Efficacy and Safety of Desvenlafaxine 50 mg/d for Prevention of Relapse in Major Depressive Disorder: A Randomized Controlled Trial

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ABSTRACT

Objective: To evaluate the long-term (11-month) efficacy and safety of desvenlafaxine (administered as desvenlafaxine succinate) at the recommended 50-mg/d dose in preventing relapse in patients with major depressive disorder (MDD).

Method: Adult outpatients (age ≥ 18 years) with MDD (*DSM-IV* criteria) and a 17-item Hamilton Depression Rating Scale ($HDRS_{17}$) total score ≥ 20 at screening and baseline were enrolled in a multicenter, double-blind, placebo-controlled, randomized withdrawal trial conducted between June 2009 and March 2011. Patients who responded to 8-week open-label treatment with desvenlafaxine 50 mg/d with continuing stable response through week 20 were randomly assigned to receive placebo or desvenlafaxine 50 mg/d in a 6-month, double-blind, randomized withdrawal period. The primary efficacy endpoint was time to relapse following randomization to double-blind treatment, which was compared between groups using the log-rank test. Relapse was defined as $HDRS_{17}$ total score ≥ 16, discontinuation for unsatisfactory response, hospitalization for depression, suicide attempt, or suicide. Safety and tolerability data were collected throughout the trial.

Results: A total of 874 patients were enrolled; 548 patients were randomly assigned to receive placebo (n = 276) or desvenlafaxine 50 mg/d (n = 272) in the double-blind withdrawal period. Time to relapse was significantly shorter for placebo versus desvenlafaxine ($P < .001$). At the end of the 6-month double-blind treatment, the estimated probability of relapse was 30.2% for placebo versus 14.3% for desvenlafaxine 50 mg/d. Safety and tolerability results were generally consistent with those in short-term studies of desvenlafaxine 50 mg/d.

Conclusions: Desvenlafaxine at the recommended dose of 50 mg/d was effective in relapse prevention of depression during a 6-month period in patients who demonstrated stable response after 20 weeks of open-label desvenlafaxine treatment.

Trial Registration: ClinicalTrials.gov identifier: NCT00887224

J Clin Psychiatry 2013;74(2):158–166

Submitted: *June 22, 2012; accepted October 29, 2012 (doi:10.4088/JCP.12m07974).*
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Major depressive disorder (MDD) is a chronic, disabling disorder,[1,2] and incomplete resolution of depressive symptoms with treatment is associated with early relapse and recurrence of depressive episodes.[3–6] Relapse following treatment response for MDD is common; up to 37% of patients with MDD are reported to relapse over 12 to 18 months; 79%, over 5.5 years; and 85%, over 15 years.[7–10] The risk of relapse is reduced significantly by continuation of antidepressant therapy after response to acute treatment.[11–13] Treatment guidelines in the United States and Europe recommend that patients with a major depressive episode continue antidepressant treatment for 4 to 9 months after successful acute-phase therapy to prevent relapse of the episode.[14–16] Retrospective database studies of medical and pharmacy claims indicate that, in clinical practice, antidepressant treatment duration is less than 4 months for approximately 30%–55% of depressed patients,[17–20] but the likelihood of achieving the minimum recommended treatment duration is higher for some antidepressant drugs (escitalopram, fluoxetine) compared with others.[17,18,21]

Desvenlafaxine (administered as desvenlafaxine succinate) is a serotonin-norepinephrine reuptake inhibitor (SNRI) approved for the treatment of MDD in adults.[22] Short-term efficacy of desvenlafaxine has been demonstrated for the recommended therapeutic dose of 50 mg/d,[23–25] with no additional efficacy benefit observed at higher doses.[26] Long-term studies of desvenlafaxine for MDD were previously limited to trials assessing higher doses of desvenlafaxine.[27–29] The safety and tolerability of flexible-dose desvenlafaxine at 200 to 400 mg/d were assessed in 2 open-label studies: a 10-month extension study in MDD patients who had completed 8-week double-blind treatment with desvenlafaxine or placebo[28] and a 12-month safety trial in MDD patients.[27] Treatment with desvenlafaxine 200 to 400 mg/d also has been demonstrated effective for the prevention of the relapse of depression in a double-blind, placebo-controlled trial.[29] Significantly longer times to relapse were observed for desvenlafaxine compared with placebo. However, this study was initiated when desvenlafaxine was primarily studied at doses of 200–400 mg/d and before the determination of the current recommended dosage of desvenlafaxine for MDD. No long-term MDD trials of efficacy in desvenlafaxine at the recommended 50-mg/d dose have been conducted previously.

This double-blind, placebo-controlled, randomized withdrawal trial assessed the long-term efficacy of the recommended 50-mg/d desvenlafaxine dose. It included an 8-week open-label response phase and 12-week open-label stabilization phase prior to the 6- month double-blind period. The primary objective of the study was to compare the long-term efficacy and safety of desvenlafaxine 50 mg/d versus placebo in MDD patients who have responded

to and been stabilized on treatment with desvenlafaxine 50 mg/d, with efficacy based on time to relapse following randomization to the double-blind treatment phase.

- Long-term continuation treatment with desvenlafaxine 50 mg/d reduces the risk of relapse of major depressive disorder during treatment.
- Patients demonstrated a stable response through 20 weeks of open-label treatment, and relapse rates were lower compared with prior withdrawal studies that used a shorter open-label period.

Clinical Points

METHOD

This phase 3, multicenter, double-blind, placebo-controlled, parallel-group, randomized withdrawal study (ClinicalTrials.gov identifier: NCT00887224) was conducted at 87 study sites in 14 countries worldwide (North America, 30; South America, 10; Europe, 44; South Africa, 3). Recruitment began in June 2009, and the study was completed in March 2011. The protocol and amendments received institutional review board or independent ethics committee approval, and the study was conducted in accordance with the International Conference on Harmonization Guideline for Good Clinical Practice and the ethical principles that have their origin in the Declaration of Helsinki. Written informed consent was obtained from all participants before any protocol-required procedures were performed.

Patients

Eligible patients included male and female adult outpatients (≥ 18 years) with a primary diagnosis of single-episode or recurrent MDD without psychotic features, based on criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Comorbid generalized anxiety, panic, or social anxiety disorders were allowed if MDD was the primary diagnosis. Eligible patients had depressive symptoms for at least 30 days before the screening visit, a 17-item Hamilton Depression Rating Scale ($HDRS_{17}$)[30] total score ≥ 20, a $HAM\text{-}D_{17}$ item 1 (depressed mood) score ≥ 2, and a Clinical Global Impressions-Severity of Illness scale (CGI-S)[31] score ≥ 4 at screening and baseline visits. Patients were excluded if they had been treated with desvenlafaxine at any time in the past or if they had a significant risk of suicide based on clinical judgment or an $HDRS_{17}$ item 3 (suicide) score greater than 3 at screening. Other major exclusion criteria included current comorbid substance use disorder, manic episode, posttraumatic stress disorder, obsessive-compulsive disorder, clinically important personality disorder (as assessed by the modified Mini-International Neuropsychiatric Interview[32] and a psychiatric interview), or clinically important medical disease.

Study Design

The study included a screening period, a 20-week open-label treatment period, and a 6-month, double-blind, placebo-controlled, randomized withdrawal period with 1-week taper and 1-week follow-up. The open-label treatment period consisted of an 8-week response phase, followed by a 12-week stability phase. Only patients who had responded to 8-week open-label treatment with desvenlafaxine 50 mg/d at week 8, as defined by an $HDRS_{17}$ total score ≤ 11 and a Clinical Global Impressions-Improvement scale (CGI-I)[31] score ≤ 2, were entered into the stability phase. Patients eligible for the stability phase received open-label desvenlafaxine 50 mg/d for an additional 12 weeks. Patients completed the $HDRS_{17}$ and CGI-I at baseline ($HDRS_{17}$ only) and weeks 1, 2, 3, 4, 6, 8, 12, 16, and 20 of the open-label period.

Patients with continued stable response ($HDRS_{17}$ total score ≤ 11 and CGI-I score ≤ 2) at the end of week 20 who did not have an $HDRS_{17}$ total score ≥ 16 or a CGI-I score ≥ 4 at any visit during the stability phase were eligible to enter the double-blind treatment period. Eligible patients were randomly assigned 1:1 to receive 6-month treatment with placebo or desvenlafaxine 50 mg/d during the double-blind, randomized withdrawal period. Patients were randomly assigned to treatment based on subject randomization numbers accessed by site personnel through a centralized, computerized treatment assignment system. Patients who were randomly assigned to receive placebo were tapered to double-blind treatment with desvenlafaxine 25 mg/d during the first week of the double-blind period. Randomized patients continued treatment with either desvenlafaxine 50 mg/d or placebo until study completion at 6 months or until relapse. Patients who were administered desvenlafaxine 50 mg/d for 14 days or more during the study received desvenlafaxine 25 mg/d for a 7-day taper period at the study conclusion or at early discontinuation. A follow-up visit was scheduled approximately 7 days after the last tapered dose. Patients completed the $HDRS_{17}$ and CGI-I at double-blind period weeks 1, 2, 3, 4, 6, 10, 14, 18, 22, and 26.

Outcomes

The primary efficacy outcome for the study was time to relapse following randomization to the double-blind period. Relapse was defined as any 1 (or more) of the following: $HDRS_{17}$ total score ≥ 16, discontinuation for unsatisfactory response (including the need for additional/alternate treatment for depression, investigator decision to remove the patient from the study for efficacy reasons, or failure to return if the investigator determined it was related to efficacy), hospitalization for depression, suicide attempt, or suicide.

Safety was assessed throughout the open-label and double-blind periods. Safety assessments included vital signs (supine and standing blood pressure, pulse rate, body weight, and height), laboratory determinations, 12-lead electrocardiogram (ECG) recordings, monitoring of adverse events (AEs; categorized based on *Medical Dictionary for Regulatory Activities* [MedDRA][33] terminology), withdrawals due to AEs, concomitant medications, and administration of the Columbia-Suicide Severity Rating Scale (C-SSRS).[34]

The C-SSRS was used to prospectively assess emergent suicide-related thoughts and behaviors during the study.

Statistical Analysis

Sample size calculations were based on results from the previous desvenlafaxine relapse prevention study.[29] A hazard ratio of 0.53 was derived from relapse rates observed in that study (approximately 42% and 24% with placebo and desvenlafaxine treatment, respectively).[29] A total of 103 events (relapses) and a corresponding sample size of 165 subjects per group would yield 90% of power to detect a hazard ratio of at least 0.53 between the desvenlafaxine and placebo groups in the current study at the 2-sided 5% level. To compensate for patients who failed to qualify for the primary efficacy analysis (estimated at approximately 3%), at least 170 patients would need to be randomized into each double-blind treatment arm. Assuming 60% of enrolled patients would continue into the stability phase and 66% of those patients would be randomized into the double-blind treatment period, a total of approximately 850 subjects were needed for enrollment into the initial open-label treatment period.

Efficacy

Hypothesis testing was performed for the double-blind period only and was conducted at a 2-sided 5% level. Efficacy analyses were based on the all-randomized population (all patients randomly assigned to double-blind treatment). The primary efficacy analysis assessed time to relapse from randomization to double-blind treatment for desvenlafaxine compared with placebo using the log-rank test. Relapses that occurred after double-blind day 185 were considered censored on double-blind day 185. The Kaplan-Meier survival curve was used to display time to relapse in each arm. The estimated probability of relapse (taking into account dropout rate over time) was calculated. Number needed to treat (NNT) for benefit based on prevention of relapse was calculated as the inverse of the difference in estimated probability of relapse for placebo versus desvenlafaxine 50 mg/d.

Two sensitivity analyses were conducted to avoid potential confounding of drug taper (discontinuation) symptoms versus relapse symptoms in the placebo arm. The analyses were performed using methods similar to those used for the primary analysis, except that one excluded the first 4 weeks of double-blind treatment and the other excluded the first 2 weeks of double-blind treatment.

The hazard function for relapse was modeled using Cox regression models to determine which factors contributed to predicting relapse in the double-blind treatment period. The first model included treatment, treatment remission status at the end of the open-label period, and the treatment-by–remission status interaction. The model with main effects only was also fit in a post hoc fashion. A second model included treatment, $HDRS_{17}$ total score at double-blind baseline, age, sex, number of prior MDD episodes, and duration of current episode as explanatory variables.

Safety

Safety analyses were based on the all-enrolled population in the open-label treatment period and on the all-randomized population for the double-blind period. Treatment-emergent AEs (TEAEs) were recorded and summarized for the open-label and double-blind treatment periods. Descriptive statistics were generated for vital signs, laboratory evaluations, and ECG parameters. Summary listings were generated for C-SSRS responses for the open-label and double-blind periods. The numbers of events in each Columbia Classification Algorithm of Suicide Assessment category were calculated by treatment group, for all patients and separately for patients with no suicidal thoughts or behaviors at baseline (based on baseline C-SSRS score).

RESULTS

Patients

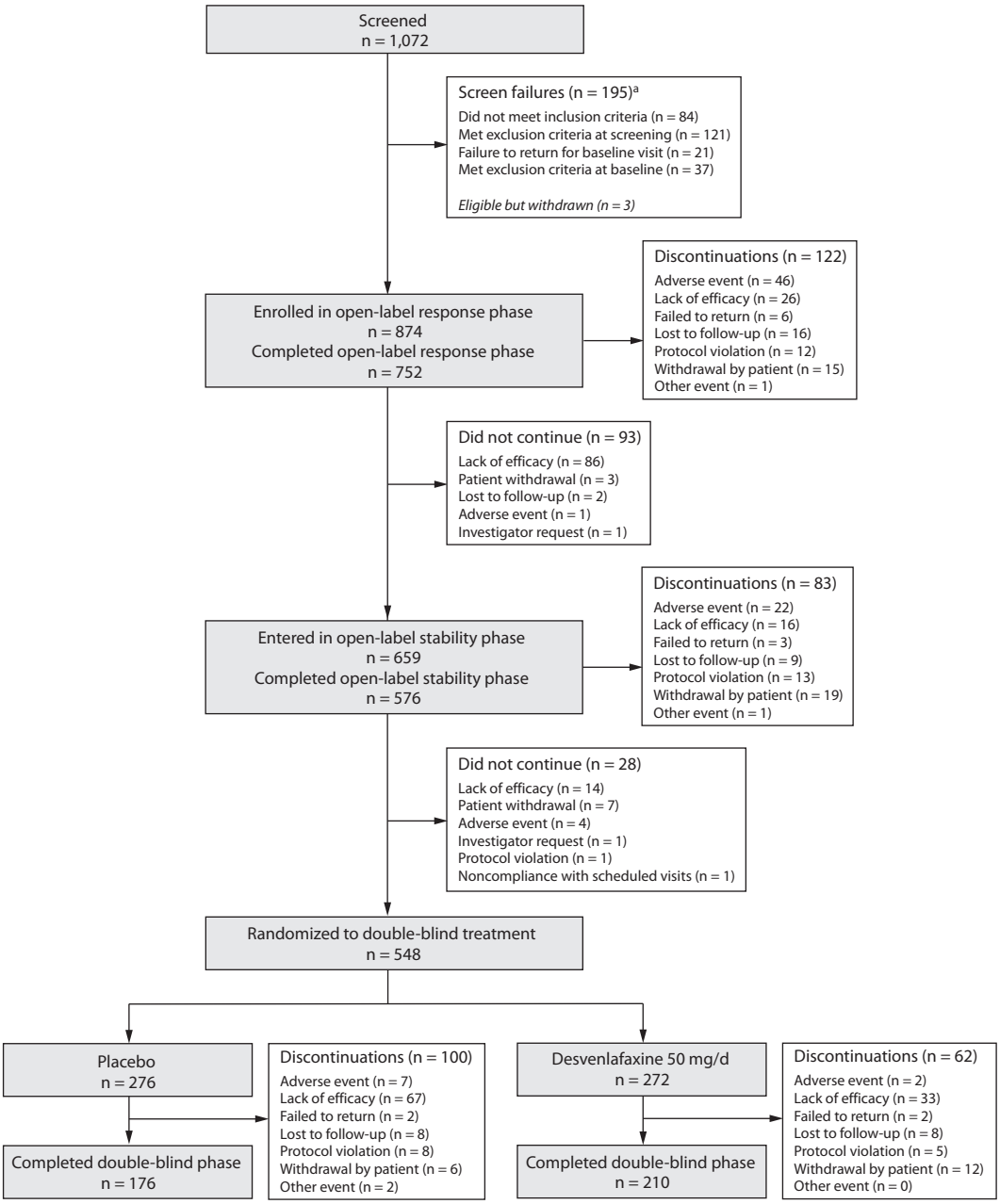
A total of 874 patients entered the open-label response phase, and 659 of the 752 who completed the response phase entered the open-label stability phase (Figure 1); 93 patients did not continue into the stability phase. Twenty-eight of 576 patients who completed the stability phase did not continue into the double-blind period. In all, 548 patients who had a continued stable response to desvenlafaxine 50-mg/d treatment through week 20 ($HDRS_{17}$ total score ≤ 11 and CGI-I score ≤ 2 at the end of week 20; no $HDRS_{17}$ total score ≥ 16 or CGI-I score ≥ 4 at any stability phase visit) were randomly assigned to placebo (n = 276) or desvenlafaxine 50 mg/d (n = 272) in the double-blind, randomized withdrawal period. Demographic and baseline characteristics were well balanced across the treatment groups (Table 1).

During the open-label period, 205 patients discontinued treatment (response phase, 122 [14.0%]; stability phase, 83 [12.6%]). During the double-blind period, 162 patients discontinued early; discontinuation rates were higher for the placebo group (36.2%) compared with the desvenlafaxine group (22.8%). Reasons for discontinuation from the open-label and double-blind phases are listed in Figure 1.

Efficacy

Patients receiving treatment with desvenlafaxine 50 mg/d had a significantly longer time to relapse compared with patients receiving placebo (log-rank test, $P < .001$). The Kaplan-Meier survival curve shows that placebo started to separate from desvenlafaxine around day 15, and the difference increased until the end of double-blind treatment (Figure 2A). The estimated probability of relapse following randomization to double-blind treatment was 30.2% for placebo-treated patients compared with 14.3% for desvenlafaxine-treated patients (Table 2). NNT based on estimated probability of relapse was 6. All patients who relapsed during the double-blind period (first event) met the criteria of $HDRS_{17}$ total score ≥ 16 (placebo, n = 60; desvenlafaxine, n = 34) and/or discontinuation due to unsatisfactory response (placebo, n = 66; desvenlafaxine, n = 33), except for 1 case of hospitalization for depression in the placebo group. No suicide attempts or suicides were reported in either treatment

Figure 1. Study Flowchart



[a]Sum of reasons for screen failure is greater than total screen failures because patients may have had multiple reasons.

group. Results of the sensitivity analyses excluding the first 4 weeks (Figure 2B) and excluding the first 2 weeks were consistent with those of the primary analysis (Table 2).

The hazard for relapse estimated in a Cox regression model including treatment and remission status at double-blind baseline was significantly lower for patients in treatment remission ($HDRS_{17}$ total score ≤ 7) compared with those who were not (estimated hazard ratio [HR] = 0.56; $P = .0072$), and treatment with desvenlafaxine 50 mg/d versus placebo significantly reduced the hazard for relapse after controlling for remission status (HR = 0.43; $P < .001$). The estimated HR for desvenlafaxine 50 mg/d versus placebo treatment was 0.42 ($P < .001$) in a second model, which included double-blind baseline $HDRS_{17}$ total score (HR = 1.08; $P = .0136$), number of prior MDD episodes (HR = 1.06; $P < .001$), age (NS), sex (NS), and duration of current episode (NS).

Safety and Tolerability

In the open-label response phase, 70.4% of patients reported TEAEs. Few TEAEs were reported during the stability phase (42.0% of patients); 57.2% of placebo-treated patients and 54.4% of desvenlafaxine-treated patients reported TEAEs during the double-blind withdrawal phase. The most common TEAEs reported are listed by phase in Table 3. In the double-blind period, TEAEs reported by ≥ 5% of the placebo group were consistent with discontinuation

Table 1. Demographic and Baseline Clinical Characteristics, Open-Label and Double-Blind Periods

Characteristic	Open-Label Desvenlafaxine (N = 874)	Double-Blind Placebo (n = 276)	Double-Blind Desvenlafaxine (n = 272)
Age, mean ± SD, y	45.0 ± 13.3	45.3 ± 13.0	46.6 ± 13.0
Sex, n (%)			
Women	608 (69.6)	198 (71.7)	193 (71.0)
Men	266 (30.4)	78 (28.3)	79 (29.0)
Race, n (%)			
White	729 (83.4)	230 (83.3)	240 (88.2)
Black or African-American	55 (6.3)	15 (5.4)	12 (4.4)
Other	90 (10.3)	31 (11.2)	20 (7.4)
Duration of current episode, mean ± SD, mo	12.4 ± 30.2	12.2 ± 34.9	11.1 ± 26.5
Current episode by duration groups, n (%)			
< 6 mo	516 (59.0)	174 (63.0)	170 (62.5)
6 to < 12 mo	167 (19.1)	49 (17.8)	45 (16.5)
12 to < 24 mo	95 (10.9)	29 (10.5)	29 (10.7)
24 to < 60 mo	62 (7.1)	13 (4.7)	20 (7.4)
60 to < 120 mo	24 (2.7)	7 (2.5)	6 (2.2)
≥ 120 mo	10 (1.1)	4 (1.4)	2 (0.7)
No. of previous episodes, mean ± SD	2.18 ± 4.39	1.95 ± 2.75	2.30 ± 6.07
$HDRS_{17}$ total score, mean ± SD			
Open-label baseline	24.2 ± 2.8	24.3 ± 2.8	23.9 ± 2.6
Double-blind baseline	NA	4.6 ± 3.0	4.7 ± 3.0
Remission at double-blind baseline ($HDRS_{17}$ score ≤ 7), n (%)			
No	NA	46 (16.7)	52 (19.1)
Yes	NA	230 (83.3)	220 (80.9)

Abbreviations: $HDRS_{17}$ = 17-Item Hamilton Depression Rating Scale, NA = not available.

symptoms or relapse of depression. The most common AEs leading to withdrawal (cited by > 2 patients/phase) were nausea (9 patients), headache (5), somnolence (5), insomnia (5), unintended pregnancy (3), and suicidal ideation (3) in the open-label response phase; unintended pregnancy (3) in the open-label stability phase; and depression (placebo, 14; desvenlafaxine, 6) in the double-blind period.

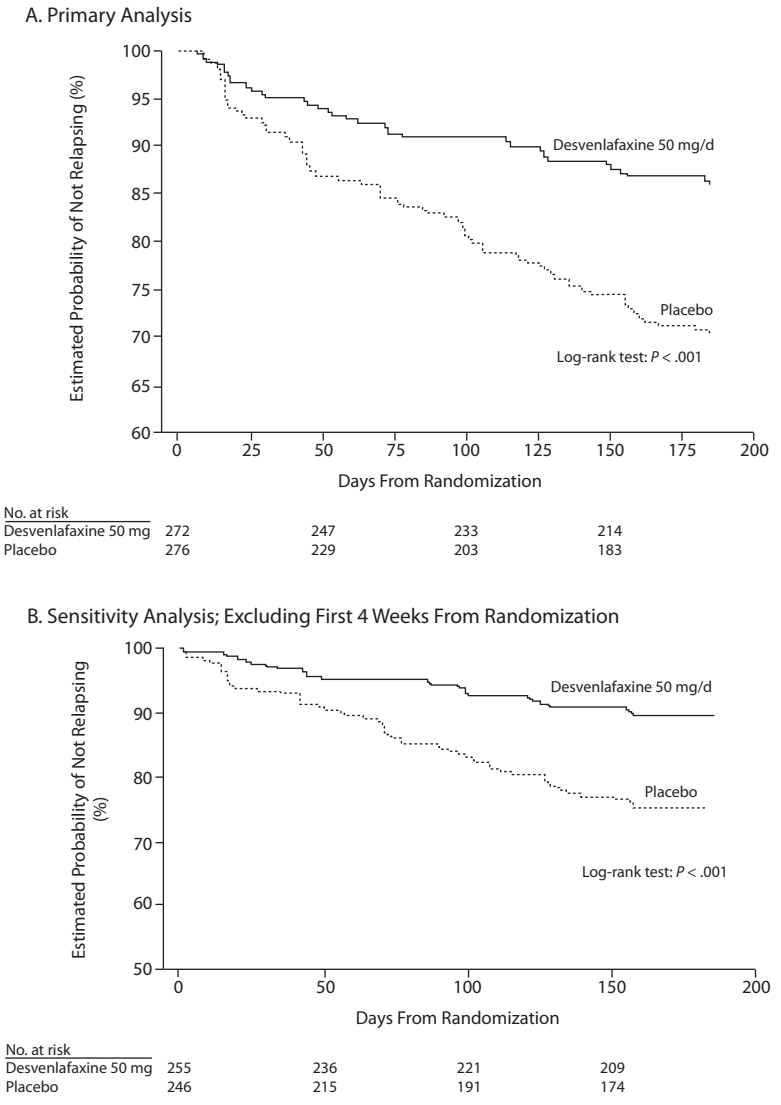
Taper/poststudy-emergent AEs (TPEAEs; any AEs that started or worsened the day after the last full dose of study medication, excluding taper dose) were reported by 17.2% of patients who were not randomized into the double-blind period; headache (2.5%) was the only TPEAE reported by at least 2% of patients. A total of 13.8% of placebo-treated patients and 17.6% of desvenlafaxine-treated patients reported TPEAEs following double-blind treatment; TPEAEs reported by at least 2% of patients in either double-blind treatment group were dizziness (placebo, 0.4%; desvenlafaxine, 4.8%), depression (placebo, 3.3%; desvenlafaxine, 1.1%), headache (placebo, 1.4%; desvenlafaxine, 2.6%), and nausea (placebo, 0.4%; desvenlafaxine, 2.6%).

The numbers of serious AEs (SAEs) reported in each study phase are listed in Table 4. There was no pattern to the SAEs reported, other than those associated with the underlying disorder (eg, suicidal ideation). One death was reported during the study: a patient died in an automobile accident, after hitting a pole while attempting to avoid an oncoming car, 35 days after discontinuing from double-blind desvenlafaxine treatment due to lack of efficacy. The death was considered by the investigator to be unrelated to study drug. At open-label baseline, 15.7% of patients reported on the C-SSRS that they had previously experienced suicidal ideation. Of patients with no previous suicidal ideation, 5.6% and 1.7% reported suicidal ideation during the response and stability phases, respectively, and 6.0% reported it during the 6-month double-blind period (placebo, 8.0%; desvenlafaxine, 4.0%). There were no completed suicides during the trial.

There was a small but significant decrease in weight compared with open-label baseline during the response phase (–0.14 kg, $P \leq .05$), followed by an increase during the stability phase (+0.46 kg, $P \leq .001$). There were no statistically significant differences between the placebo and desvenlafaxine 50-mg/d groups for mean change in weight from open-label baseline (+1.02 kg vs +0.73 kg; $P > .05$) or from double-blind baseline (+0.52 kg vs +0.30 kg; $P > .05$) at final double-blind evaluation. The percentages of patients with a clinically important increase in weight (≥ 7% of body weight) were 14% and 18% for placebo and desvenlafaxine, respectively, from open-label baseline, and 7% and 5%, respectively, during the double-blind period. Mean pulse rate increased slightly in each open-label phase (response phase: +1.49 bpm, $P \leq .001$; stability phase: +1.30 bpm; $P \leq .001$). No significant difference was observed between desvenlafaxine and placebo groups at the final double-blind evaluation (mean change: desvenlafaxine, +2.06 bpm; placebo +1.34 bpm from open-label baseline). No significant change from baseline in supine blood pressure was observed at response or stability phase final evaluations. No significant change (from time of randomization) was observed at the final double-blind evaluation (desvenlafaxine: systolic, –0.18 mm Hg; diastolic, –0.19 mm Hg; placebo: systolic, –0.67 mm Hg; diastolic, –0.50 mm Hg). Small but statistically significant increases were observed in QRS, QTcB, QTcF, QT, and QTcN intervals during both open-label phases (all $P \leq .05$). At final double-blind evaluation, mean changes from open-label baseline in ECG parameters for the desvenlafaxine group did not differ statistically from placebo.

At the final open-label response phase evaluation, there were significant mean changes from open-label baseline in total bilirubin (–0.76 umol/L; $P \leq .001$), fasting high-density lipoprotein cholesterol (+0.028 mmol/L; $P \leq .05$), aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT) (+2.0 U/L; $P \leq .05$), and alkaline phosphatase (+1.1 U/L; $P \leq .01$). At final open-label stability phase evaluation, significant mean changes from open-label baseline were observed in total bilirubin (–0.72 umol/L; $P \leq .001$), AST/SGOT (+1.4 U/L; $P \leq .05$), alanine aminotransferase/serum glutamic pyruvic transaminase (+1.6 U/L; $P \leq .05$), and alkaline phosphatase (+1.3 U/L; $P \leq .01$). Alkaline phosphatase was the only laboratory evaluation for which the mean change from open-label baseline for desvenlafaxine differed significantly from placebo at final double-blind evaluation (placebo, –0.8 U/L; desvenlafaxine, +1.5 U/L; $P = .035$).

Figure 2. Kaplan-Meier Survival Curve for Relapse[a]



[a]Patients who relapsed after double-blind day 185 or completed the double-blind therapy without relapse were considered as censored on double-blind day 185.

DISCUSSION

The current study is the first to provide long-term, double-blind, placebo-controlled efficacy data for the recommended therapeutic desvenlafaxine dose of 50 mg/d. Desvenlafaxine 50 mg/d was superior to placebo based on time to relapse ($P < .001$) in patients who responded to 8-week open-label desvenlafaxine 50-mg/d treatment and were stabilized on an additional 12 weeks of open-label therapy. The estimated probability of relapse was approximately twice as high for placebo compared with the desvenlafaxine group (30.2% vs 14.3%). On average, continued treatment of 6 patients with a stable response to 20-week therapy with desvenlafaxine 50 mg/d would prevent 1 additional relapse over 6 months. Results of the 2 sensitivity analyses (excluding data from the first 4 weeks of double-blind treatment and from the first 2 weeks of double-blind treatment, respectively) were consistent with the primary analysis.

The overall safety results are consistent with previous short- and long-term studies of desvenlafaxine for the treatment of MDD, indicating that desvenlafaxine 50 mg/d is generally safe and well-tolerated.[27–29,35] As expected, the frequency of most common AEs and rate of discontinuation due to AEs were substantially lower (half or less) in our 50-mg/d study compared with the long-term studies of desvenlafaxine 200 to 400 mg/d.[27–29] Furthermore, tolerability, especially with regard to nausea, improved between the open-label response phase and the stability or double-blind phases. Few TEAEs were reported during the stability phase: the only TEAE reported by greater than 5% of patients in the stability phase was headache (5.5%). Changes in vital signs and laboratory values were also consistent with results for desvenlafaxine 50-mg/d in short-term studies[35]; however, in this longer-term study, there were no significant changes in blood pressure from baseline at open-label final evaluation or compared with placebo at double-blind final evaluation. No new safety signals were observed. The C-SSRS results showed no evidence of treatment-emergent suicidal thoughts or behaviors during the study.

This study extends the findings of the previous desvenlafaxine relapse prevention study conducted using higher desvenlafaxine doses (200–400 mg/d)[29] to the recommended 50-mg/d dose. Relapse rates for both treatment groups in the current study (desvenlafaxine, 14%; placebo, 28%) were lower than those in the previous trial (desvenlafaxine, 24%; placebo, 42% [estimated probabilities of relapse not reported]), and several changes in study design may account, in part, for the difference in rates. Definitions of both response and relapse differed between the 2 studies. The more stringent criteria for response in the current trial compared with the high-dose trial ($HDRS_{17}$ score ≤ 11 score and CGI-I score ≤ 2 vs $HDRS_{17}$ score ≤ 11 only, respectively) might have resulted in a patient population with fewer residual symptoms, which is associated with a lower risk of relapse.

An important strength of the current study is the inclusion of the open-label stability phase in the study design. This is the first randomized withdrawal study evaluating prevention of relapse with an antidepressant to use this design. Patients randomly assigned to double-blind treatment in this study had both responded to acute-phase treatment ($HDRS_{17}$ total score ≤ 11 and CGI-I score ≤ 2 at week 8 were required to enter the stability phase) and demonstrated a stable response to treatment through 20 weeks of therapy ($HDRS_{17}$ total score ≤ 11 and CGI-I score ≤ 2 at the end of week 20 plus no $HDRS_{17}$ total score ≥ 16 or a CGI-I score ≥ 4 at any visit

Table 2. Survival Analysis of Time to Relapse, 6-Month Double-Blind Period, Randomized Population

	Desvenlafaxine 50 mg/d	Placebo	*P* Value
Primary analysis			
Rate of relapse,[a] % (n/n)	13.6 (37/272)	28.3 (78/276)	< .001
Estimated probability of relapse, day 185, %	14.3	30.2	
Sensitivity analysis excluding first 4 weeks of double-blind treatment			
Rate of relapse,[a] % (n/n)	9.8 (25/255)	23.6 (58/246)	< .001
Estimated probability of relapse, day 185, %	10.4	24.7	
Sensitivity analysis excluding first 2 weeks of double-blind treatment			
Rate of relapse,[a] % (n/n)	12.4 (33/266)	26.4 (70/265)	< .001
Estimated probability of relapse, day 185, %	13.1	28.1	

[a]Patients who relapsed after double-blind day 185 or completed the double-blind therapy without relapse were considered as censored on double-blind day 185.

Table 3. Most Common (≥ 5% of Patients) Treatment-Emergent Adverse Events During On-Therapy Period (%)

Adverse Event[a]	Desvenlafaxine 50 mg/d	Placebo
Open-label response phase (8 wk)	N = 874	
Any adverse event	70	
Nausea	21	
Headache	18	
Dry mouth	12	
Dizziness	7	
Constipation	6	
Hyperhidrosis	6	
Somnolence	5	
Diarrhea	5	
Insomnia	5	
Open-label stability phase[b] (12 wk)	n = 659	
Any adverse event	42	
Headache	5	
Double-blind period[b] (6 mo)	n = 272	n = 276
Any adverse event	54	57
Headache	13	12
Dizziness	5	11
Depression	3	7

[a]Classifications of adverse events are based on the *Medical Dictionary for Regulatory Activities*.
[b]Using open-label baseline.

Table 4. Incidence of Serious Adverse Events and Events Related to Suicidal Thoughts and Behaviors, n (%)

	Desvenlafaxine 50 mg/d	Placebo
Open-label response phase (8 wk)	N = 874	
Any serious adverse event	9 (1.0)	
Suicidal ideation	2 (0.2)	
Suicide attempt	2 (0.2)	
Overdose of nonstudy medication	2 (0.2)	
Open-label stability phase[a] (12 wk)	n = 659	
Any serious adverse event	6 (0.9)	
Suicidal ideation	2 (0.3)	
Self-injurious behavior	1 (0.2)	
Double-blind period[a] (6 mo)	n = 272	n = 276
Any serious adverse event	8 (2.9)	7 (2.5)
Open-label taper/posttherapy (2 wk)	n = 326	
Any serious adverse event	4 (1.2)	
Suicidal ideation	1 (0.3)	
Double-blind taper/posttherapy (2 wk)	n = 272	n = 276
Any serious adverse event	1 (0.4)	1 (0.4)

during the stability phase). Continuation of pharmacotherapy beyond acute-phase treatment is known to reduce the risk of relapse.[14] The lower rates of relapse in the current study compared with the study by Rickels and colleagues,[29] which did not include a stability phase, thus may be related to the longer open-label treatment period (20 weeks vs 12 weeks) prior to randomization as well as the more enriched subset of patients eligible for randomization.

Estimated probabilities of relapse for both placebo and active drug vary across relapse prevention studies of different designs, but the 2:1 ratio for relapse with placebo versus active drug observed in this study is consistent with results with other antidepressants. Estimated probabilities of relapse in the range of 34%–52% for placebo versus 20%–28% for active drug have been reported in double-blind randomized withdrawal studies of other SNRIs or selective serotonin reuptake inhibitors.[36–41] The lower probabilities of relapse in our study (30% for placebo and 14% for desvenlafaxine) could be attributable to the use of a longer period of stabilization compared with studies in which only acute-phase treatment was administered.

Several study limitations should be noted. First, the inclusion and exclusion criteria used in this study selected for a population of generally healthy patients with a primary diagnosis of MDD. Findings therefore may not generalize to a broader population of depressed patients with other clinical characteristics. A possible limitation of the study design (randomizing desvenlafaxine-treated patients to placebo in the double-blind period) was the potential for confounding discontinuation symptoms and symptoms of relapse, as the placebo group had their previous desvenlafaxine dose tapered in the first week of the double-blind period.[42] However, the sensitivity analyses, which excluded data from the first weeks of the double-blind period (when discontinuation symptoms were most likely to occur[43]), were included in the study design specifically to address this potential limitation. Third, the trial duration was less than 1 year (11 months); there remains a need for efficacy and safety data for desvenlafaxine

50-mg/d treatment durations beyond 1 year. Finally, the criteria used in the current study to define treatment response differed from definitions used in other published relapse prevention trials. Our criteria for randomization were less stringent than in some studies that required $HDRS_{17}$ scores of less than 11[36,37,39] or remission as a criterion,[40] but more stringent than those that used a single threshold based on the Montgomery-Asberg Depression Rating Scale,[44–46] the $HAM\text{-}D_{17}$,[47] or the CGI-I or CGI-S alone.[4,38] We also believe that the inclusion of the stability phase quite likely served to reduce the number of patients who were not true responders randomized into the double-blind period.

CONCLUSIONS

Long-term continuation treatment with desvenlafaxine 50 mg/d reduced the risk of relapse of MDD compared with the group who discontinued desvenlafaxine treatment (placebo patients). No new safety signals for desvenlafaxine 50 mg/d were observed during this study; the benefit/risk profile of desvenlafaxine 50 mg/d for long-term treatment of MDD remains favorable.

Drug names: desvenlafaxine (Pristiq), escitalopram (Lexapro and others), fluoxetine (Prozac and others).

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Potential conflicts of interest: **Dr Boyer** has been on a speakers/advisory board for Servier, has been a consultant to Institut de Recherche Pierre Fabre, and has received honoraria from Pfizer. **Ms Vialet** and **Dr Hwang** are employees of Pfizer, and **Dr Tourian** is an employee of and stock shareholder in Pfizer. **Dr Rosenthal** reports no potential conflict of interest.

Funding/support: This study was sponsored by Pfizer Inc. Medical writing support was provided by Kathleen M. Dorries, PhD, at Peloton Advantage and was funded by Pfizer Inc.

Previous presentation: Presented at the 165th Annual Meeting of the American Psychiatric Association; May 5–9, 2012; Philadelphia, Pennsylvania.

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