The Prevention of Recurrent Episodes of Depression With Venlafaxine for Two Years (PREVENT) Study: Outcomes From the 2-Year and Combined Maintenance Phases

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Objective: To report second-year results from the 2-year maintenance phase of a long-term study to evaluate the efficacy and safety of venlafaxine extended release (ER) in preventing recurrence of depression.

Method: Outpatients with recurrent unipolar depression (DSM-IV criteria; N = 1096) were randomly assigned in a 3:1 ratio to 10 weeks of treatment with venlafaxine ER or fluoxetine. Responders (17-item Hamilton Rating Scale for Depression [HAM-D_{17}] total score ≤ 12 and ≥ 50% decrease from baseline) entered a 6-month, double-blind continuation phase on the same medication. Continuation-phase responders were enrolled into maintenance treatment consisting of 2 consecutive 12-month phases. At the start of each maintenance phase, venlafaxine ER responders were randomly assigned to receive double-blind treatment with venlafaxine ER or placebo, and fluoxetine responders were continued for each period. The second 12-month maintenance phase compared the time to recurrence of depression with venlafaxine ER (75 to 300 mg/day) versus placebo as the primary efficacy measure. The primary definition of recurrence was a HAM-D_{17} total score > 12 and < 50% reduction from baseline (acute phase) at 2 consecutive visits or at the last valid visit prior to discontinuation. The time to recurrence was evaluated using Kaplan-Meier methods and compared between the venlafaxine ER and placebo groups using log-rank tests. Secondary outcome measures included rates of response and remission (defined as HAM-D_{17} ≤ 7). The study was conducted from December 2000 through July 2005.

Results: The cumulative probabilities of recurrence through 12 months in the venlafaxine ER (N = 43) and placebo (N = 40) groups were 8.0% (95% CI = 0.0 to 16.8) and 44.8% (95% CI = 27.6 to 62.0), respectively (p < .001). At month 12, using last-observation-carried-forward analysis, the rate of response or remission was significantly higher in the venlafaxine ER group (93%) than in the placebo group (63%; p = .002). Overall discontinuation rates were 28% and 63% in the venlafaxine ER and placebo groups, respectively. Adverse events were the primary reason for discontinuation for 1 patient (2%) in the venlafaxine ER group and 4 (10%) in the placebo group. An analysis of the combined maintenance phases, which compared the risk of recurrence over 24 months for patients assigned to venlafaxine ER (N = 129) or placebo (N = 129) for the first maintenance phase, showed a significantly greater cumulative probability of recurrence through 24 months for the placebo group (47.3% [95% CI = 36.4 to 58.2]) than for the venlafaxine ER group (28.5% [95% CI = 18.3 to 38.7]; p = .005).

Conclusion: In this study, an additional 12 months of maintenance therapy with venlafaxine ER was effective in preventing recurrence of depression in patients who had been responders to venlafaxine ER after acute (10 weeks), continuation (6 months), and initial maintenance (12 months) therapy.

Trial Registration: ClinicalTrials.gov identifier NCT00046020 (http://www.clinicaltrials.gov).

(J Clin Psychiatry 2007;68:1246–1256)

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This clinical trial and analysis were sponsored by Wyeth Research, Collegeville, Pa. Funding for the development of this scientific article was provided by Wyeth Pharmaceuticals.

Data presented as a poster at the 159th annual meeting of the American Psychiatric Association, May 20–25, 2006, Toronto, Ontario, Canada; the 46th annual meeting of the New Clinical Drug Evaluation Unit, June 12–15, 2006, Boca Raton, Fla.; the 29th annual meeting of the Collegium Internationale Neuro-Psychopharmacoligicum, July 9–13, 2006, Chicago, Ill.; the 19th annual congress of the European College of Neuropsychopharmacology, Sept. 16–20, 2006, Paris, France; the 111th annual meeting of the American Osteopathic Association, October 1–20, 2006, Las Vegas, Nev.; the 24th Congress of the Latin American Psychiatric Association, Nov. 1–4, 2006, Santo Domingo, Dominican Republic; the 56th annual meeting of the Canadian Psychiatric Association, Nov. 9–12, 2006, Toronto, Ontario, Canada; and the 19th annual meeting of the U.S. Psychiatric and Mental Health Congress, Nov. 2006, New Orleans, La.

The authors wish to thank Sherri D. Jones, Pharm.D., Jennifer B. Hutcheson, and Lorraine M. Sweeney of Advogent for their writing and editorial assistance.

Financial disclosure appears at the end of the article.

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The majority of patients who experience an episode of major depressive disorder (MDD) will eventually experience at least 1 recurrence.[1] Data from the National Institute of Mental Health Collaborative Program on the Psychobiology of Depression indicate an 85% risk of recurrence within 15 years following recovery from an index episode of depression; even among patients who remained well for 5 years, the risk was 58%.[1] The risk of recurrence increases over time and with each subsequent depressive episode.[1,2] Further, as the number of recurrences increases, depressive episodes tend to become more frequent and symptoms more severe.[3] Additional factors that may be associated with a greater likelihood of recurrence are the duration of the depressive episode before treatment is sought[1] and the presence of residual symptoms.[4]

Although long-term antidepressant maintenance therapy may not be necessary for all patients with MDD, it may be considered for patients who exhibit residual symptoms and is recommended for patients with histories of multiple depressive episodes.[5–8] Most guidelines, however, do not indicate a specific duration of treatment, leaving clinicians to determine what is appropriate on a case-by-case basis, depending on a patient's history and clinical characteristics. In contrast to the vast body of literature describing short-term antidepressant treatment studies, there have been relatively few controlled clinical trials of maintenance treatment for patients with recurrent depression. Long-term data for selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are primarily from studies that have evaluated recurrence prevention during a 12-month period following successful acute and/or continuation treatment.[9–13] Studies of maintenance treatment beyond 1 year with these agents are even more scarce.[11,14,15]

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. The maintenance phase, divided into two 12-month periods of randomized, double-blind, placebo-controlled treatment (maintenance phases A and B), evaluated the long-term efficacy and safety of the SNRI venlafaxine extended release (ER) in preventing recurrence of depression. We report the results of the second 12-month period of the maintenance phase (maintenance phase B). The primary objective for maintenance phase B was to compare the efficacy of venlafaxine ER and placebo in preventing recurrence of MDD in patients who were responders (satisfactory therapeutic response or remission) to venlafaxine ER during maintenance phase A treatment. In addition, 2-year data from the combined maintenance phases A and B were examined. Specifically, 24-month outcomes were compared for patients randomly assigned to venlafaxine ER or placebo at the beginning of maintenance phase A.

METHOD

Study Design

This study (conducted from December 2000 through July 2005) enrolled outpatients at 29 sites in the United States. The study was conducted 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. The study consisted of 3 phases: acute, continuation, and maintenance. In the acute phase, 1096 outpatients with recurrent unipolar depression were randomly assigned (in a 3:1 ratio) to receive double-blind treatment with venlafaxine ER or fluoxetine for 10 weeks. Patients achieving a response (therapeutic response, defined as a 17-item Hamilton Rating Scale for Depression [HAM-D_{17}] total score ≤ 12 and ≥ 50% decrease from baseline, or remission, defined as HAM-D_{17} score ≤ 7) during the acute phase were eligible to enter the 6-month continuation phase, during which double-blind treatment with venlafaxine ER or fluoxetine was

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continued (715 patients enrolled in the continuation phase). Patients who continued to demonstrate a response at the end of the continuation phase entered maintenance phase A (12 months). Patients continuing to respond at the end of maintenance phase A were eligible to enter maintenance phase B (12 months). At the start of each maintenance phase, venlafaxine ER responders were randomly assigned to receive double-blind treatment with venlafaxine ER or placebo, and fluoxetine responders were continued for each period. Details of the methods and data from the acute, continuation, and maintenance A phases have been described previously.[16,17]

Study Population

Inclusion criteria. Eligible patients were men or women aged 18 years or older who met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)[18] diagnostic 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 of at least 20 on the HAM-D_{17}[19] at screening and at least 18 at randomization 1 week later were required for participation. Patients in maintenance phase B included those who had either a response (HAM-D_{17} total score ≤ 12 and ≥ 50% decrease from acute phase baseline) or a remission (HAM-D_{17} score ≤ 7) of the intake episode of MDD at the end of maintenance phase A .

Exclusion criteria. Patients for whom an adequate trial of fluoxetine, venlafaxine, or venlafaxine ER had failed during the current episode of MDD or who had treatment-resistant depression (for whom ≥ 3 previous adequate trials of ≥ 2 classes of antidepressant medication, electroconvulsive therapy, or 2 adequate trials of psychotherapy in the past 3 years had failed) were not eligible to participate. Patients with known hypersensitivity to venlafaxine or fluoxetine were excluded, as were those with histories 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; current postpartum depression; any psychotic disorder, including psychotic depression; significant Axis II disorders; or any organic mental disorder. 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 precautions against suicide were required or if they had clinically significant abnormalities on prestudy physical examination, electrocardiogram, or laboratory tests; had diagnoses 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, breast-feeding, 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; electroconvulsive therapy within 3 months of randomization; any antidepressant within 14 days of randomization; any anxiolytic, sedative-hypnotic drug (except chloral hydrate or zaleplon), sumatriptan (or similar agent), 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 at least 1 month prior to randomization.

Treatment Protocol

At the beginning of maintenance phase B, patients who were taking venlafaxine ER during maintenance phase A were randomly assigned in a double-blind fashion in a 1:1 ratio to receive either venlafaxine ER (75 to 300 mg/day) or placebo. Patients taking fluoxetine remained on fluoxetine treatment (20 to 60 mg/day). Patients who continued to respond to placebo (placebo A) at the end of maintenance phase A were continued on placebo in maintenance phase B. The dose at the end of maintenance phase A was maintained, with dose increases allowed to optimize treatment response. For patients randomly assigned to placebo, there was a 4-week taper period at the start of the phase.

Efficacy Assessments

The primary efficacy assessment was the HAM-D_{17}, administered at each monthly visit. The primary efficacy measure was time to recurrence of MDD in this phase. The primary definition of recurrence included having HAM-D_{17} total scores above 12 and HAM-D_{17} reduction from acute phase baseline that was not more than 50% at 2 consecutive visits or at the last valid visit prior to discontinuation. Patients also had to meet DSM-IV criteria for MDD and be judged by the investigator to have had a recurrence. The secondary (clinical) definition also included patients who, at 1 visit, had HAM-D_{17} scores above 12 and HAM-D_{17} reductions from acute phase baseline that were not more than 50% but did not meet the primary definition of recurrence and were reviewed by a committee of experienced psychiatrists, which assessed whether each of these patients experienced recurrence

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after a review of blinded clinical data. This clinical definition of recurrence therefore included all patients who met the primary definition and patients who the committee determined had experienced recurrence.

Ratings were performed by individuals who had been trained and certified in their assessment of the HAM-D. Certification included submitting an interview tape to a subcommittee of investigators and a review of the tape indicating that the ratings were satisfactory.

Secondary efficacy measures included the Clinical Global Impressions-Severity of Illness scale,[20] Inventory for Depressive Symptomatology–Self-Report,[21] and Rothschild Scale for Antidepressant Tachyphylaxis,[22] administered monthly; and the Hamilton Rating Scale for Anxiety,[23] Longitudinal Interval Follow-up Evaluation,[24] 36-item Short-Form Health Survey,[25] Quality of Life Enjoyment and Satisfaction Questionnaire,[26] Life Enjoyment Scale-Short Version (derived from the Fawcett-Clark Pleasure Scale),[27] Social Adjustment Scale–Self-Report,[28] and Health Services Utilization Questionnaire (available from the authors on request), administered at each 3-month visit.

Safety Assessments

Safety was monitored via reports of adverse events, vital sign measurements (supine pulse and standing and supine blood pressure), and laboratory evaluations. Standard 12-lead electrocardiography was performed at screening for all patients at least 50 years of age and those for whom the investigator considered it to be medically indicated. Comprehensive physical examinations were performed at screening.

Statistical Analyses

The intent-to-treat population included all patients who took at least 1 dose of study medication and had at least 1 postbaseline HAM-D_{17} assessment during maintenance phase B; the intent-to-treat population was the primary population of interest for all efficacy analyses. The safety population (used for all safety analyses) was defined as all patients who took at least 1 dose of study medication while enrolled in maintenance phase B.

Statistical analyses were performed by the Biostatistics group of Quintiles, Inc. (Research Triangle Park, N.C.), on behalf of Wyeth Research. Statistical analyses were performed using SAS, Version 8 software (SAS Institute Inc., Cary, N.C.). The results of 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 $p \leq .050$ unless stated otherwise.

Time until recurrence, the primary efficacy outcome, was calculated using the date of the maintenance phase B 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 acute phase baseline) and remission (defined as HAM-D_{17} score ≤ 7), probability of recurrence at month 6 and month 12, and the percentage of patients who maintained or improved their responses during maintenance phase B. 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. For the 2-year combined-phase analysis, time to recurrence was compared between patients randomly assigned to venlafaxine ER and placebo (placebo A) at the beginning of maintenance phase A.

Because the fluoxetine group was not re-randomized during the maintenance phases, the primary comparisons are those between venlafaxine ER and placebo. The fluoxetine group was included as a reference group during the maintenance phases. Although the venlafaxine ER and fluoxetine groups can be compared, the degree of attrition and number of unknown variables that affect attrition reduce the confidence that the initial randomization remained intact. Fluoxetine data will be reported in a separate manuscript.

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

RESULTS

The disposition of the 131 patients in the venlafaxine ER and placebo groups who were enrolled in maintenance phase B is presented in Figure 1. Clinical and demographic characteristics of these patients are presented in Table 1.

Efficacy

Maintenance phase B. Venlafaxine ER was associated with a significantly longer time to recurrence than was placebo, on the basis of both the primary ($p < .001$) (Figure 2) and secondary (clinical) ($p < .001$) definitions (Figure 3). The estimated probability of recurrence at month 12 was 44.8% in the placebo group and 8.0% in the venlafaxine ER group. The estimated probability of recurrence at months 6 and 12 of maintenance phase B, for each definition of recurrence, is presented in Table 2.

Response and remission rates throughout maintenance phase B were significantly greater in the venlafaxine ER group than in the placebo group. At month 12, the rate of response or remission was 93% (40/43) in the venlafaxine ER group and 63% (25/40) in the placebo group ($p = .002$). Among patients who were remitters at the end of

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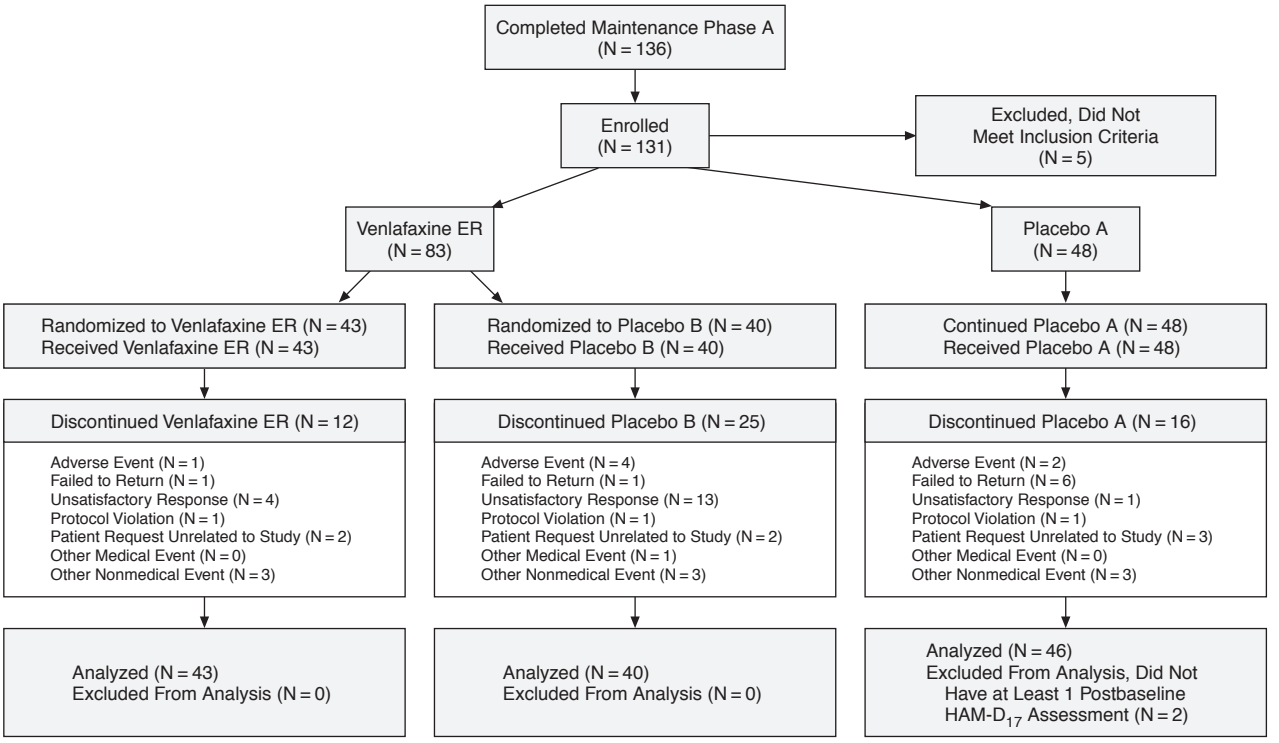
Figure 1. CONSORT Flowchart for Maintenance Phase B of the PREVENT Study



Abbreviations: CONSORT = Consolidated Standards of Reporting Trials, ER = extended-release, HAM-D_{17} = 17-item Hamilton Rating Scale for Depression, PREVENT = Prevention of Recurrent Episodes of Depression With Venlafaxine for Two Years.

Table 1. Baseline[a] and Demographic Characteristics (patients enrolled in maintenance phase B of the PREVENT study)

Characteristic	Placebo B (N = 40)	Venlafaxine ER (N = 43)	Placebo A (N = 48)
Age, mean, y	42.8	44.8	45.2
Sex, %			
Male	30	40	31
Female	70	60	69
Race, white, %	80	81	90
Total HAM-D_{17} score, mean (SD)			
Acute phase baseline	21.5 (2.7)	22.2 (3.0)	22.3 (2.5)
Maintenance phase B baseline	4.1 (3.7)	4.8 (2.6)	4.4 (3.3)
Duration of current episode, mean, mo	5.62	7.03	8.29

[a]Refers to acute phase baseline unless otherwise indicated.
Abbreviations: ER = extended-release, HAM-D_{17} = 17-item Hamilton Rating Scale for Depression, PREVENT = Prevention of Recurrent Episodes of Depression With Venlafaxine for Two Years.

maintenance phase A, 79% (30/38) of those taking venlafaxine ER maintained remission at the end of maintenance phase B versus 52% (17/33) of those taking placebo (p = .006). Among those patients who were responders but not remitters at the end of maintenance phase A, 60% (3/5) of those taking venlafaxine ER went on to achieve remission during maintenance phase B compared with 29% (2/7) of those taking placebo (p = .747).

Several secondary efficacy and quality of life outcomes showed significant differences between the venlafaxine ER and placebo groups throughout the phase (data not shown) and at end point (Table 3).

Two-year combined data. Data from 258 patients (the efficacy evaluable population from maintenance phase A) were included in the 2-year analysis (venlafaxine ER, N = 129; placebo A, N = 129). Venlafaxine ER was associated with a significantly longer time to recurrence than was placebo, on the basis of both the primary (p = .005; Figure 4) and secondary (p < .001) definitions (Figure 5). The model-estimated cumulative probability of recurrence at months 6, 12, 18, and 24 for each definition of recurrence is shown in Table 2.

Safety

The mean daily dose of venlafaxine ER during maintenance phase B was 213.5 mg (standard deviation = 75.2); the median daily dose was 221.8 mg.

Adverse events. In maintenance phase B, the most common treatment-emergent adverse events (incidence ≥ 10% in either group) among placebo B and venlafaxine ER patients were headache (8% and 14%, respectively), asthenia (10% and 5%), diarrhea (10% and 2%), upper respiratory infection (15% and 23%), nausea (10% and

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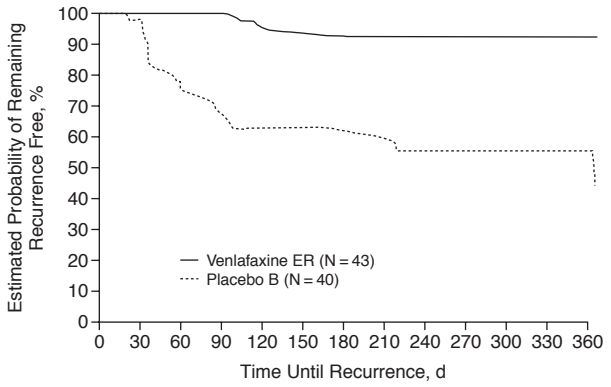
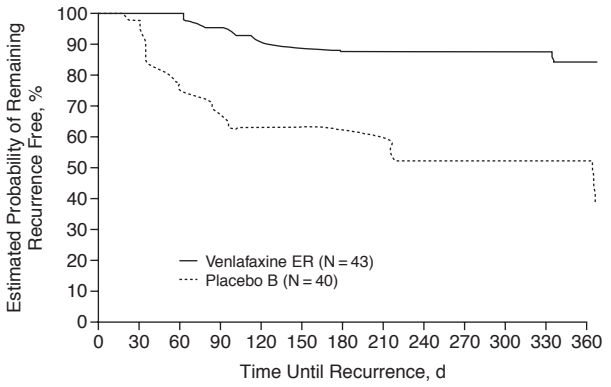
Figure 2. Time to Recurrence, Primary Definition (maintenance phase B of the PREVENT study)[a,b]



[a]p < .001, 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, PREVENT = Prevention of Recurrent Episodes of Depression With Venlafaxine for Two Years.

Figure 3. Time to Recurrence, Secondary Definition (maintenance phase B of the PREVENT study)[a,b]



[a]p < .001, 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 phase baseline and is determined clinically to have experienced recurrence.
Abbreviations: ER = extended-release, HAM-D_{17} = 17-item Hamilton Rating Scale for Depression, PREVENT = Prevention of Recurrent Episodes of Depression With Venlafaxine for Two Years.

Table 2. Kaplan-Meier Estimate of Recurrence Probability From the PREVENT Study (intent-to-treat population)

Recurrence	Placebo B, % (95% CI)	Venlafaxine ER, % (95% CI)	Placebo A, % (95% CI)	p Value
Maintenance phase B	(N = 40)	(N = 43)	(N = 46)	
Primary definition[a]				< .001[b]
Month 6	37.4 (21.2 to 53.6)	5.3 (0.0 to 12.5)	6.8 (0.0 to 14.3)	
Month 12	44.8 (27.6 to 62.0)	8.0 (0.0 to 16.8)	12.5 (2.1 to 22.8)	
Secondary definition[c]				< .001[b]
Month 6	37.4 (21.2 to 53.6)	10.4 (0.7 to 20.1)	20.6 (8.6 to 32.7)	
Month 12	48.4 (31.0 to 65.9)	16.5 (4.3 to 28.6)	29.2 (15.0 to 43.3)	
2-Year combined maintenance phase		(N = 129)	(N = 129)	
Primary definition[a]				.005
Month 6	…	18.8 (11.9 to 25.8)	28.4 (20.1 to 36.6)	
Month 12	…	23.1 (15.3 to 30.9)	42.0 (31.8 to 52.2)	
Month 18	…	28.5 (18.3 to 38.7)	47.3 (36.4 to 58.2)	
Month 24	…	28.5 (18.3 to 38.7)	47.3 (36.4 to 58.2)	
Secondary definition[c]				< .001
Month 6	…	21.3 (14.0 to 28.6)	36.5 (27.6 to 45.5)	
Month 12	…	26.5 (18.4 to 34.6)	51.5 (41.1 to 61.9)	
Month 18	…	34.0 (23.1 to 44.8)	62.1 (51.0 to 73.1)	
Month 24	…	39.0 (25.2 to 52.9)	62.1 (51.0 to 73.1)	

[a]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 visit prior to patient's discontinuation, and meeting DSM-IV criteria for major depressive disorder as judged by a senior investigator.
[b]Venlafaxine ER vs. placebo B.
[c]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 phase baseline and is determined clinically to have experienced recurrence.
Abbreviations: ER = extended-release, HAM-D_{17} = 17-item Hamilton Rating Scale for Depression, PREVENT = Prevention of Recurrent Episodes of Depression With Venlafaxine for Two Years.
Symbol: … = not applicable.

9%), and dizziness (18% and 14%). A significantly higher incidence of accidental injury occurred in the venlafaxine ER group than in the placebo B group (19% vs. 0%, respectively, p = .006), and a statistically significant higher incidence of vasodilation occurred in the placebo B group (10%) than in the venlafaxine ER group (0%, p = .05). Discontinuations due to adverse events were reported for 1 patient (2%) in the venlafaxine ER group and 4 patients (10%) in the placebo B group. Six patients (2 venlafaxine ER, 2 placebo B, and 2 placebo A) experienced a total of 10 serious adverse events during maintenance phase B (some patients experienced > 1 serious adverse event), the majority of which were considered not related to treatment. One patient in the placebo A group experienced psychosis, suicidal ideation, and hostility, which were considered possibly related to study treatment. There

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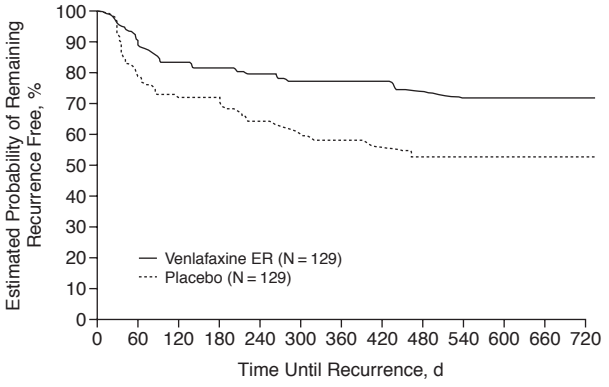
Table 3. Secondary Efficacy Outcomes at End Point of the PREVENT Study[a]

Assessment	Placebo B (N = 40)	Venlafaxine ER (N = 43)	Placebo A (N = 46)	p Value[b]
Depression-related				
HAM-D_{17} total score	8.8 (1.0)	4.4 (1.0)	5.2 (0.8)	.001
CGI-S score	2.5 (0.2)	1.6 (0.2)	1.6 (0.1)	< .001
IDS-SR total score	18.7 (1.7)	11.9 (1.7)	13.9 (1.7)	.006
IDS-SR anxiety/arousal score	6.9 (0.6)	4.1 (0.6)	4.6 (0.7)	.003
HAM-A score	8.8 (0.8)	4.5 (0.8)	5.6 (0.9)	< .001
Quality of life				
SF-36 percentile scores[c]				
Physical functioning	84.8 (2.8)	86.2 (2.7)	87.0 (2.9)	.706
Role functioning-physical	65.8 (5.2)	74.2 (4.9)	76.1 (4.8)	.240
Bodily pain	71.2 (3.4)	77.4 (3.2)	80.5 (2.9)	.192
General health	65.9 (2.5)	73.0 (2.3)	73.1 (3.1)	.042
Vitality	47.3 (3.3)	57.9 (3.1)	55.2 (2.9)	.024
Social functioning	63.1 (3.4)	71.5 (3.2)	71.4 (3.0)	.073
Role functioning-emotional	55.8 (6.4)	80.2 (6.0)	68.9 (5.9)	.007
Physical component summary	51.9 (1.1)	51.8 (1.1)	53.4 (1.5)	.959
Mental component summary	39.2 (1.9)	47.6 (1.8)	44.5 (1.8)	.002
Q-LES-Q total score[c]	66.9 (2.2)	74.7 (2.1)	73.7 (2.0)	.013
LES-S total score[c]	55.2 (3.4)	66.1 (2.9)	61.3 (2.7)	.018
SAS-SR total score[d]	1.99 (0.07)	1.79 (0.06)	1.84 (0.06)	.036

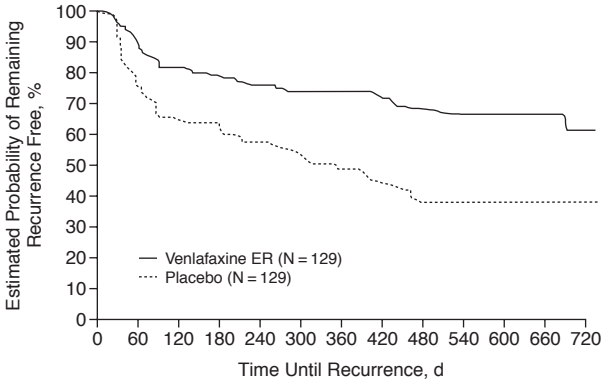
[a]Values expressed as least squares mean (SE).
[b]Venlafaxine ER vs. placebo B, analysis of covariance.
[c]For these scales, higher scores indicate better functioning.
[d]For this scale, lower scores indicate less impairment.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, 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, PREVENT = Prevention of Recurrent Episodes of Depression With Venlafaxine for Two Years, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, SAS-SR = Social Adjustment Scale–Self-Report, SF-36 = 36-item Short Form Health Survey.

Figure 4. Time to Recurrence, Primary Definition (combined 2-year analysis of the PREVENT study)[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, PREVENT = Prevention of Recurrent Episodes of Depression With Venlafaxine for Two Years.

Figure 5. Time to Recurrence, Secondary Definition (combined 2-year analysis of the PREVENT study)[a,b]



[a]p < .001, 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 phase baseline and is determined clinically to have experienced recurrence.
Abbreviations: ER = extended-release, HAM-D_{17} = 17-item Hamilton Rating Scale for Depression, PREVENT = Prevention of Recurrent Episodes of Depression With Venlafaxine for Two Years.

were no other reports of suicide-related events in the venlafaxine ER or placebo groups during this phase, and there were no deaths during the study.

Vital signs, weight, and laboratory evaluations. There were few individual clinically significant changes in vital signs, weight, or laboratory evaluations observed. One venlafaxine ER patient had significantly increased supine systolic blood pressure (SBP; ≥ 180 mm Hg and ≥ 20 mm Hg increase from baseline), 1 venlafaxine ER patient had significantly increased standing SBP, and 1 placebo patient had significantly decreased standing SBP (≤ 90 mm Hg and ≥ 20 mm Hg decrease from baseline). One placebo patient had supine diastolic blood pressure (DBP) categorized as sustained hypertension (≥ 90 mm Hg and ≥ 10 mm Hg increase from baseline for ≥ 3 consecutive visits), 1 venlafaxine ER patient had increased supine

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DBP (≥ 105 mm Hg and ≥ 15 mm Hg increase from baseline), 2 placebo patients had standing DBP categorized as sustained hypertension, and 1 placebo patient had increased standing DBP. There were no patients with clinically significant changes in pulse rates (≥ 120 or ≤ 40 bpm). Clinically significant (± 7% of baseline weight) weight gain was reported for 17 placebo patients and 20 venlafaxine ER patients, and clinically significant weight loss for 4 placebo patients and 4 venlafaxine ER patients. One placebo patient had increased white blood cells ($> 16 \times 10^9$/L), and there were significant increases in cholesterol (≥ 7.758 mmol/L or ≥ 6.75 mmol/L and ≥ 1.29 mmol/L increase from baseline) for 2 placebo patients and 3 venlafaxine ER patients.

DISCUSSION

In this study of patients who were responders to venlafaxine ER following acute, continuation, and 1-year maintenance treatment, a second year of maintenance treatment with venlafaxine ER was associated with a significantly reduced likelihood of recurrence (8.0% vs. 44.8% with placebo at the end of maintenance B) and a significantly longer time to recurrence than with placebo treatment. The likelihood of recurrence during the entire 2-year maintenance phase was significantly lower among patients who continued treatment with venlafaxine ER than among patients who were switched to placebo treatment. Rates of response and remission were significantly greater among responders who continued venlafaxine ER treatment than among those who were switched to placebo. Additional secondary efficacy and quality of life measures reflected significant superiority of venlafaxine ER over placebo.

Although it is widely agreed that patients who have experienced several episodes of depression should receive maintenance antidepressant therapy,[5–8] the optimal duration of maintenance treatment remains somewhat ambiguous. Of the relatively few long-term antidepressant recurrence-prevention studies, a limited number have evaluated outcomes after 2 or more years (notably, those conducted by Frank et al.[29] and Kupfer et al.[30] at the University of Pittsburgh, which followed patients for 3[29] and 5 years[30] of maintenance treatment), the majority of which evaluated tricyclic antidepressants or MAOIs.[31–36] Such studies of SSRIs are even fewer,[11,37,38] generally had smaller sample sizes than did the present study,[11,14,15] and used open-label treatment during the acute and continuation phases.[11,14,15] The present study, therefore, is an important contribution to the literature and supports the hypothesis that extending maintenance antidepressant treatment for up to 2 years reduces the risk of and prolongs the time to recurrence of depression.

The absolute difference in recurrence rates between venlafaxine ER and placebo during the second year of maintenance treatment (37% using the primary definition and 32% using the secondary definition) was somewhat larger than that seen during the first year of maintenance treatment (19% and 27%, respectively).[17] There was a notable decrease in recurrence rate from maintenance phase A (23%) to maintenance phase B (8%) among patients who continued taking venlafaxine ER for the second year, suggesting that protection against recurrence may increase with longer treatment, whereas the risk for placebo patients was consistent across both phases (42% and 45%, respectively). It is interesting to note the similar pattern of recurrence following discontinuation of venlafaxine ER in each maintenance phase, which suggests that an additional year of maintenance treatment apparently does not afford any extra protection against recurrence once treatment is discontinued.

The primary definition of recurrence used in this study required fulfillment of recurrence criteria at 2 consecutive visits (or the last visit before study discontinuation). This definition did not, however, account for patients who may have met recurrence criteria at only 1 visit and continued to experience symptoms to a degree that would be considered clinical recurrence but did not meet full recurrence criteria. The secondary definition, which included patients who were determined to have experienced recurrence on the basis of a blinded review by a panel of experts, was considered a "clinical" definition. As expected, recurrence rates in this phase differed somewhat on the basis of the definition of recurrence used, with higher rates and earlier between-group differentiation associated with the clinical definition than with the primary definition. This pattern was also observed in maintenance phase A.[17]

Regardless of the definition of recurrence used, there was a substantial drop-off in the survival curve for the placebo group at the end of maintenance phase B, which was also observed at the end of maintenance phase A. Such a finding was not observed with the venlafaxine ER data, which strongly supports the value of maintaining patients on venlafaxine ER treatment for a minimum of 2 years after an initial 10-week acute-treatment stabilization period followed by 6 months' continuation treatment.

Analysis of the combined 2-year data revealed a significantly greater risk of recurrence with placebo treatment than with venlafaxine ER treatment. The overall pattern of recurrence over 2 years was generally similar to what was observed in the individual maintenance phases. The early separation between venlafaxine ER and placebo survival curves in the analysis of the clinical definition of recurrence was particularly evident in this combined analysis. It is interesting that the notable drop-off in the survival curve for the placebo group at the end of the individual maintenance phases was not seen in the combined analysis.

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Venlafaxine ER treatment was well tolerated and safe during maintenance phase B. There were few statistically significant differences in the rates of individual adverse events. Four patients in the placebo group discontinued the study because of adverse events during this phase, compared with only 1 venlafaxine ER-treated patient. Although patients randomly assigned to placebo had their doses of venlafaxine ER tapered over several weeks, some patients may have experienced discontinuation-related events that led to their withdrawal from the study. There were few individual clinically significant abnormalities in vital signs, weight, or laboratory assessments, which were evenly distributed between the venlafaxine ER and placebo groups.

Some limitations of this study should be noted. The sample sizes were relatively small, with approximately 40 patients per group. As in other similarly designed recurrence-prevention studies, the design may have introduced a selection bias, because patients who entered this phase of the study had already responded to the treatment being evaluated (venlafaxine ER).[39] This, in addition to the inclusion and exclusion criteria, 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

Twelve additional months of maintenance treatment with venlafaxine ER was effective in preventing recurrence of depression in patients with MDD who had been treated successfully with venlafaxine ER during acute, continuation, and initial maintenance (12 months) therapy. Likewise, 24 months of continuous maintenance treatment with venlafaxine ER was effective for patients who had responded to venlafaxine ER during acute and continuation therapy. The unique design of the PREVENT study, with medication discontinuation at different time points, contributes to our understanding of the value of longer maintenance treatment.

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

Financial disclosure: Dr. Keller is a consultant to and has received honoraria from Cenerex, Cephalon, Cypress, Cyberonics, Forest, Janssen, JDS, Organon, Novartis, Pfizer, and Wyeth; has received grant/research support from Pfizer; and has participated in advisory boards for Abbott, Bristol-Myers Squibb, Cenerex, Cyberonics, Cypress, Forest, Janssen, Novartis, Organon, and Pfizer.

Dr. Trivedi has received research support from Bristol-Myers Squibb, Cephalon, Corcept Therapeutics, Cyberonics, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Merck, the National Institute of Mental Health (NIMH), the National Alliance for Research on Schizophrenia and Depression (NARSAD), Novartis, Pfizer, Pharmacia & Upjohn, Predix, Solvay, and Wyeth-Ayerst; has participated in advisory boards and is a consultant for Abbott, Akzo (Organon), AstraZeneca, Bayer, Bristol-Myers Squibb, Cephalon, Cyberonics, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Johnson & Johnson, Meade Johnson, Neuronetics, Parke-Davis, Pfizer, Pharmacia & Upjohn, Sepracor, Solvay, and Wyeth-Ayerst; and has participated in speakers boards for Abdi Brahim, Akzo (Organon), Bristol-Myers Squibb, Cephalon, Cyberonics, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Pharmacia & Upjohn, Solvay, and Wyeth-Ayerst.

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In the past 3 years, Dr. Nemeroff has been a consultant to, served on the speakers' bureau and/or board of directors for, has been a grant recipient, and/or owned equity in one or more of the following: Abbott, Acadia, the American Foundation for Suicide Prevention (AFSP), the American Psychiatric Institute for Research and Educations (APIRE), AstraZeneca, BMC-JR LLC, Bristol-Myers Squibb, CeNeRx, Corcept, Cypress, Cyberonics, Eli Lilly, Entrepreneur's Fund, Forest, George West Mental Health Foundation, GlaxoSmithKline, i3 DLN, Janssen, Lundbeck, NARSAD, Neuronetics, NIMH, the National Foundation for Mental Health, NovaDel, Otsuka, Pfizer, Quintiles, Reevax, UCB Pharma, and Wyeth-Ayerst. Currently, Dr. Nemeroff serves on the Scientific Advisory Boards for AstraZeneca, Johnson & Johnson, Pharma Neuroboost, Forest, Quintiles, and NARSAD; has received grant support from the National Institutes of Health, NARSAD, and AFSP; serves on the board of directors of AFSP, APIRE, NovaDel, and the George West Mental Health Foundation; owns equity in CeNeRx and Reevax; and owns stock or stock options in Corcept, Cypress, and NovaDel.

Dr. Friedman has provided scientific consultation to Cephalon, GlaxoSmithKline, and Wyeth-Ayerst; has participated in speakers/advisory boards for Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest Specialty Sales, GlaxoSmithKline, Roerig Division of Pfizer, Pfizer, and Wyeth-Ayerst; has received grant/research support from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest Specialty Sales, GlaxoSmithKline, Roerig Division of Pfizer, Sanofi-Aventis, and Wyeth-Ayerst; and is a stock shareholder of Cephalon.

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