiety. Venlafaxine XR and fluoxetine demonstrated consistent superiority over placebo on primary and most secondary efficacy scales beginning as early as 2 weeks. Of note, once-daily venlafaxine XR was superior to fluoxetine for the proportion of patients responding on the HAM-A. This is an important finding because previous studies have shown that patients with comorbid anxiety and depression are more difficult to treat, have a more chronic course of disease, and experience poorer outcomes than patients with depression alone.[2,3]

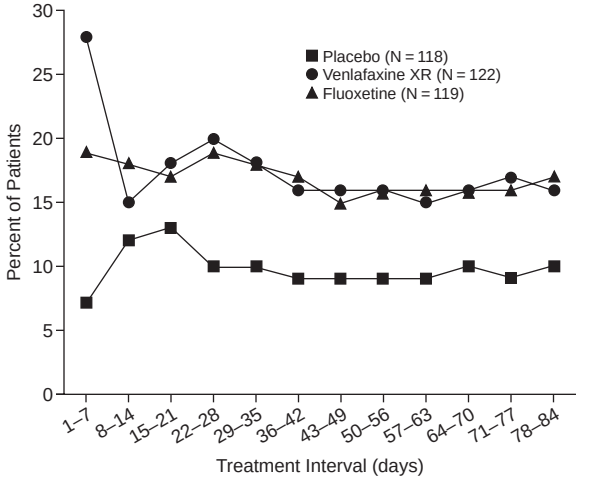
These results indicate that venlafaxine XR may be an effective treatment among patients with depression and anxiety. Further, the results are even more impressive considering that no attempt was made to exclude possible drug-induced side effects from symptoms reported on the HAM-D or HAM-A scales even though many of these side effects are similar to rated symptoms of depression or anxiety. In the present study, we were trying to determine the medication effects in patients with both major depression and anxiety by combining results from the HAM-D and HAM-A scales. Few studies have examined patients with this overlap of disorders, and the treatment of mixed

Table 4. Most Common (≥ 10% and at least twice that of placebo)[a] Treatment-Emergent Adverse Effects Occurring During Double-Blind Treatment With Venlafaxine XR or Fluoxetine

	No. (%) of Patients With Events			
Adverse Effect	Placebo (N = 119)	Venlafaxine XR (N = 128)	Fluoxetine (N = 121)	p Value[b]
Anorexia	3 (3)	13 (10)	8 (7)	.046
Dizziness	20 (17)	49 (38)	22 (18)	< .001
Dry mouth	14 (12)	30 (23)	22 (18)	.055
Insomnia	12 (10)	41 (32)	30 (25)	< .001
Nervousness	8 (7)	23 (18)	14 (12)	.027
Somnolence	7 (6)	17 (13)	17 (14)	.075
Sweating	12 (10)	36 (28)	21 (17)	.001
Tremor	4 (3)	13 (10)	12 (10)	.064

[a]Regardless of whether adverse event was treatment related.
[b]Fisher exact test.

Figure 5. Incidence of Nausea by Treatment Interval With Placebo, Venlafaxine XR, and Fluoxetine



anxiety-depressive disorders remains unclear. However, we believe that in this patient population, the use of the paired outcome criterion (HAM-D plus HAM-A) provides a more relevant overall perspective of the global outcome for these patients. This approach may be useful for other studies dealing with patients having concomitant depression and anxiety disorders.

This study used a flexible dosage schedule that allowed an increase in the doses of both venlafaxine XR and fluoxetine at the investigators' discretion. Typically, patients with depression and concomitant anxiety may be characterized as less responsive to antidepressant therapy, which was demonstrated by the high proportion of patients in both groups requiring dosage escalation. Consistent with other findings,[21–23] greater separation between venlafaxine XR and fluoxetine was observed at higher doses despite a lower response rate in both groups, which might be consistent with a subgroup of patients who are more difficult to treat. These differences became most apparent when strict criteria for response were used, in effect a HAM-D score less than 8, which has been suggested by others as the optimal criterion for response to antidepressant therapy.[24,25] Venlafaxine XR has a linear dose-response curve that produces an increased response at higher doses, which offers the potential to tailor antidepressant treatment to response. One limitation of this study is that no information was available on previous use of SSRI antidepressants. Inclusion of SSRI nonresponders may have biased the results toward venlafaxine XR. Further study is needed of the response to antidepressants of a different class among patients with a history of nonresponse to SSRIs.

Patients with depression and concomitant anxiety may be less responsive to antidepressant treatment than those with major depression alone and may have a higher rate of adverse events. Use of tricyclic antidepressants in patients with comorbid anxiety may be limited by excessive sedation and other adverse events and by uncertain efficacy.[26] The newer SSRIs may be associated with agitation, insomnia, and sexual dysfunction,[27] and they are well known to be associated with numerous clinically significant drug-drug interactions.[28] In this trial, most patients reported at least 1 adverse event; nonetheless, only 10% of venlafaxine XR–treated and 7% of fluoxetine-treated patients withdrew because of adverse events. Although nausea, headache, anxiety, and dizziness were the most common adverse events with venlafaxine XR and fluoxetine, the incidence after the first week of therapy was not greatly different from placebo. This finding is consistent with previous reports on venlafaxine XR[12,13] and immediate release venlafaxine.[29] Results from this study showed no clinically significant changes in supine diastolic blood pressure between the venlafaxine XR group for doses up to 225 mg/day and the placebo or fluoxetine groups. This finding is similar to results from other studies of venlafaxine XR.[12,13] A comparative study of venlafaxine and paroxetine found no differences in blood pressure between groups.[30]

In summary, once-daily venlafaxine XR was significantly more effective than placebo for treating patients with major depression and concomitant anxiety and at least comparable to fluoxetine as measured on primary efficacy variables and on some secondary variables. However, at week 12 on the HAM-A response rate, venlafaxine XR exhibited a significant difference from fluoxetine. Comparison of venlafaxine XR at doses above 75 mg/day and fluoxetine at doses above 20 mg/day showed higher response rates at week 12 with venlafaxine XR than with fluoxetine. After week 1, the tolerability profile of venlafaxine XR was comparable to that of fluoxetine. These results further support the suggestion that drugs with combined serotonergic and noradrenergic reuptake blockade may be more efficacious than drugs blocking serotonin reuptake alone.[31–33]

Drug names: chloral hydrate (Noctec), cisapride (Propulsid), fluoxetine (Prozac), paroxetine (Paxil), venlafaxine (Effexor).

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