Efficacy and Tolerability of Once-Daily Venlafaxine Extended Release (XR) in Outpatients With Major Depression

Michael E. Thase, M.D., for the Venlafaxine XR 209 Study Group

Background: This was a randomized, double-blind, placebo-controlled evaluation of the efficacy and safety of once-daily venlafaxine extended release (XR) in outpatients with DSM-IV major depression.

Method: Patients were randomly assigned to venlafaxine XR (75–225 mg) once daily or placebo for up to 8 weeks. The primary efficacy variables were the 21-item Hamilton Rating Scale for Depression (HAM-D) total score and HAM-D depressed mood item, the Montgomery-Asberg Depression Rating Scale (MADRS) total scores, and the Clinical Global Impressions (CGI) Severity scale. Data were analyzed on a modified intent-to-treat basis using the last-observation-carried-forward method.

Results: Venlafaxine XR (N = 91) was significantly more effective than placebo (N = 100) beginning at Week 2 on the CGI Severity scale, at Week 3 on the HAM-D depressed mood item, and at Week 4 on the HAM-D and MADRS; this superiority was maintained through Week 8. The most common treatment-emergent adverse events associated with venlafaxine XR were nausea, insomnia, and somnolence. The incidence of nausea was highest during the first week, decreased by 50% during the second week, and was comparable to that of placebo from Week 3 onward.

Conclusion: These results demonstrate that venlafaxine XR is an effective and well-tolerated treatment of major depression.

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Venlafaxine XR 209 Study Group: J. Carman, M.D. (Carman Research, Atlanta, Ga.), L. Charles, M.D. (Southern New Jersey Medical Institute, Stratford), C. Cohn, M.D. (The Cohn Research Center, Houston, Tex.), J. Farrell, D.O. (Midwest Pharmaceutical Research, St. Peters, Mo.), M. Fava, M.D. (Massachusetts General Hospital, Boston), A. Feiger, M.D. (Feiger PsychMed Center, Wheat Ridge, Colo.), J. Feighner, M.D. (Feighner Research Institute, San Diego, Calif.), J. Ferguson, M.D. (Pharmacology Research Corporation, Salt Lake City, Utah), S. Goldstein, M.D. (Center for Psychobiology, New York, N.Y.), M. E. Thase, M.D. (University of Pittsburgh, Pittsburgh, Pa.), R. Weisler, M.D. (Holly Hill Hospital, Raleigh, N.C.), and K. Yonkers, M.D. (The University of Texas Southwestern Medical Center, Dallas).

Reprint requests to: Michael E. Thase, M.D., University of Pittsburgh, WPIC, 3811 O'Hara Street, Pittsburgh, PA 15213.

Venlafaxine is an effective and well-tolerated treatment of major depressive disorder.[1–8] Venlafaxine differs from other newer antidepressants in that it selectively inhibits neuronal reuptake of both serotonin and norepinephrine, yet it has a low affinity for muscarinic cholinergic, histaminergic, and α_1-adrenergic receptors that are associated with side effects characteristic of tricyclic antidepressants (TCAs).[9]

Following oral administration, venlafaxine is rapidly absorbed and reaches peak plasma levels in approximately 2 hours. Venlafaxine has an elimination half-life of approximately 5 hours, and that for its active metabolite, O-desmethylvenlafaxine, is approximately 11 hours.[10] As a consequence, most patients take venlafaxine twice a day. Although single daily dosing of venlafaxine is feasible,[10] a new formulation with a pharmacokinetic profile better suited to once-a-day dosing may have important advantages in tolerability. A once-daily extended release (XR) formulation of venlafaxine was developed using a microsphere encapsulated preparation. In pilot single- and multiple-dose pharmacokinetic studies, the duration of absorption for once-daily venlafaxine XR was prolonged compared with the standard venlafaxine formulation so that the time to peak absorption was 6.3 hours for the XR compared with 2.3 hours for the conventional formulation. The extent of venlafaxine absorption and the extent of formation of the active metabolite, O-desmethylvenlafaxine, were similar for the XR and conventional formulations. Additionally, the pharmacokinetic profile of venlafaxine XR is not affected by administration with food or by morning or evening administration when assessed by the area-under-the-curve at steady state.

The purpose of this placebo-controlled study was to investigate the efficacy and tolerability of an extended release (XR) formulation of venlafaxine administered once daily in outpatients with major depression.

METHOD

This was a multicenter, double-blind, placebo-controlled, randomized clinical trial to determine the efficacy and safety of once-daily venlafaxine XR in outpatients with major depression. Investigators enrolled 8 to

20 patients at each of 12 study sites. The protocol was approved by the appropriate ethics committees at each clinical site, and explicit written informed consent was obtained from all patients.

Patient Selection

Eligible patients (1) were outpatients, (2) aged 18 years or older, (3) satisfied DSM-IV criteria for major depressive disorder for at least 1 month, and (4) had a minimum baseline score of 20 on the 21-item Hamilton Rating Scale for Depression (HAM-D),[11] with not more than a 20% decrease in score between screening and baseline.

Patients were excluded if they had previously been treated with venlafaxine. Women who were lactating or pregnant (i.e., a positive β-subunit of human chorionic gonadotropin test) were not included. Patients were also excluded if they had a history of clinically significant medical disease or clinically significant abnormalities on a screening physical examination, an electrocardiogram (ECG), or laboratory tests. Additional exclusion criteria included acute suicidal tendencies, a history of a seizure disorder, a history or presence of a mental disorder due to a general medical condition, bipolar disorder, drug or alcohol abuse or dependence within the past year, or a history of any psychotic disorder not associated with depression. Patients could not have received an investigational drug, an antipsychotic drug, or electroconvulsive therapy within 30 days, fluoxetine within 21 days, or a monoamine oxidase inhibitor within 14 days. Patients could not take any antidepressant, anxiolytic, sedative-hypnotic, or other psychotropic drug or substance within 7 days of the start of double-blind treatment. Use of nonpsychotropic drugs with psychotropic effects (e.g., β-adrenergic blockers) was permitted if the dosage was stable for a minimum of 1 month before double-blind treatment.

Study Procedure

A single-blind, placebo-controlled, prestudy "lead-in" was completed 7 ± 3 days prior to baseline. Baseline assessments included the HAM-D, the Montgomery-Asberg Depression Rating Scale (MADRS),[12] and the Clinical Global Impressions (CGI) scale.[13]

Patients satisfying the selection criteria were randomly assigned to either venlafaxine XR 75 mg once daily in the morning or an identically appearing placebo. After Day 14, the dosage could be increased to two capsules (i.e., 150 mg/day) at the investigator's discretion if the response was not adequate. A further increase to three capsules (225 mg/day) was allowed after Day 28. The venlafaxine dosage was maintained within the range of 75 to 225 mg/day for the remainder of the study period. At the end of the double-blind treatment period, study medications were tapered over a period of up to 2 weeks. Patient compliance was assessed by capsule counts of returned medications at each study visit. Chloral hydrate (500 mg to 1000 mg) could be administered at bedtime as needed for sleep. No other psychopharmacologic drugs were permitted during the study period.

Study Assessments

Efficacy was assessed on Days 7, 14, 28, 42, and 56 using the 21-item HAM-D, MADRS, and the CGI scale. The HAM-D score also was obtained on Day 21. The primary efficacy variables were the 21-item HAM-D, the HAM-D depressed mood item, the MADRS total, and CGI scales. For the HAM-D and MADRS scales, a response was defined as a decrease in total score of at least 50% from baseline; response was defined as a score of 1 (very much improved) or 2 (much improved) on the CGI Improvement item. A sustained response was defined as improvement that, once observed, persisted until the end of the trial. A final 21-item HAM-D total score of 8 or less defined a remission.

Patients who withdrew before study completion had efficacy assessments performed within 3 days of the last full dose of study medication. A post-study evaluation was also conducted 4 to 10 days after study medication was discontinued.

Safety evaluation was based on reported adverse events and changes (pre-post) in physical examination, vital signs, weight, ECG, and laboratory test results. Adverse events included treatment-emergent signs or symptoms, a new intercurrent illness, or clinically significant changes in any laboratory test, vital signs, weight, or ECG. Treatment-emergent study events were all new adverse events or adverse events that worsened during treatment.

Statistical Analysis

Efficacy analyses were performed on a modified intent-to-treat basis, which included all patients who received at least one double-blind dose of study drug and had at least one primary efficacy evaluation during treatment. A last-observation-carried-forward (LOCF) analysis was used so that the outcome of patients who discontinued could be retained in the analysis. All tests were two-tailed at an alpha level of .05 with a 90% power.

Analyses of variance (ANOVAs) were used to test for comparability of treatment groups with respect to age, weight, and baseline scores for the HAM-D total and factors, MADRS total, and CGI Severity. Chi-square tests or Fisher's exact probability tests were used to compare baseline categorical characteristics, such as sex, concurrent diagnoses, and concomitant medications, and for comparisons among groups in the proportion of patients discontinuing therapy. Paired t tests were used to test within-group changes in mean laboratory values, vital signs, weight, and ECG data over time. Comparisons between groups were made with two-way analyses of covariance (ANCOVAs).

Table 1. Baseline Demographics and Clinical Characteristics of Study Population*

Characteristic	Placebo (N = 102)	Venlafaxine XR (N = 95)
Sex (female:male)	61:41	60:35
Age (y)[a]	42 ± 12	40 ± 11
Age range (y)	21–77	18–66
Weight (kg)[a]	175 ± 43	173 ± 44
Duration of depression, N (%)		
0–4 wk	4 (4)	4 (4)
5–12 wk	11 (11)	11 (12)
13–24 wk	18 (18)	15 (16)
25–48 wk	15 (15)	23 (24)
48–96 wk	14 (14)	13 (14)
> 96 wk	40 (39)	29 (31)
Mean HAM-D total	24	25
Mean MADRS total	28	28
CGI Severity of Illness, N (%)		
Mildly ill (3)[b]	1 (1)	1 (1)
Moderately ill (4)[b]	75 (74)	62 (65)
Markedly ill (5)[b]	19 (19)	24 (25)
Severely ill (6)[b]	7 (7)	8 (8)

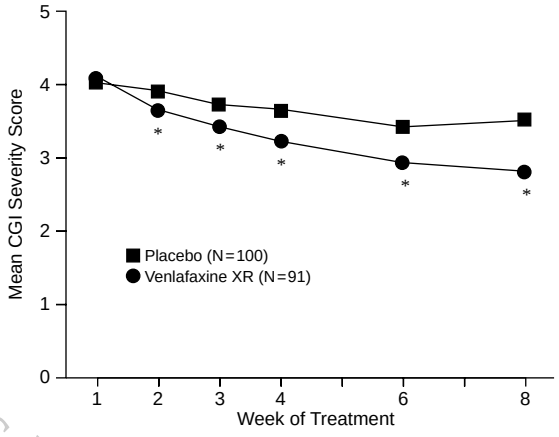
*Abbreviations: CGI = Clinical Global Impressions scale, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, Venlafaxine XR = Venlafaxine extended release formulation.
[a]Mean ± standard deviation.
[b]Number in parentheses refers to CGI score.

Table 2. Reasons for Premature Withdrawal From the Study by Primary Reason

	Placebo (N = 102)		Venlafaxine XR (N = 95)	
Reason	N	%	N	%
Any reason	41	40	26	27
Adverse reaction	6	6	10	11
Failed to return	6	6	8	8
Patient/subject request	4	4	0	0
Unsatisfactory response/efficacy	22	22	5	5[a]
Protocol violation	1	1	2	2
Other medical/nonmedical event	2	2	1	1

[a]p ≤ .001 vs placebo; Fisher's exact probability test.

Figure 1. Mean CGI Severity Scores for Venlafaxine XR and Placebo



*p < .05 vs placebo.

Changes from baseline for HAM-D, MADRS, and CGI scores were assessed using two-way ANCOVAs, with treatment and investigator as factors and the baseline score as a covariate. Response and remission rates were compared at each time point using Fisher's exact probability test.

RESULTS

One hundred ninety-seven patients were randomly assigned to study medication and were included in the safety analyses. Data from 6 patients were excluded from the efficacy analyses because on-treatment assessments were not recorded. The venlafaxine XR (N = 91) and placebo (N = 100) treatment groups were comparable with respect to baseline demographic and clinical characteristics (Table 1). Forty-one (40%) placebo-treated and 26 (27%) venlafaxine XR–treated patients withdrew before the end of the study (Table 2). Although the discontinuation rate per week of treatment was comparable between placebo and venlafaxine XR groups, significantly more patients withdrew from the placebo group because of unsatisfactory response (22% vs. 5%; p ≤ .001). Attrition due to other causes, including adverse events, was comparable in the two groups (18% vs. 22%). The mean daily dose of venlafaxine XR from Days 29 to 56 ranged from 172 to 177 mg. Chloral hydrate was given to 7 patients in each group.

Efficacy

Venlafaxine XR was significantly more effective (p < .05) than placebo beginning at Week 2 on the CGI Severity scale (Figure 1), at Week 3 on the HAM-D depressed mood item, and at Week 4 on the HAM-D and MADRS scales (Table 3). These significant differences were maintained through the end of the study. By Week 8, the change in scores from baseline on all dependent measures was approximately twice as large in the venlafaxine XR group compared with placebo.

The HAM-D response rates for venlafaxine XR and placebo were 49% and 34% at Week 6 (p = .04) and 58% and 29% at Week 8 (p < .001). Similarly, the MADRS response rate at Week 8 was 48% with venlafaxine XR and 28% with placebo (p = .005). On the CGI Improvement scale, the response rates at Weeks 6 and 8 were 58% and 60% with venlafaxine XR and 42% and 37% with placebo (p = .03 and p = .001, respectively). Sustained response rates on the HAM-D total, MADRS total, and CGI Improvement scales also were significantly higher (p < .05) with venlafaxine XR than with placebo (Figure 2). Remission was achieved in 19 (19%) of 100 patients on placebo and 32 (35%) of 91 patients on venlafaxine XR treatment.

Safety

Adverse events were the primary reason for premature discontinuation in 6 (6%) placebo-treated and 10 (11%)

Table 3. Adjusted* Mean Scores and Between-Group Comparisons of Primary Efficacy Variables

	Placebo (N = 100)		Venlafaxine XR (N = 91)		
Measure	Mean	SE	Mean	SE	p values[a]
HAM-D Total					
Baseline	24.1		24.1		
Week 1	20.5	0.51	20.2	0.54	.76
2	19.1	0.56	17.6	0.59	.07
3	17.5	0.69	16.2	0.71	.16
4	17.6	0.70	15.0	0.75	.008
6	16.0	0.79	13.5	0.82	.02
8	16.8	0.81	12.4	0.86	< .001
HAM-D Depressed Mood Item					
Baseline	2.8		2.8		
Week 1	2.4	0.08	2.2	0.08	.09
2	2.2	0.10	2.0	0.10	.08
3	2.1	0.10	1.8	0.10	.02
4	2.1	0.10	1.7	0.11	.005
6	2.0	0.11	1.5	0.12	.002
8	2.1	0.12	1.3	0.12	< .001
MADRS Total					
Baseline	27.9		27.9		
Week 1	23.2	0.65	23.6	0.68	.64
2	22.5	0.76	20.9	0.80	.14
3	21.5	0.85	19.5	0.89	.10
4	21.4	0.90	18.3	0.95	.02
6	19.3	1.02	16.0	1.08	.02
8	20.6	1.08	15.2	1.14	< .001
CGI Severity					
Baseline	4.4		4.4		
Week 1	4.0	0.07	4.1	0.07	.56
2	3.9	0.08	3.6	0.09	.03
3	3.7	0.10	3.4	0.10	.03
4	3.6	0.10	3.2	0.11	.004
6	3.4	0.12	2.9	0.13	.004
8	3.5	0.13	2.8	0.14	< .001

*Adjusted for baseline severity.
[a]Difference between groups based on comparison of adjusted means; p value determined by ANCOVAs of intent-to-treat sample with last observation carried forward.

Figure 2. Sustained Response Rates on the HAM-D, MADRS, and CGI Improvement Scales With Venlafaxine XR and Placebo

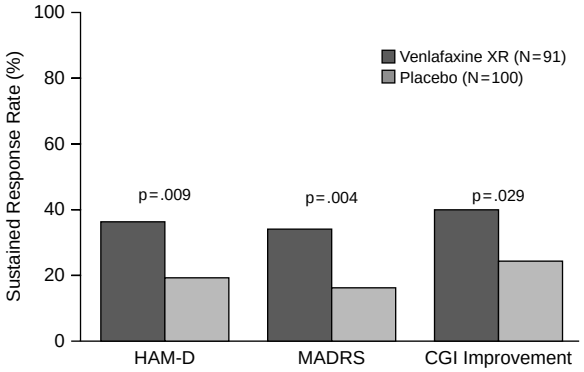


Table 4. Most Common (≥ 10% and Twice the Placebo Incidence)* Treatment-Emergent Adverse Effects Occurring During Double-Blind Treatment With Venlafaxine XR

	Placebo (N = 102)		Venlafaxine XR (N = 95)	
Adverse Effect	N	%	N	%
Nausea	18	18	34	36
Insomnia	15	15	33	35
Somnolence	11	11	26	27
Dry mouth	9	9	17	18
Nervousness	4	4	16	17
Anorexia	4	4	15	16
Sweating	4	4	13	14
Impotence (male only)	0	0	5/35	14
Abnormal ejaculation/orgasm				
Men	1/41	2	8/35	23
Women	0	0	2/60	3
Anorgasmia (women)	1/61	2	4/60	7
Dysmenorrhea	6/61	10	5/60	8

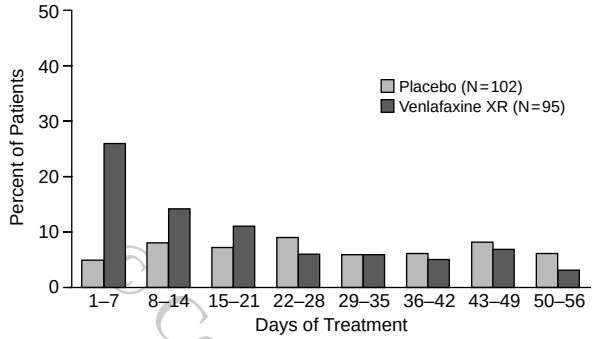
*Number and percent given are total regardless of treatment relatedness.

venlafaxine XR–treated patients (Table 2). Of these adverse events, the most common reasons for discontinuation in the venlafaxine XR group were nausea (4%) and insomnia (3%) and in the placebo group were headache (3%) and dizziness (3%). Table 4 summarizes the treatment-emergent adverse events that were reported by ≥ 10% of venlafaxine XR–treated patients, with an incidence at least twice that of placebo. The most common adverse events in the venlafaxine XR group were nausea (36%), insomnia (35%), and somnolence (27%). The most common adverse events in the placebo group were nausea (18%), insomnia (15%), and somnolence (11%).

The incidence of nausea was highest during the first week of treatment with venlafaxine XR (26%) but decreased to 14% by Week 2 and thereafter was similar to the incidence with placebo (Figure 3). The decline in self-reported nausea was not explained by the selective attrition of patients reporting this adverse effect: among the 28 venlafaxine XR–treated patients who remained on active treatment, only 4 to 6 patients per week continued to report nausea after the fourth week of therapy (see Figure 3).

Treatment with venlafaxine XR was associated with few clinically significant changes in laboratory test results, in vital signs and weight, or in ECG assessments. Mean supine diastolic blood pressure did increase by 3.1 mm Hg in the venlafaxine XR group from 75.3 (SD = 7.5) mm Hg at baseline to 78.4 (SD = 9.2) mm Hg at Week 8 ($p < .01$ vs. baseline). A clinically significant increase in supine diastolic blood pressure, defined by at least a 10 mm Hg increase from baseline to a value > 90 mm Hg at some point in the trial, was observed in 4 venlafaxine-treated patients and 1 patient in the placebo group. All episodes were transient and were not associated with any adverse events or discontinuations. Importantly, no clinically significant withdrawal syndromes were observed

Figure 3. Incidence of Nausea With Venlafaxine XR and Placebo Treatment



during double-blind discontinuation of study medications.

DISCUSSION

Clinical trials with the standard venlafaxine formulation have consistently demonstrated its efficacy across the broad range of patients with major depressive disorder.[2–4,6,7,14–17] The results of this double-blind, placebo-controlled, randomized clinical trial demonstrate that once-daily venlafaxine XR is an efficacious and well-tolerated treatment for major depression.

The major limitation of this study is that it did not include a parallel group treated with the standard formulation of venlafaxine. The response rates with venlafaxine XR in the current study were comparable to those observed in earlier studies of the standard venlafaxine formulation. However, it is not yet possible to directly compare the efficacy and, more importantly, tolerability of the two forms of venlafaxine. Some evidence suggests that the standard formulation of venlafaxine may have a rapid onset of action when it is titrated rapidly to doses above 200 mg/day.[1,15] Because of the gradual dose titration over 2 to 4 weeks, this trial was not designed to test the rapidity of onset of action of the XR formulation. Nevertheless, a significant difference from placebo was observed on the CGI Severity scale by the second week of therapy.

This study used a flexible dosage schedule that permitted the treating psychiatrist to increase the dose of once-daily venlafaxine XR to a maximum of 225 mg daily if medically indicated. The mean daily dose was about 170 mg/day. Previous studies with the standard venlafaxine formulation found that the minimum effective dose was 75 mg/day and that approximately 50% of responders benefit from this dose.[4,8] Nevertheless, clinical studies have documented greater response rates with higher doses of venlafaxine.[4,5] The capacity to improve the response by increasing the dose of venlafaxine may offer an advantage in patients not responding at initial doses. Thus, it will be important to study the efficacy and safety of venlafaxine XR at 300-mg and 375-mg doses among patients not responsive to 225 mg/day.

Overall, venlafaxine XR was well tolerated; comparable numbers of patients in both treatment groups discontinued study medication because of adverse effects. Nausea was the most commonly reported adverse event with venlafaxine XR, and, while the incidence was higher than with placebo, it was somewhat lower than observed in other studies with the standard venlafaxine formulation.[3,5] As in previous reports,[4] the incidence of nausea decreased rapidly after the first 1 to 2 weeks of treatment and was comparable to that of placebo for the remainder of the study.

Venlafaxine XR was also associated with a small, but statistically significant, increase in supine diastolic blood pressure. This effect, which is well documented with the immediate release formulation,[18] was generally not clinically significant and was largely dose dependent.[19] Nevertheless, the manufacturer recommends regular monitoring of blood pressure at all doses.

In summary, the results from this double-blind, placebo-controlled study demonstrate that once-daily administration of venlafaxine XR is safe, effective, and well tolerated for the treatment of major depression. The once-daily extended release formulation of venlafaxine offers the safety, efficacy, and tolerability of the standard venlafaxine formulation combined with increased convenience and the potential for improved patient compliance.

Drug names: chloral hydrate (Noctec), fluoxetine (Prozac), venlafaxine (Effexor).

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