Venlafaxine Versus Placebo in the Preventive Treatment of Recurrent Major Depression

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Background: Major depression is often chronic and recurrent, yet most long-term therapeutic trials are not adequately designed to assess antidepressant efficacy in recurrence prevention. Long-term efficacy and safety of prophylactic venlafaxine treatment were evaluated in outpatients with recurrent major depression.

Method: Patients with a history of recurrent DSM-III-R major depression received open-label treatment with venlafaxine, 100 to 200 mg/day, for 6 months. Those who responded to treatment (Hamilton Rating Scale for Depression [HAM-D_{21}] score ≤ 12, day 56) and remained relapse-free (no more than 2 HAM-D_{21} scores > 10 and no Clinical Global Impressions-Severity of Illness [CGI-S] score ≥ 4, months 2–6) either continued taking venlafaxine, 100 to 200 mg/day, or were switched in a double-blind fashion to placebo for 12 months. The primary efficacy outcome was the number of patients experiencing a recurrence of major depression (CGI-S score ≥ 4). The cumulative probability of recurrence was calculated using the Kaplan-Meier method of survival analysis. Data were collected from November 1992 through December 1995.

Results: Of the 235 patients who enrolled in the recurrence-prevention period, 225 (N = 109, venlafaxine; N = 116, placebo) provided efficacy data. Survival analysis determined a 22% cumulative probability of recurrence in venlafaxine-treated patients after 12 months compared with 55% for the placebo group ($p < .001$). More than twice as many placebo-treated patients (48%) as venlafaxine-treated patients (21%) discontinued treatment because of lack of efficacy ($p < .001$).

Conclusion: Twelve-month maintenance venlafaxine treatment was significantly more efficacious than placebo in preventing major depression recurrence in patients who had been successfully treated with venlafaxine for 6 months.

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Major depression is a chronic and highly recurrent psychiatric disorder[1,2] with a lifetime prevalence of approximately 17%.[3,4] Recurrence, a new depressive episode that occurs during the maintenance phase of treatment (i.e., beyond 4 to 6 months from the index episode),[5–7] is distinct from relapse, which typically occurs during a continuation phase of treatment (i.e., 4 to 6 months following the index episode). The cumulative probability of recurrence of depression at 15 years is about 86%.[8–10]

The high risk of recurrence of major depression and its associated impairment, morbidity, and mortality[11–14] underscore the importance of long-term maintenance treatment for this disorder.[5,15] Although effective pharmacotherapeutic agents are available, depressed patients are often undertreated[11] or treated for an inadequate length of time.[9,11,16] Various consensus groups have recommended that all depressed patients should continue treatment with an antidepressant for at least 4 months after a treatment response has been achieved to optimize the likelihood of attaining an asymptomatic state and returning to premorbid functioning, i.e., remission.[17,18] Hence, to distinguish recurrence from relapse, a symptom-free period corresponding to the length of the continuation treatment phase is required to demonstrate that the patient has recovered from the index episode.

Recurrence is predicted by a number of factors including the severity of depression,[19] the number of prior episodes,[2,10] the time since the previous episode,[2] and the absence of remission[20] or presence of subsyndromal symptoms.[10] The probability of recurrence of depression increases with the number of prior episodes—the probability of recurrence over a 5-year period is < 60% for 1 previous episode but > 95% for 3 or more episodes.[9,14,21] To study recurrence prevention, it is helpful to include a population with a minimum number of recurrences and a measure of recency of the last episode. The most com-

monly used criterion, which covers both requirements, is the criterion of 2 episodes within a 5-year period.

Recurrence-prevention studies are methodologically challenging because they must be long-term studies that rely heavily on patients who maintain good adherence to taking daily doses of antidepressant medication regardless of how they are feeling. The methodological challenges of evaluating recurrence prevention may contribute to the relative dearth of long-term studies evaluating the prophylactic efficacy of antidepressants—existing reports mostly involve either tricyclic antidepressants (TCAs)[22–24] or selective serotonin reuptake inhibitors (SSRIs).[25–28] Venlafaxine, a serotonin and norepinephrine reuptake inhibitor,[29] is an effective antidepressant. Clinical studies suggest that it has a rapid onset of action, producing significant clinical improvement in the first or second week of treatment,[30–32] and long-term efficacy[33] and may have consistently superior remission rates compared with the SSRIs.[34–38]

The present study was carried out to investigate the efficacy of venlafaxine in the prevention of recurrence of depression in patients who have responded to treatment. Given that the severity of depression may be a predictor of recurrence, patients in the present study were required to have at least moderate severity of depression to qualify for the acute treatment phase. Patients also had to achieve a defined response within the first 8 weeks of acute venlafaxine treatment and maintain their response during a 4-month continuation treatment phase to be eligible for entry into the double-blind evaluation of the efficacy and safety of venlafaxine in outpatients with recurrent major depression.

METHOD

Patients

Outpatients 18 years or older who met DSM-III-R[39] criteria for major depression were eligible to participate in the study if they had a history of recurrent major depression (≥ 1 previous episode in the last 5 years with a symptom-free period of > 6 months between episodes) and symptoms of depression for > 1 month before study entry. Eligible subjects had to have a 21-item Hamilton Rating Scale for Depression (HAM-D_{21})[40] score of ≥ 20 at the prestudy screening and at the baseline visit, and no more than a 20% decrease in HAM-D_{21} scores between the 2 evaluations. Patients with a history of drug or alcohol dependence as defined by DSM-III-R criteria within 2 years of the start of the open treatment period were excluded. Subjects with a recent history of myocardial infarction; history of hepatic or renal disease; seizure disorder, psychotic disorder, or bipolar disorder; or hypersensitivity to venlafaxine were excluded from participation, as were pregnant or breastfeeding women and patients with concomitant psychiatric disorders meeting DSM-III-R criteria.

All subjects gave written consent before entering the study, and an institutional review board or an independent ethics committee at each study site approved the research protocol. Data were collected from November 1992 through December 1995.

Study Design

This multicenter double-blind placebo-substitution study was conducted at 31 psychiatric centers (15 in the United States and 16 in Europe) and consisted of 2 periods (after a 4- to 10-day single-blind placebo lead-in period). Period 1 (i.e., acute treatment and continuation phase) was a 6-month, open-label, safety and efficacy evaluation of patients who received venlafaxine immediate release (IR) (100–200 mg/day). Period 2 (recurrence prevention/maintenance phase) was a randomized, double-blind, placebo-controlled, 12-month comparison of venlafaxine (100–200 mg/day) or placebo. Only those patients who responded to acute venlafaxine treatment within 8 weeks (i.e., a HAM-D_{21} score of ≤ 12 at study day 56) and who sustained their response in the continuation treatment period (i.e., had no HAM-D_{21} score of ≥ 20, no more than 2 HAM-D_{21} scores of > 10, and no Clinical Global Impressions-Severity of Illness [CGI-S][41] item score of ≥ 4 [i.e., moderately ill] between study days 56 and 180) were eligible to enter the placebo-controlled maintenance phase of the study.

In the open treatment study period, venlafaxine IR treatment was begun at 50 to 75 mg twice daily and titrated up to 150 mg/day over the first 13 days. On days 14 to 80, the venlafaxine dose was titrated into the 100- to 200-mg/day range. The aim of the study was to examine the efficacy of conventional doses of venlafaxine in recurrence prevention. The dosage was selected according to the manufacturers' recommended dose range. Patients fulfilling the criteria for entry to the double-blind maintenance treatment period were randomly assigned to either continue venlafaxine 100 to 200 mg/day or receive placebo for ≤ 12 months under double-blind conditions. Those assigned to the placebo group had their venlafaxine dose tapered off in a blinded fashion over the first 2 weeks of the double-blind treatment period to minimize any potential for discontinuation symptoms.

Concomitant psychotropic medications were not permitted during the study with the exception of chloral hydrate in the United States and short-acting benzodiazepines in Europe (to improve sleep). Patients with established psychotherapy or counseling were allowed to enter the open treatment phase of the study, but initiation or change in intensity of either modality was not permitted.

Efficacy Assessments

Efficacy was assessed using the HAM-D_{21}, Montgomery-Asberg Depression Rating Scale (MADRS),[42]

and CGI-S. Recurrence was defined as a CGI-S score of ≥ 4 (moderate-to-severe depression).

Secondary efficacy variables included time to discontinuation in patients who withdrew from the study because of lack of efficacy and mean HAM-D_{21} total, MADRS total, and CGI-S scores.

Patients who had recurrence of depression were discontinued from the study and treated according to usual practice.

Interrater-reliability training was conducted at an investigator meeting prior to the start of the study. Training focused on the MADRS, the HAM-D_{21}, and the CGI.

Safety

Prestudy evaluations included a physical examination, vital signs, electrocardiogram (ECG), clinical laboratory evaluations, medical and psychiatric history, and recordings of current and prior medication.

Safety assessments were based on results of physical examinations, vital signs, ECGs, and clinical laboratory tests. Adverse events were monitored and patients' reports were recorded throughout the study.

Statistical Analysis

The primary efficacy outcome measure was the number of patients who had a recurrence of depression. Time to recurrence was analyzed by a survival analysis procedure using the log-rank test. The cumulative probability of recurrence was estimated with the Kaplan-Meier method of survival analysis, and comparisons of cumulative recurrence rates were calculated using z scores at selected timepoints. Survival function estimates were made for each month of the double-blind treatment period. The population analyzed consisted of those patients who had taken at least 1 dose of double-blind study medication and had at least 1 on-therapy CGI-S evaluation. To test whether possible discontinuation symptoms associated with the switch from venlafaxine to placebo might have contributed to recurrence, a secondary analysis was performed, excluding data from the patients who discontinued during the first 28 days of period 2. Time to discontinuation in patients who withdrew from the study because of lack of efficacy was also analyzed by survival analysis procedure.

Mean HAM-D_{21} total, MADRS total, and CGI-S scores were analyzed parametrically at baseline (last observation during the open-label treatment period) and at each timepoint during the double-blind treatment period using a 2-way analysis of covariance (ANCOVA) with treatment and study center as factors. Both observed cases (OC) and last-observation-carried-forward (LOCF) analyses were performed.

Fisher exact test was used to compare groups with respect to patient discontinuation rates and incidence of adverse events. Changes in laboratory test results and vital signs over time were assessed with the paired t test, and between-group comparisons were determined with a 1-way ANCOVA with treatment as a factor.

Table 1. Demographic and Baseline Characteristics of the Primary Survival-Analysis, Double-Blind Period Population

Characteristic	Venlafaxine (N = 109)	Placebo (N = 116)
Age, mean (SD), y	43.8 (11.0)	43.5 (11.2)
Sex, %		
Women	71	67
Men	29	33
Body weight, mean (SD), kg	67.2 (15.7)	68.4 (18.4)
No. of previous episodes in past 5 y (excluding index episode), mean (SD)	1.3 (0.6)	1.5 (0.8)
Lifetime no. of episodes (including index episode), N (%)[a]		
2	26 (25)	30 (28)
3	48 (47)	46 (43)
4	19 (18)	18 (17)
5	7 (7)	7 (6)
6	2 (2)	3 (3)
7	1 (1)	4 (4)
HAM-D_{21} total score, mean (SE)	4.5 (3.4)	4.9 (3.7)
MADRS total score, mean (SD)	4.3 (3.5)	5.2 (4.8)
CGI-S score, %		
1	48	44
2	37	30
3	14	26

[a]Venlafaxine IR, N = 103; placebo, N = 108.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D_{21} = 21-item Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale.

RESULTS

Patients

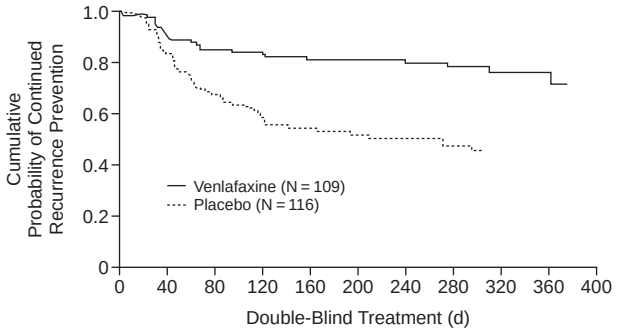
A total of 495 patients met the study inclusion criteria and entered the open-label treatment period. Of the 286 patients who completed the open treatment period, 235 entered the double-blind study and contributed data beyond baseline. Two hundred twenty-five (109 in venlafaxine group; 116 in placebo group) of these patients qualified for the survival analysis. Table 1 summarizes the demographic and baseline characteristics of the survival analysis population. The 2 groups were comparable on these characteristics and also on the use of hypnotics during the study.

Mean dosages of venlafaxine calculated for each month were 145 to 153 mg/day in the open-label period after titration and 132 to 152 mg/day in the double-blind period.

Efficacy

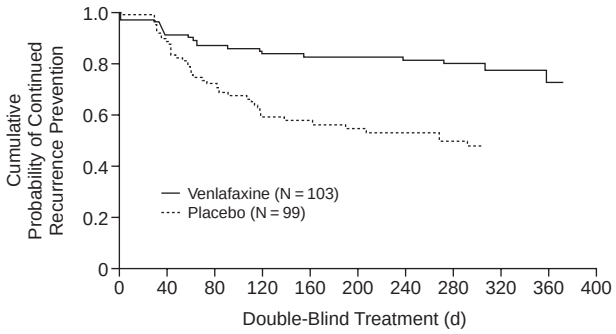
Open treatment phase. Patients had a mean ± SD HAM-D_{21} total score of 25.2 ± 4.2 upon entering the open-label trial. At the end of the 8-week acute treatment phase, the mean HAM-D_{21} total score (OC) was 8.89, and at the end of the 6-month open treatment period, the mean

Figure 1. Cumulative Probability of Continued Recurrence Prevention Accounting for All Months of Double-Blind Treatment[a]



[a]p < .001, venlafaxine vs. placebo.

Figure 2. Cumulative Probability of Continued Recurrence Prevention After Day 28 of Double-Blind Treatment[a]



[a]p < .001, venlafaxine vs. placebo.

Table 2. Summary of Survival Analysis Results

Type of Survival Analysis	Population[a]	Definition of Recurrence	N	Cumulative Recurrence Rates at 12 Mo	Log-rank χ^{2b}	p Value
Primary analysis	ITT	CGI-S score ≥ 4	Venlafaxine: 109 Placebo: 116	Venlafaxine: 22% Placebo: 55%	17.6	< .001
Excluding patients who withdrew in the first 28 d	ITT patients who remained in study for > 28 d	CGI-S score ≥ 4	Venlafaxine: 103 Placebo: 99	Venlafaxine: 20% Placebo: 52%	15.6	< .001
Discontinuation for lack of efficacy at endpoint	All randomized	Withdrawn for lack of efficacy	Venlafaxine: 112 Placebo: 123	Venlafaxine: 21% Placebo: 48%	20.1	< .001
Excluding patients with CGI-S score > 2 at randomization	ITT patients with CGI-S score ≤ 2 at randomization	CGI-S score ≥ 4	Venlafaxine: 89 Placebo: 79	Venlafaxine: 21% Placebo: 55%	16.8	< .001
Stratified by no. of previous episodes	ITT patients with > 2 previous episodes	CGI-S score ≥ 4	Venlafaxine: 30 Placebo: 35	Venlafaxine: 10% Placebo: 64%	16.5	.001

[a]ITT patients took at least 1 dose of double-blind medication and had at least 1 on-therapy CGI-S evaluation.
[b]df = 1.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, ITT = intent to treat.

HAM-D_{21} total score was 7.24 (OC). At the time of randomization, the mean HAM-D_{21} total scores for patients entering the recurrence-prevention phase of the study were 5.1 ± 3.8 for the placebo group and 4.6 ± 3.2 for the venlafaxine group (p = NS); 90% of the patients had a HAM-D_{21} score of < 10, and 75% met a stricter remission criterion of a HAM-D_{21} score of < 8.

Placebo-controlled recurrence prevention. The primary efficacy survival analysis results show that significantly (log-rank $\chi^2 = 17.6$, df = 1, p < .001) more patients in the placebo group than patients in the venlafaxine group experienced recurrence of depression during the 1-year double-blind recurrence-prevention period (Figure 1). After 1 year of treatment, the cumulative probability of recurrence of depression was 55% for placebo-treated patients and 22% for venlafaxine-treated patients.

An analysis of depression recurrence rates excluding all patients who withdrew from the study during the first 28 days of double-blind treatment for any reason (N = 17 placebo, N = 6 venlafaxine) produced similar results (Figure 2). This survival analysis was performed to evaluate if placebo-treated subjects who withdrew early might have done so because of potential discontinuation symptoms associated with the switch from venlafaxine to placebo, rather than because of recurrence of depression. After 1 year of treatment, the cumulative probability of recurrence of depression in this secondary analysis was 52% for placebo-treated subjects and 20% for venlafaxine-treated subjects (log-rank $\chi^2 = 15.6$, df = 1, p < .001) (Table 2).

Another analysis was carried out in the subpopulation of patients with a CGI-S score ≤ 2 at the time of randomization. In this analysis, significantly (log-rank $\chi^2 = 16.8$, df = 1, p < .001) more placebo-treated than venlafaxine-treated patients experienced recurrence of depression during the 1-year double-blind period. After 1 year of treatment, the cumulative probability of recurrence was 55% for placebo-treated patients and 21% for venlafaxine-treated patients (Table 2).

A further subpopulation analysis was carried out in patients with 3 or more episodes of depression within the previous 5 years. In this analysis, the overall cumulative probability of continued recurrence prevention was sig-

Table 3. Comparison Between Treatment Groups for HAM-D_{21} Total, HAM-D Depressed Mood Item, MADRS Total, and CGI-S Scores at the End of Study (month 12, LOCF)

Efficacy Measure	N	Mean ± SE	Adjusted Mean[a] (95% CI)	p Value
HAM-D_{21} total score				
Placebo	107	12.6 ± 0.87	12.2 (10.3 to 14.1)	< .001
Venlafaxine	106	8.2 ± 0.82	7.8 (5.9 to 9.7)	
HAM-D depressed mood item score				
Placebo	107	1.5 ± 0.11	1.5 (1.2 to 1.7)	< .001
Venlafaxine	106	0.9 ± 0.11	0.9 (0.6 to 1.1)	
MADRS total score				
Placebo	107	15.1 ± 1.14	14.0 (11.6 to 16.4)	< .001
Venlafaxine	106	9.5 ± 1.01	8.8 (6.3 to 11.2)	
CGI-S score				
Placebo	107	2.9 ± 0.13	2.8 (2.5 to 3.1)	< .001
Venlafaxine	106	2.2 ± 0.13	2.02 (1.8 to 2.4)	

[a]Adjusted for baseline scores.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale.

nificantly greater for patients treated with venlafaxine than that for patients treated with placebo (log-rank $\chi^2 = 16.5$, df = 1, p = .001). After 1 year of treatment, the cumulative probability of recurrence of an episode of depression was 64% for placebo-treated patients and 10% for venlafaxine-treated patients (Table 2).

When measured in terms of patient discontinuation due to lack of treatment efficacy, the cumulative probability of sustained recurrence prevention during 12 months of double-blind prophylactic treatment consistently favored venlafaxine over placebo. At 12 months, significantly more placebo-treated patients (48%, p < .001) had discontinued treatment because of lack of efficacy compared with venlafaxine-treated patients (21%) (Table 2).

Significant differences (p < .001) in favor of venlafaxine compared with placebo were also observed on the secondary outcome measures (HAM-D_{21} total, HAM-D depressed mood item [item 1], MADRS total, and CGI-S scores) using intent-to-treat LOCF analysis (Table 3). The mean HAM-D_{21} total scores of the patients in the venlafaxine group rose from 4.5 to 8.2, while those of the patients in the placebo group rose from 4.9 to 12.6. In the OC analysis, HAM-D_{21} total (Figure 3), MADRS total, and CGI-S scores were significantly lower for the venlafaxine-treated patients than for those in the placebo group at months 1 through 4 and at the final on-therapy observation of period 2 (p < .001).

Safety and Tolerability

One or more treatment-emergent adverse events (TEAEs) were reported by 80% of patients in the placebo group and by 79% in the venlafaxine group. No unexpected TEAEs were reported during the entire study. The most common TEAEs reported during the recurrence-prevention period for the venlafaxine-treated group included headache, dizziness, nausea, and pharyngitis, and for the placebo group, dizziness, headache, nausea, and nervousness (Table 4). Thirteen patients (11%) in the venlafaxine group and 7 (6%) in the placebo group experienced serious adverse events, which were composed of accidents (e.g., car crash, fall resulting in fracture), medical conditions (e.g., aortic aneurysm, Bell's palsy, myeloma, ovarian carcinoma, pancreatitis), and elective surgery (e.g., total hip replacement). Most of these serious adverse events were due to exacerbation of preexisting conditions, and none were related to study medication. Sexual dysfunction was reported by 6% of men during open treatment with venlafaxine.

A total of 149 patients (63%) discontinued treatment during the double-blind recurrence-prevention period, with significantly (p < .001) fewer venlafaxine-treated patients (50%) discontinuing than placebo-treated patients (76%). The most common reason for treatment discontinuation was lack of treatment efficacy, venlafaxine 21% and placebo 48% (p < .001). Discontinuations due to adverse events were similar for the placebo (7%) and venlafaxine (5%) groups.

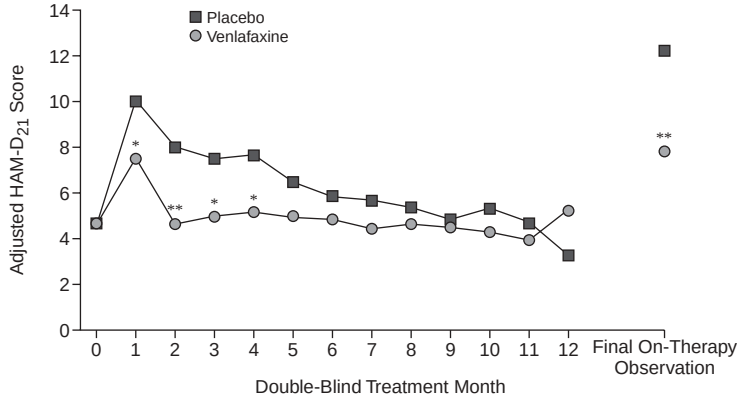
With the exception of cholesterol, the changes in individual or mean laboratory test results that were observed in the venlafaxine group were similar to those for the placebo group. Any changes in laboratory test results, vital signs, body weight, and ECG assessments (relative to baseline) were not clinically meaningful except for the increase in serum cholesterol observed in both the open-label and maintenance phases of the study. Mean total serum cholesterol increased significantly (p < .001) during the open-label treatment phase with an increase of 8.91 mg/dL at the final on-therapy evaluation. There was a further nonsignificant increase for patients continuing on venlafaxine treatment (5.79 mg/dL at month 12) and a return toward the prestudy baseline value for patients switched to placebo (–9.62 mg/dL at month 12). The difference between the adjusted mean changes in cholesterol in the venlafaxine and placebo groups was statistically significant (p = .002).

DISCUSSION

The results of this study show that venlafaxine is effective in reducing the risk of future episodes of recurrent depression. The significant advantage for venlafaxine compared with placebo was seen in the lower cumulative 12-month recurrence rate observed in patients who received prophylactic treatment with venlafaxine and in the total number of recurrences, which were both significantly higher in the placebo group. In other words, the number of recurrences was reduced and emergence of recurrence was delayed during treatment with venlafaxine.

The mean scores for all of the depression rating scales (HAM-D_{21}, MADRS, and CGI-S) remained low for the

Figure 3. HAM-D_{21} Total Scores (observed cases) During the Double-Blind, Recurrence-Prevention Period



*p < .05, venlafaxine vs. placebo.
**p < .001, venlafaxine vs. placebo.
Abbreviation: HAM-D_{21} = 21-item Hamilton Rating Scale for Depression.

Table 4. Treatment-Emergent Adverse Events During the Double-Blind Recurrence-Prevention Period With Incidence ≥ 10% in Venlafaxine-Treated Patients

Event	Venlafaxine N (%)	Placebo N (%)
Headache	30 (27)	26 (21)
Nausea	21 (19)	17 (14)
Pharyngitis	21 (19)	11 (9)
Dizziness	19 (17)	31 (25)
Flu syndrome	18 (16)	11 (9)
Accidental injury	16 (14)	4 (3)
Infection	15 (13)	9 (7)
Pain	15 (13)	9 (7)
Diarrhea	13 (12)	8 (7)
Asthenia	12 (11)	7 (6)
Nervousness	12 (11)	15 (12)
Rhinitis	12 (11)	9 (7)

venlafaxine group throughout the recurrence-prevention period, while those for the placebo group increased over time in both the LOCF analysis and the OC analysis (Figure 3). At the 12-month timepoint, most patients taking venlafaxine appeared to be in remission (MADRS score ≤ 12)[43] with a mean adjusted MADRS score of 8.8 (LOCF).

Because patients who were randomly assigned to the placebo group had their venlafaxine dose tapered over the course of 2 weeks in accordance with clinical practice to reduce the risk of possible discontinuation symptoms, depending on their open treatment dose, some patients did not begin placebo treatment for up to 2 weeks after randomization. After the first month of double-blind treatment, depression scores had increased for both the placebo and venlafaxine groups. Increases at the start of treatment with placebo have been attributed by some to the presence of possible discontinuation symptoms. This explanation, however, could not account for the increase in depression scores in the patients continuing to receive venlafaxine. The increases in both groups suggest that some other factor may be at play. One possible explanation is that both groups were deriving an extra clinical benefit from the knowledge that they were being treated with an effective antidepressant. While the scores were greatly reduced at the end of open treatment, this effect was not fully sustained after patients entered the placebo-controlled phase of the study. Similar results have been observed at the start of other placebo-substitution trials.[24,43]

In placebo-substitution designs such as the one used in this study, the results might be affected by a possible confusion between discontinuation symptoms and true recurrence of depression. This study sought to reduce the influence of this potential contaminant by gradually discontinuing treatment with venlafaxine over a 2-week period at the start of the double-blind treatment period. Studies of abrupt discontinuation from antidepressants such as imipramine[44] and the SSRIs[45,46] indicate that discontinuation symptoms are greatest in the first few days after treatment is stopped. It may be assumed that this time period represents a roughly 3 times multiplication of the half-life of the drug. After abrupt discontinuation from most antidepressants (including venlafaxine), discontinuation symptoms decline rapidly during the first week and are significantly lower in the second week; this has been confirmed in a specific study with venlafaxine.[47] A further check was made by conducting a secondary survival analysis of recurrence of depression, which excluded all patients who left the study for any reason during the first 28 days of double-blind treatment (i.e., the taper period and the first 2 weeks after patients started receiving placebo), the period when possible discontinuation symptoms would be most likely. The results of the secondary analysis show that excluding the data from patients who discontinued the study during the first 28 days of double-blind treatment did not influence the highly significant advantage for venlafaxine in recurrence prevention, though the recurrences observed in the first 28 days satisfied the full criteria and occurred at rates that were only slightly higher than the predicted rate.

There has been some discussion as to whether a continuation period of 4 months, which was used in this study, is sufficient to separate relapses due to an inadequately treated episode of depression from the recurrence of new episodes. A number of analyses have pointed to a 4- to 6-month period during which patients

are vulnerable to the return of the initial depression.[43,48,49] The increased hazard of relapse in the first 4 to 6 months following achievement of response, which appears to be the same for first-episode patients, in whom a new episode of depression might not be expected so soon, and for those with recurrent depression, is sufficiently persuasive that a period of stabilization on treatment is required before the predicted recurrence rate establishes itself.[20,48] A recent study of patients with largely first-episode depression in which serial discontinuation of responders was undertaken indicates that the risk of relapse is highest in the first 3 months and declines rapidly thereafter, such that the rate of relapse in the following 3-month period is barely significant.[28] This observation supports the recommendation that the length of the continuation period be 4 months. The continuation period adopted for the present study is in accord with these data and is in line with the 4-month criterion used by Prien et al.[19,23] and the 4- to 5-month continuation period used by Montgomery et al.[26] and recommended by Prien and Kupfer.[17]

Although the 2 groups were not significantly different with respect to baseline depression or CGI-S scores, patients in the placebo group had slightly higher scores than those in the venlafaxine group, and more patients entered the recurrence-prevention phase with a CGI-S score higher than 2 in the placebo group than the venlafaxine group. It is possible that this might later have influenced the recurrence rate because these patients might not have been in full remission. However, a post hoc survival analysis showed that excluding these patients did not change the highly significant difference in favor of venlafaxine. A stricter criterion of remission at randomization would be unlikely to affect the results since at randomization in this study, 90% of the patients had a HAM-D_{21} score of < 10 and 75% met the stricter remission criterion of a HAM-D_{21} score of < 8.

The expected recurrence rate in the population studied varies according to a number of factors, the most important of which may be the prior recurrence rate. To qualify for this study, a prior recurrence rate of at least 1 episode in the previous 5 years (excluding the index episode) was required, for a total of 2 or more episodes in 5 years, as recommended by various consensus groups[6,7,50,51] and used in previous recurrence-prevention studies.[26,52,53] The mean number of episodes of depression, including the index episode, was 2.4 over a 5-year period, a recurrence rate that was almost identical to that reported by Montgomery et al.[26] This criterion therefore appears appropriate for selecting a population in which recurrence prevention can be demonstrated. The question about whether venlafaxine may reduce the risk of recurrences in a population with even higher recurrence is answered by a further analysis in the subset of patients with 3 or more episodes in a 5-year period, which also found a significant advantage for venlafaxine.

It has been suggested that the severity of the index episode of major depression may predict subsequent recurrence rates.[23,54] Patients entered this study with a mean HAM-D_{21} total score of 25. This represents a degree of severity of the index episode of depression that is in line with mean scores found in many populations with major depression studied to establish the efficacy of both acute and long-term treatment in placebo-controlled trials. The results of the present study therefore merit the same sort of generalizability that applies to the results from acute-treatment studies in major depression.

The criterion for recurrence in the present study was a CGI-S score of 4 or greater, which corresponds to at least moderately severe depression. This is a rigorous criterion, because it is often difficult for a patient with increasing symptoms of depression to wait for the return of such a level of severity, which would have allowed the individual to qualify for entry into an acute-treatment study of major depression, before leaving the study. Many patients might have withdrawn from the study because of clinical deterioration before this point. However, a secondary survival analysis undertaken to capture these extra patients using the criterion of withdrawal from the study because of clinical deterioration also showed that the cumulative recurrence rate was significantly higher for the placebo group (48%) than the venlafaxine group (21%) and again showed a significant advantage for venlafaxine ($p < .001$). A CGI-S score of 4 or more has been shown to be a less sensitive outcome measure to detect drug-placebo differences than other measures.[20] However, it has the advantage of being more robust and clinically relevant in that there is no doubt that an increase in severity of illness to moderate or greater levels requires a change in treatment.

It is difficult to compare the results from one study to another because the designs, recurrence criteria, and populations studied vary widely and such factors affect the recurrence rate in both the placebo and the active treatment groups. One method of making comparisons that takes many of these differing factors into account is to compare the ratio of recurrence rates on placebo and venlafaxine treatment with that found in other studies. The ratio in this study was 2.5 (55% for placebo compared with 22% for venlafaxine). The ratio reported for fluoxetine in a study of similar design[26] was 2.2 (57% vs. 26%). Ratios ranging from 2 to 3 have been reported in successful recurrence-prevention studies.

In general, side effects were low in this study and discontinuation rates due to side effects were similar in the venlafaxine- and placebo-treated patients. While an increase in cholesterol level was observed during treatment with venlafaxine, values returned to normal in patients switched to placebo. While this finding has clinical implications in the treatment of patients with cardiovascular disorders, the increase in serum cholesterol following

venlafaxine treatment supports evidence that a significant increase in total cholesterol is associated with the remission of depressive symptoms.[55] Conversely, numerous studies have established a significant correlation between low serum cholesterol and suicidal ideation.[56–58]

Study Limitations

This study was carried out in 15 centers in the United States, which contributed the majority of the patients (182), and 16 centers in Europe, which contributed 53 patients. In multicenter studies, there may be a concern that disproportionate contribution of patients from some centers may influence the overall results. In this study, the number of patients per site ranged from 6 to 16 in the United States, with a mean of 12.13 and median of 11.5. For the European sites, the number of patients per site ranged from 0 to 14, with a mean of 3.31 and median of 2.5. To address the possibility of study center influence, center was used as a factor in the ANCOVA with pooling of the sites that enrolled only a few patients.

In long-term studies, there is the possibility that psychotherapy may be delivered, which might have an effect on the results. Psychotherapy that had already been established was not proscribed in our study, but any change during the study was not permitted. The importance of this aspect of the protocol was emphasized at the prestudy investigator meeting, and it was emphasized that the interaction with the patients should be kept as business-like as possible to avoid delivering "psychotherapy." It is therefore unlikely, but nevertheless possible, that some investigators delivered some form of psychotherapy. However, if that were the case and psychotherapy were effective in reducing the risk of recurrence, one could expect that it might be more difficult to differentiate between treatment groups.

The 2-week taper period for patients who were discontinued onto placebo treatment might be considered relatively short. However, the period chosen conforms to the dosing instructions in the venlafaxine IR package insert[59] and is consistent with those in other studies of venlafaxine that included a flexible taper period at the end of the study of up to 2 weeks.

The rate of sexual side effects was lower in this study than is often reported with SSRIs, and this may have been influenced by the method of collecting side effects, which was self-report. In studies for the registration of drugs, great emphasis is placed on collecting spontaneously reported adverse event information, and the study centers are instructed to avoid asking any leading questions.

CONCLUSION

The results of the present study provide robust evidence that maintenance treatment with venlafaxine is effective in reducing the risk of a new episode of depression during 12 months of double-blind treatment in a population with recurrent major depression that was in sustained remission after 6 months of acute/continuation treatment with venlafaxine. The results are consistent with those of a range of different placebo-controlled studies with various antidepressants that used similar placebo-substitution designs. The results support earlier findings of the long-term efficacy and safety of venlafaxine in the treatment of major depression and underscore the importance of maintenance treatment for recurrent depression.

Drug names: fluoxetine (Prozac and others), imipramine (Tofranil and others), venlafaxine (Effexor).

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