Prevention of Recurrent Episodes of Depression With Venlafaxine ER in a 1-Year Maintenance Phase From the PREVENT Study

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Objectives: To test the long-term efficacy and safety of venlafaxine extended-release (ER) in preventing recurrence in patients with major depression.

Method: This multiple-phase study, entitled "Prevention of Recurrent Episodes of Depression With Venlafaxine for Two Years" (PREVENT), was conducted from December 2000 through July 2005 in patients with recurrent unipolar depression (DSM-IV) who were initially randomly assigned to double-blind treatment with venlafaxine ER (75 mg/day to 300 mg/day) or fluoxetine (20 mg/day to 60 mg/day) for 10 weeks of acute treatment. Responders then received 6 months of continuation treatment. Those who remained responders were then enrolled into a 12-month maintenance period. Venlafaxine ER responders were randomly assigned to receive double-blind treatment with venlafaxine ER or placebo. Fluoxetine responders were not randomly assigned but continued taking fluoxetine in order to maintain the blind during the maintenance study. Time to recurrence of depression (17-item Hamilton Rating Scale for Depression total score > 12 and < 50% reduction from acute phase baseline) with venlafaxine ER versus that of placebo were compared.

Results: The efficacy evaluable sample consisted of 129 patients in each group. The mean daily dose of venlafaxine ER was 224.7 mg (SD = 66.7). The cumulative probability of recurrence through 12 months, based on the primary definition, was 23.1% (95% CI = 15.3 to 30.9) for venlafaxine ER and 42.0% (95% CI = 31.8 to 52.2) for placebo (p = .005, log-rank test).

Conclusion: Patients who had been successfully treated with venlafaxine ER during acute and continuation therapy were significantly less likely to experience recurrence with venlafaxine ER than with placebo over a 12-month maintenance treatment period.

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A list of previous presentations of data appears at the end of the article.

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The recurrent nature of major depressive disorder (MDD) is well established.[1–12] Naturalistic studies have reported recurrence rates of approximately 40% within 1 year[12] and 85% within 15 years[9] of the index episode. Although it is difficult to predict whether specific patients will experience recurrence based solely on demographic or pretreatment clinical characteristics,[9] long-term observational studies have found that the risk of recurrence increases with the number of previous epi-

sodes and decreases with the duration of recovery.[12] Other factors that may increase the risk of recurrence include the presence of residual symptoms despite a therapeutic response,[13] the presence of comorbid medical and psychiatric conditions,[14] and the persistence of psychosocial impairment.[15]

It is recommended that antidepressant therapy be continued beyond acute treatment to reduce the risk of relapse or recurrence, particularly in patients who have experienced several depressive episodes.[16–19] In patients with a history of recurrent depression, longer-term (12-month) maintenance therapy with tricyclic antidepressants,[20] selective serotonin reuptake inhibitors (SSRIs),[21–23] or serotonin-norepinephrine reuptake inhibitors (SNRIs)[24,25] has been shown to reduce the likelihood of recurrence and to prolong the time to recurrence.

The Prevention of Recurrent Episodes of Depression with Venlafaxine for Two Years (PREVENT) study was a long-term, 3-phase, double-blind, placebo-controlled study of patients with recurrent unipolar MDD. Patients were initially randomly assigned to double-blind treatment with venlafaxine extended-release (ER) or fluoxetine for 10 weeks of acute treatment. Responders then received 6 months of continuation treatment. Those who remained responders were then enrolled into a 12-month maintenance period, during which venlafaxine ER responders were randomly assigned to receive double-blind treatment with venlafaxine ER or placebo. A second randomization and second year of maintenance treatment followed but will be reported separately. Maintenance treatment was divided into two 12-month periods and evaluated the long-term efficacy and safety of the SNRI venlafaxine ER in preventing recurrence of depression. We report the results of the first 12-month period of the maintenance phase herein. Data from the acute and continuation phases, which were blind to treatment assignment to venlafaxine ER or fluoxetine, have been reported elsewhere demonstrating comparable efficacy across both phases of treatment (M.B.K.; M.H.T.; M.E.T.; et al., manuscript submitted).

METHOD

Study Design

Outpatients with recurrent unipolar major depression were enrolled at 29 sites in the United States. The study was conducted from December 2000 through July 2005 in accordance with the Declaration of Helsinki and its amendments, the institutional review boards of each study site approved the study protocol, and all patients provided written informed consent. Patients with recurrent unipolar depression were initially randomly assigned to double-blind treatment with venlafaxine ER (75 mg/day to 300 mg/day) or fluoxetine (20 mg/day to 60 mg/day) for 10 weeks of acute treatment. Those experiencing a satisfactory therapeutic response, defined as a 17-item Hamilton Rating Scale for Depression (HAM-D-17)[26] total score ≤ 12 and ≥ 50% decrease from baseline (i.e., response) or HAM-D-17 score ≤ 7 (i.e., remission), then received 6 months of continuation treatment. Those who remained responders were then enrolled into a 12-month maintenance period. Venlafaxine ER responders were randomly assigned to receive double-blind treatment with venlafaxine ER or placebo. Fluoxetine responders were not randomly assigned but were continued on fluoxetine in order to maintain the blind during the maintenance study. Time to recurrence of depression (HAM-D-17 total score > 12 and < 50% reduction from acute phase baseline) with venlafaxine ER versus that with placebo was compared. A second randomization and second year of maintenance treatment followed but will be reported separately. Details of the acute and continuation phase methods have been described previously (M.B.K.; M.H.T.; M.E.T.; et al., manuscript submitted).

Study Population

Inclusion criteria. Eligible patients for the acute phase were men and women aged 18 years or older who met *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV)[27] criteria for MDD confirmed by a structured diagnostic interview, experienced depressive symptoms for at least 1 month prior to the start of the study, and met the following criteria for recurrent depression: history of at least 3 episodes of major depression, with at least 2 episodes in the past 5 years (including the current episode), and an interval of at least 2 months between the end of the previous episode and the beginning of the current episode. In addition, a total score ≥ 20 on the HAM-D-17 at screening and ≥ 18 at randomization 1 week later were required for participation. Subjects in the maintenance phase included those who had either a response or a remission of the intake episode of major depression at the end of the continuation phase.

Exclusion criteria. Patients who had failed an adequate trial of fluoxetine, venlafaxine, or venlafaxine ER during the current episode of major depression or those who were treatment-resistant (i.e., had failed [1] ≥ 3 previous adequate trials of at least 2 classes of antidepressant medication, or [2] electroconvulsive therapy, or [3] 2 adequate trials of psychotherapy for mood disorder in the past 3 years) were not eligible to participate. Patients with a known hypersensitivity to venlafaxine or fluoxetine were excluded, as were those with a history or presence of any of the following: clinically significant hepatic, cardiovascular, renal, or other serious medical disease that might compromise the study; seizure disorder other than a single childhood febrile seizure; bipolar disorder; obsessive-compulsive disorder; eating disorder (if not remitted for 5 years); drug or alcohol dependence or abuse within 6 months prior to screening; any psychotic disor-

der, including psychotic depression; current postpartum depression; significant Axis II disorders; or any mental disorder due to a substance or medical condition. Patients were not eligible to participate if they met DSM-IV criteria for a primary diagnosis of panic disorder, obsessive-compulsive disorder, generalized anxiety disorder, social phobia, or posttraumatic stress disorder. Patients were excluded if the investigator judged them to be at risk for suicide to such a degree that required precautions against suicide; had clinically significant abnormalities on pre-study physical examination, electrocardiogram (ECG), or laboratory tests; had a diagnosis of cancer in the past 3 years (excluding squamous or basal cell carcinoma) and/or had active neoplastic disease; or were women of childbearing age who were pregnant, breastfeeding, or not using a medically acceptable method of birth control. Use of any of the following was prohibited: any investigational drug, antipsychotic drug, fluoxetine, or monoamine oxidase inhibitor (MAOI) within 30 days, or electroconvulsive therapy within 3 months of randomization; any antidepressant, other than fluoxetine or an MAOI, within 14 days of randomization; any anxiolytic, sedative-hypnotic drug (except chloral hydrate or zaleplon), sumatriptan (and similar agents), or any other psychotropic drug or substance within 7 days of randomization; or any nonpsychopharmacologic drug with psychotropic effects within 7 days of randomization, unless a stable dose of the drug had been maintained for ≥ 1 month prior to randomization.

Treatment Protocol

At the beginning of maintenance treatment, responders to venlafaxine ER were randomly assigned in a double-blind fashion in a 1:1 ratio to receive either venlafaxine ER (75 mg/day to 300 mg/day) or placebo. Responders taking fluoxetine remained on double-blind treatment with fluoxetine (20 mg/day to 60 mg/day). Both patients and investigators remained blinded to treatment assignment. The dose being received at the end of the continuation phase was maintained during the maintenance phase, with dose increases allowed to optimize treatment response. For patients randomly assigned to placebo, a single down-titration kit, which tapered the dose of venlafaxine ER over 4 weeks, was dispensed at the start of the maintenance phase.

Efficacy Assessments

The primary efficacy assessment was the HAM-D-17, administered at each monthly visit. Patients with a HAM-D-17 score > 12 were considered to be at risk for recurrence and were to be reevaluated within 14 days. The primary efficacy measure was time to recurrence of major depression. The primary definition of recurrence included having a HAM-D-17 score > 12, having a HAM-D-17 score that was less than 50% lower than the acute phase baseline at 2 consecutive visits or at the last valid visit prior to patient's discontinuation, and meeting DSM-IV criteria for major depressive disorder as judged by a senior investigator. The secondary definition (i.e., clinical definition) included having 1 visit with a HAM-D-17 score > 12, having a difference in HAM-D-17 score from acute phase baseline of not more than 50%, and not meeting the primary definition of recurrence. Data for these patients were presented in tabular form by Quintiles, Inc. (Research Triangle Park, N.C.), the study management group. Abstracts of the data, including mood ratings and clinical notes from the case report forms, were presented to the recurrence review committee: a committee of experienced psychiatrists who assessed whether each of these patients experienced recurrence after a review of the blinded clinical data. HAM-D-17 ratings were performed by individuals who had been trained and certified. Certification included submitting an interview tape to a subcommittee of investigators that reviewed the tape and determined that the ratings were satisfactory.

Secondary efficacy measures included the Clinical Global Impressions-Severity of Illness (CGI-S) scale,[28] Inventory for Depressive Symptomatology Self-Report,[29] and Rothschild Scale for Antidepressant Tachyphylaxis,[30] administered monthly; and the Hamilton Rating Scale for Anxiety (HAM-A),[31] Longitudinal Interval Follow-up Evaluation,[32] 36-item Short-Form Health Survey (SF-36),[33] Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q),[34] Life Enjoyment Scale-Short Version (derived from the Fawcett-Clark Pleasure Scale),[35] and Social Adjustment Scale Self-Report (SAS-SR),[36] administered at each 3-month visit.

Safety Assessments

Safety was monitored by reports of adverse events, vital sign measurements (supine pulse, standing and supine blood pressure [BP]), and laboratory evaluations. A standard 12-lead ECG was performed at screening on all patients ≥ 50 years of age, as well as those considered by the investigator to be medically so indicated. A comprehensive physical exam was done at acute phase screening.

Statistical Analyses

Statistical analyses were performed by the Biostatistics group of Quintiles, Inc., on behalf of Wyeth Research. Statistical analyses were performed using SAS, Version 8 software (SAS Institute Inc., Cary, N.C.). The results from any statistical comparisons of the treatment groups were presented as 2-sided p values rounded to 3 decimal places. The criterion for statistical significance ("significant") in all comparisons was a p value ≤ .050, unless stated otherwise.

Time until recurrence, the primary efficacy outcome, was calculated using the date of the maintenance phase baseline visit as the start date and the date of the first of

the 2 consecutive visits used to diagnose recurrence as the end date. Time to recurrence was evaluated using Kaplan-Meier methods and compared between the venlafaxine ER and placebo groups using log-rank tests. Secondary efficacy variables included rates of response (HAM-D-17 total score ≤ 12 and ≥ 50% decrease from baseline) and remission (defined as a HAM-D-17 score ≤ 7), probability of recurrence at month 6 and month 12, and the percentage of patients that maintained or improved their response (i.e., continued to meet criteria for response or achieved remission) during the maintenance phase. Rates of response and remission were compared between the venlafaxine ER and placebo groups using a Cochran-Mantel-Haenszel χ^2 test for ordinal data using standardized mid-rank scores with stratification for center. No corrections were made for multiple statistical tests, so the results of these and the other secondary outcomes should be interpreted with caution. The fluoxetine group was continued on fluoxetine treatment during the maintenance phases in order to protect the blind. Because the fluoxetine group was not re-randomized and compared to placebo, the fluoxetine data will be reported in a separate manuscript.

The data were presented to the investigators in tabular form by Quintiles, Inc. Abstracts of the data, including mood ratings and clinical notes from the case report forms, were presented to the recurrence review committee.

RESULTS

Patients

A total of 336 patients who had been treated with venlafaxine ER during the acute and continuation phases were enrolled into the maintenance treatment period. Patients taking venlafaxine ER were randomly assigned to maintenance with medication (N = 164) or placebo (N = 172); 104 patients were enrolled from the fluoxetine treatment arm. However, approximately 33 placebo patients, all of whom were enrolled on or before March 24, 2002, inadvertently received down-titration kits at more than 1 posttaper period visit (when they should have received placebo kits). Therefore, an efficacy evaluable population was defined, which excluded all patients directly affected by the kit dispensing error as well as all patients who were enrolled into maintenance treatment during the same period. Thus, the efficacy evaluable population included all patients in the intent-to-treat population who were enrolled into maintenance treatment after March 24, 2002, and was the primary population of interest for all efficacy analyses (venlafaxine ER, N = 129; placebo, N = 129). The safety evaluable population included all subjects in the safety population who were enrolled after March 24, 2002 (venlafaxine ER, N = 132; placebo, N = 135). The numbers of patients in these populations and the disposition of patients in the safety evaluable population are presented in Table 1. Baseline and demographic characteristics of the efficacy evaluable population are presented in Table 2.

Table 1. Patient Disposition[a,b]

Patient Disposition	Placebo	Venlafaxine ER	p Value
Enrolled/randomized, N	172	164	…
ITT population, N	164	160	…
Efficacy evaluable, N[c]	129	129	…
Safety population, N	172	164	…
Safety evaluable, N[d]	135	132	…
Completed, N (%)[e]	37 (27)	66 (50)	…
Discontinued, N (%)	98 (73)	66 (50)	< .001
Adverse experience	11 (8)	4 (3)	.1084
Failed to return	14 (10)	20 (15)	.2735
Unsatisfactory response	34 (25)	25 (19)	.2401
Protocol violation	4 (3)	4 (3)	> .999
Patient request unrelated to study	18 (13)	7 (5)	.0342
Other medical event	3 (2)	1 (1)	.6223
Other nonmedical event	14 (10)	5 (4)	.0547

[a]Percentages are based on the number of patients in the safety evaluable population.
[b]The safety population includes all patients who took at least 1 dose of study medication. The ITT population includes all patients who took at least 1 dose of study medication and have at least 1 postbaseline HAM-D-17 assessment.
[c]The efficacy evaluable population included all patients in the ITT population who were enrolled into maintenance treatment after March 24, 2002.
[d]The safety evaluable population included all subjects in the safety population who were enrolled after March 24, 2002.
[e]Completed includes patients who completed the 12-month treatment phase and were eligible to continue to the next phase.
Abbreviations: ER = extended-release, HAM-D-17 = 17-Item Hamilton Rating Scale for Depression, ITT = intent-to-treat.

Table 2. Baseline[a] and Demographic Characteristics (efficacy evaluable population)

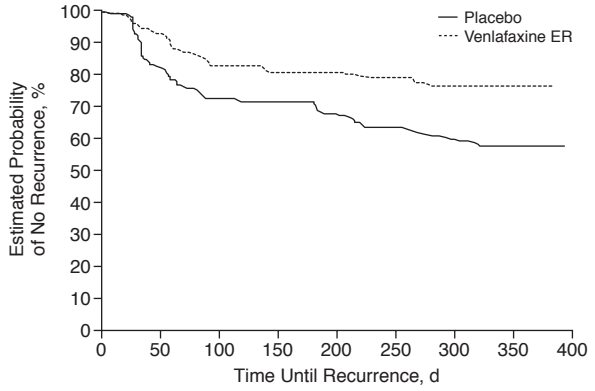
Characteristic	Placebo (N = 129)	Venlafaxine ER (N = 129)
Age, mean, y	42.6	42.0
Sex, %		
Male	33	31
Female	67	69
Ethnicity, white, %	88	81
Total HAM-D-17 score, mean (SD)		
Acute phase baseline	22.5 (3.0)	22.3 (3.3)
Maintenance phase baseline	4.9 (3.5)	4.3 (3.3)
Duration of current episode, mean, mo	7.10	6.32

[a]Refers to acute phase baseline unless otherwise indicated.
Abbreviations: ER = extended-release, HAM-D-17 = 17-item Hamilton Rating Scale for Depression.

Efficacy

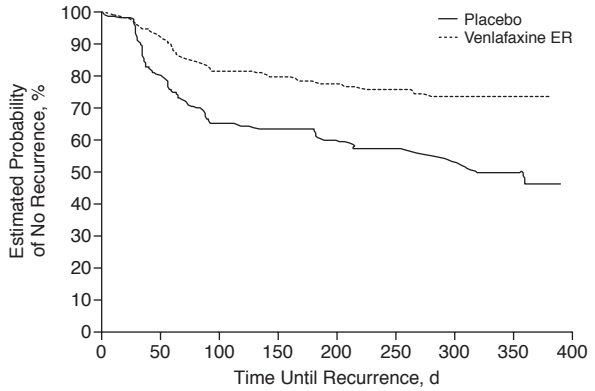
Venlafaxine ER was associated with a significantly lower risk of recurrence, based on both the primary (p = .005) (Figure 1) and secondary (p < .001) definitions (Figure 2). At month 12, the probability of recurrence (primary definition) was 42.0% in the placebo group and 23.1% in the venlafaxine ER group. The probability of recurrence at month 6 and month 12 for each definition is presented in Table 3.

Figure 1. Time to Recurrence, Primary Definition[a,b]



[a]p = .005, venlafaxine ER vs. placebo.
[b]Recurrence defined as HAM-D-17 score > 12 and reduction in HAM-D-17 score from acute phase baseline that was not more than 50% at 2 consecutive visits or at the last valid visit prior to discontinuation.
Abbreviations: ER = extended-release, HAM-D-17 = 17-item Hamilton Rating Scale for Depression.

Figure 2. Time to Recurrence, Secondary Definition[a,b]



[a]p < .0001, venlafaxine ER vs. placebo.
[b]Secondary definition of recurrence: a patient, at any 1 visit, has a total HAM-D-17 score > 12 and a HAM-D-17 score reduction no more than 50% from acute baseline and is determined clinically to have experienced recurrence.
Abbreviations: ER = extended-release, HAM-D-17 = 17-item Hamilton Rating Scale for Depression.

Overall response and remission rates throughout this phase were significantly greater in the venlafaxine ER group compared with the placebo group (Figure 3). However, there were no significant differences in the proportions of patients who maintained remission or who improved from response to remission. Among patients who were remitters at maintenance baseline, 69% (75/109) of those taking venlafaxine ER maintained remission at the end of 12 months of maintenance treatment, compared with 55% (56/102) of those taking placebo (p = .07). Among those patients who were responders but not remitters at maintenance baseline, 56% (10/18) of those taking venlafaxine ER went on to achieve remission compared with 35% (8/23) of those taking placebo (p = .07).

Table 3. Kaplan-Meier Estimate of Probability of Recurrence During Maintenance (efficacy evaluable population)

Recurrence	Placebo (N = 129), % (95% CI)	Venlafaxine ER (N = 129), % (95% CI)	p Value[a]
Primary definition[b]			.005
Month 6	28.4 (20.1 to 36.6)	18.8 (11.9 to 25.8)	
Month 12	42.0 (31.8 to 52.2)	23.1 (15.3 to 30.9)	
Secondary definition[c]			< .001
Month 6	36.5 (27.6 to 45.5)	21.3 (14.0 to 28.6)	
Month 12	53.7 (41.8 to 65.6)	26.5 (18.4 to 34.6)	

[a]p Values obtained from log-rank tests.
[b]The primary definition of recurrence included having a HAM-D-17 score > 12, having a HAM-D-17 score that was less than 50% lower than the acute phase baseline at 2 consecutive visits or at the last valid visit prior to patient's discontinuation, and meeting DSM-IV criteria for major depressive disorder as judged by a senior investigator.
[c]The secondary definition (i.e., clinical definition) of recurrence included having 1 visit with a HAM-D-17 score > 12, having a difference in HAM-D-17 score from acute phase baseline of not more than 50%, and not meeting the primary definition of recurrence.
Abbreviations: ER = extended-release, HAM-D-17 = 17-item Hamilton Rating Scale for Depression.

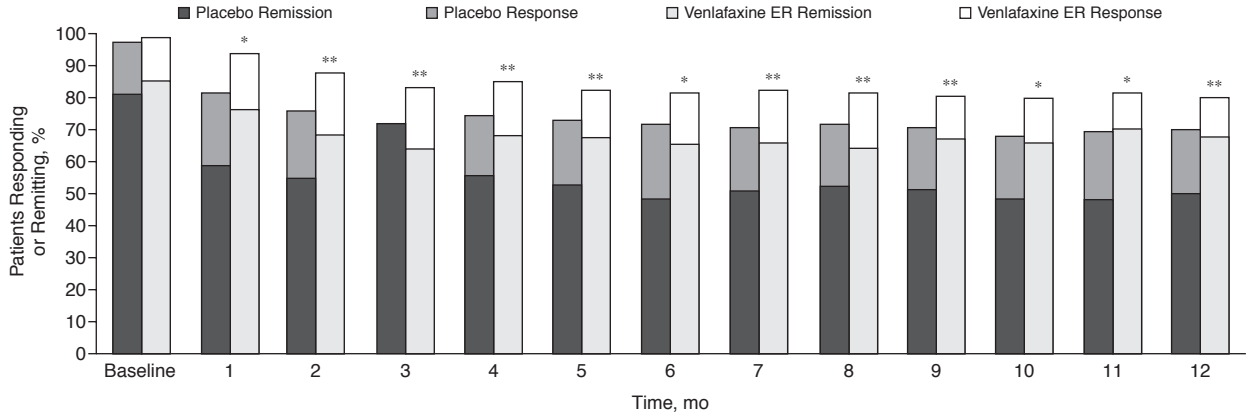
Some secondary efficacy and quality-of-life (QOL) outcomes showed significant differences between the venlafaxine ER and placebo groups throughout the phase (data not shown). End point scores on these measures are summarized in Table 4.

Safety

The mean daily dose of venlafaxine ER during this phase, for the efficacy evaluable population, was 220.8 mg (SD = 71.8); the median daily dose was 225.0 mg.

The adverse events most commonly reported during this phase are presented in Table 5. The rates of adverse events were comparable in the venlafaxine ER and placebo groups, with the exceptions of nervous system events and paresthesias, which were more common in the placebo group, and pharyngitis, which was more common in the venlafaxine ER group. Overall, 3% (4/132) of patients in the venlafaxine ER group and 8% (11/135) in the placebo group discontinued the study due to adverse events during this phase. There were no deaths during the study. Twelve patients (8 placebo, 4 venlafaxine ER) reported a total of 16 serious adverse events (SAEs) during this maintenance phase (some had more than 1 SAE), the majority of which were considered not related to treatment. One venlafaxine ER–treated patient experienced anxiety, auditory hallucinations, and suicidal thoughts; however, these were considered not related to treatment. Suicidal ideations were also reported by 1 placebo patient. There were no suicide attempts during this phase. Emotional lability was reported for 5 placebo patients (4%) and 0 venlafaxine ER patients.

Figure 3. Distribution of Response and Remission Rates



*p < .01 venlafaxine ER vs. placebo.
**p < .05 venlafaxine ER vs. placebo.
Abbreviation: ER = extended-release.

Small changes in mean vital sign values (from acute phase baseline to maintenance end point) were observed in both groups. Mean supine systolic BP decreased from 120.4 mm Hg to 119.7 mm Hg in the placebo group and increased from 120.6 mm Hg to 123.1 mm Hg in the venlafaxine ER group. Mean supine diastolic BP decreased from 75.8 mm Hg to 75.5 mm Hg in the placebo group and increased from 76.4 mm Hg to 78.5 mm Hg in the venlafaxine ER group. Mean pulse increased from 71.4 beats per minute (bpm) to 72.3 bpm in the placebo group and from 70.5 bpm to 75.2 bpm in the venlafaxine ER group. Mean weight increased from 185.1 lb to 187.9 lb in the placebo group and from 178.9 lb to 183.1 lb in the venlafaxine ER group.

There were few clinically significant changes in vital signs or laboratory assessments. The most commonly reported clinically significant changes in vital signs were decreased supine systolic BP (mean postbaseline value ≤ 90 mm Hg and ≥ 20 mm Hg decrease from baseline; 3% in the placebo group and 4% in the venlafaxine ER group) and decreased standing systolic BP (same criteria as above; 3% placebo, 5% venlafaxine ER). Sustained supine diastolic hypertension (≥ 10 mm Hg increase from baseline for 3 consecutive visits and a mean of ≥ 90 mm Hg averaged over 3 consecutive visits) was observed in 4% of venlafaxine ER patients and 1% of placebo patients. Standing diastolic hypertension (same criteria as above) was reported in 5% of venlafaxine ER patients and 2% of placebo patients. The incidence of clinically significant weight gain or loss (± 7% of baseline weight) was comparable for the placebo and venlafaxine ER groups (increased: 28% and 32%, respectively; decreased: 21% and 14%, respectively). There were 11 cases of clinically significant blood chemistry values: 5 in the placebo group, which included 4 with increased cholesterol (≥ 7.758 mmol/L or ≥ 6.75 mmol/L and ≥ 1.29 mmol/L increase from baseline) and 1 patient with decreased high-density lipoprotein (HDL) cholesterol (< 0.91 mmol/L and > 0.21 mmol/L decrease from baseline). Six patients in the venlafaxine ER group had significant increases in cholesterol (same criteria as above).

DISCUSSION

In this study of patients with recurrent depression who had responded to acute and continuation treatment with venlafaxine ER, 12 months of maintenance therapy with venlafaxine ER was effective in preventing recurrence. Patients who remained on treatment with venlafaxine ER had a significantly longer time to recurrence and lower likelihood of recurrence compared with those switched to placebo (23.1% vs. 42.0%, respectively). Accordingly, rates of response and remission were significantly greater with venlafaxine ER treatment compared with placebo. At end point, some secondary efficacy and QOL measures (CGI-S, HAM-A, SF-36, Q-LES-Q, and SAS-SR) also reflected greater efficacy with venlafaxine ER. Similar results were observed in a major depression recurrence prevention study with venlafaxine immediate-release.[24]

The recurrence rates observed in this study (23% venlafaxine ER vs. 42% placebo) are generally consistent with those in placebo-controlled recurrence prevention studies of tricyclic antidepressants, MAOIs, or SSRIs.[20–23] However, such comparisons should be interpreted cautiously due to differences in study design (e.g., duration and masking of treatment prior to randomization), patient populations, and definitions of recurrence.

Differences in definitions of recurrence, including time factors as well as symptom criteria, can significantly influence results. For example, a study that requires

Table 4. Secondary Efficacy Outcomes at End Point (efficacy evaluable population)

Secondary Measure	Placebo (N = 129)	Venlafaxine ER (N = 129)	p Value[a]
Depression/disease-specific, LS mean (SE)			
HAM-D-17 total score[b]	9.1 (0.7)	7.5 (0.7)	.064
CGI-S score[b]	2.3 (0.1)	2.0 (0.1)	.022
IDS-SR total score[b]	18.6 (1.2)	15.5 (1.2)	.066
IDS-SR anxiety/arousal score[b]	6.2 (0.5)	5.3 (0.5)	.123
HAM-A score[b]	8.4 (0.7)	6.5 (0.6)	.030
Quality of life, LS mean (SE)			
SF-36 percentile scores[b,c]			
Physical functioning	83.2 (1.6)	85.5 (1.5)	.200
Role functioning–physical	69.0 (3.8)	76.2 (3.8)	.142
Bodily pain	74.6 (2.2)	75.1 (2.1)	.866
General health	71.0 (1.6)	72.7 (1.5)	.440
Vitality	48.4 (2.2)	51.3 (2.1)	.321
Social functioning	68.6 (2.1)	70.7 (2.0)	.443
Role functioning–emotional	58.5 (4.4)	73.2 (4.1)	.010
Physical component summary	53.3 (0.8)	52.6 (0.8)	.490
Mental component summary	40.5 (1.3)	44.5 (1.3)	.020
Q-LES-Q total score[b,c]	67.3 (1.3)	72.3 (1.3)	.004
LES-S total score[b,c]	58.1 (2.2)	62.9 (2.1)	.103
SAS-SR total score[b,d]	2.01 (0.04)	1.86 (0.04)	.006

[a]Venlafaxine ER vs. placebo. No correction for multiple statistical tests was applied to these outcomes; results should be interpreted with caution.
[b]ANCOVA; SE for venlafaxine ER and placebo from ANOVA model; SE for fluoxetine from univariate statistics.
[c]For these scales, higher scores indicate better functioning.
[d]For this scale, lower scores indicate less impairment.
Abbreviations: ANCOVA = analysis of covariance, ANOVA = analysis of variance, CGI-S = Clinical Global Impressions-Severity of Illness, ER = extended-release, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, IDS-SR = Inventory for Depressive Symptomatology Self-Report, LES-S = Life Enjoyment Scale-Short Version, LS = least squares, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, SAS-SR = Social Adjustment Scale Self-Report, SE = standard error, SF-36 = 36-item Short-Form Health Survey.

Table 5. Most Common Treatment-Emergent Adverse Events (≥ 5% in either treatment group) (safety evaluable population)[a,b]

Preferred Term	Placebo (N = 135), %	Venlafaxine ER (N = 132), %	p Value[a]
Headache	24	25	.887
Upper respiratory infection	12	17	.296
Dry mouth	11	15	.368
Insomnia	13	14	.860
Sweating	12	14	.589
Weight gain	7	12	.220
Dizziness	**21**	**11**	**.032**
Nausea	10	11	.846
Abnormal ejaculation/orgasm	7	11	.299
Abnormal dreams	7	11	.204
Asthenia	11	10	.842
Libido decreased	8	10	.673
Accidental injury	7	10	.519
Constipation	6	9	.360
Hypertension	7	8	.816
Pharyngitis	**2**	**8**	**.049**
Flu syndrome	7	7	> .999
Infection	4	7	.284
Pain	8	6	.636
Nervousness	10	5	.152
Somnolence	8	5	.466
Sinusitis	7	5	.441
Rhinitis	6	5	> .999
Back pain	5	5	> .999
Anorgasmia	4	5	.768
Abdominal pain	4	5	> .999
Vasodilatation	3	5	.373
Cough increased	3	5	.537
Dyspepsia	5	4	.769
Arthralgia	9	3	.068
Diarrhea	7	3	.168
Paresthesia	**10**	**2**	**.003**

[a]p Values were obtained using Fisher exact test.
[b]Items in bold are significant ($p < .050$).

recurrence criteria be met at a single visit would likely report higher recurrence rates than one that requires the same criteria be met at multiple visits. In this study, several definitions of recurrence were used. The primary definition required that patients meet recurrence criteria at 2 consecutive visits or at the visit prior to discontinuation. The secondary definition, which required criteria be met at only 1 visit but the patient's overall clinical evaluation indicated recurrence, found higher recurrence rates than did the primary definition (see Table 3). In terms of symptomatic criteria, there may be patients who actually experience a new episode of depression with symptoms present for several weeks or months, but are not accounted for because their symptoms do not quite reach the threshold for the official definition of recurrence or because they discontinued from the study before meeting recurrence criteria. Further analysis would be necessary to determine to what extent this occurred in the present study.

Venlafaxine ER was well tolerated during maintenance treatment. Discontinuations due to adverse events were more common in the group of patients that received placebo, which may reflect adverse events associated with discontinuation of venlafaxine ER. Long-term tolerability of an antidepressant is an important consideration in initial treatment selection, since the recommendations for treatment of depression involve maintenance treatment, which may last for several years after resolution of the index depressive episode.

There were few individual clinically significant observations in vital signs, laboratory tests, or ECGs. Mean changes in BP associated with venlafaxine ER were small and few patients experienced hypertension. However, increased cholesterol was more common among venlafaxine ER–treated patients. This has been observed in other studies of venlafaxine ER, and monitoring of cholesterol levels is recommended during long-term treatment.[37]

The results of this study support existing literature and treatment guidelines that recommend long-term maintenance treatment with antidepressants for preventing recurrence of depression. However, important issues remain unresolved. For example, it is challenging to determine which patients are at the greatest risk for recurrence.

Unfortunately, at this time, relatively few strong predictors of recurrence have been identified to guide clinicians' decisions.[9,12,13,15] In addition, it is unclear whether there is a finite period of time following discontinuation of treatment during which patients are particularly vulnerable, if this vulnerability changes with the duration of treatment, or whether this is true for only a certain subgroup of patients. Additional analyses (to be reported in separate manuscripts) incorporating data from this phase of this study and continuation phase data may reveal patterns of symptoms that precede recurrence, which may aid clinicians in identifying high-risk patients, or symptom patterns associated with a high likelihood of early recurrence, indicating the need to follow up with such vulnerable patients more frequently for a certain period of time if treatment is discontinued.

A second issue is that the optimal duration of maintenance treatment is unclear. Recurrence prevention studies have evaluated outcomes at up to 3 years[20] and 1 study rerandomized 20 patients with recurrent major depression who had been maintained without recurrence on imipramine treatment for 3 years to an additional 2 years of treatment with imipramine or placebo,[38] but treatment guidelines remain nonspecific.[19] Data from the second 12-month maintenance phase of this study may help to clarify this issue. Long-term antidepressant therapy, while generally safe and well tolerated, is not without risk; therefore, the decision to extend treatment and the appropriate duration of maintenance treatment should take into account not only the patient's history of recurrent depression but also the overall health and preferences of each patient.

As in most long-term studies, attrition accounted for the loss of a significant proportion of the study population. The study design may have introduced a selection bias, because patients who entered the maintenance phase of the study had already responded to the treatment being evaluated (i.e., venlafaxine ER).[39] A limitation of this study, and all similarly designed studies, is that patients who are lost to follow-up cannot be rated and may have discontinued because of a relapse or recurrence. These limitations, in addition to the inclusion and exclusion criteria and the large portion of white patients, may limit the generalizability of the results. The flexible dosing design of the study allowed clinicians to optimize treatment response, but did not allow for evaluation of dose-response relationships.

CONCLUSION

The PREVENT study showed that 12 months of maintenance treatment with venlafaxine ER was significantly more effective than treatment with placebo in preventing recurrence of MDD among patients with recurrent unipolar depression who had achieved and maintained a response to venlafaxine ER treatment during acute and continuation therapy. The safety and tolerability profile of venlafaxine ER during the first year of maintenance treatment was not remarkably different from that of placebo.

Drug names: fluoxetine (Prozac and others), imipramine (Tofranil and others), sumatriptan (Imitrex), venlafaxine (Effexor and others), zaleplon (Sonata).

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