Short-Term Efficacy and Safety of Desvenlafaxine in a Randomized, Placebo-Controlled Study of Perimenopausal and Postmenopausal Women With Major Depressive Disorder

Susan G. Kornstein, MD; Qin Jiang, MS; Sujana Reddy, MD; Jeff J. Musgnung, MS; and Christine J. Guico-Pabia, MD, MBA, MPH

Background: The risk for major depressive disorder (MDD) increases during the menopausal transition. Nonetheless, no large, placebo-controlled studies have prospectively assessed the efficacy of antidepressants in perimenopausal or postmenopausal women. This randomized, double-blind, placebo-controlled trial evaluated the short-term efficacy and safety of desvenlafaxine (administered as desvenlafaxine succinate) in perimenopausal and postmenopausal women with *DSM-IV*–defined MDD.

Method: 387 depressed perimenopausal and postmenopausal women aged 40 to 70 years were randomly assigned to placebo or desvenlafaxine (100 or 200 mg/d at the discretion of the investigator) in an 8-week, flexible-dose trial conducted from September 2006 to June 2008. The primary efficacy variable was change from baseline in 17-item Hamilton Depression Rating Scale ($HDRS_{17}$) total score, analyzed using a mixed-effects model for repeated-measures analysis. Safety data were collected throughout the trial.

Results: The reduction in adjusted $HDRS_{17}$ total scores from baseline to week 8 (mean daily dose after titration, 162 to 176 mg/d) was significantly greater for desvenlafaxine (–12.64) compared with placebo (–8.33; $P < .001$). Statistical separation from placebo was observed at week 1 and was sustained through week 8. Both the perimenopausal and postmenopausal subgroups achieved significant reductions in $HDRS_{17}$ total scores with desvenlafaxine treatment (perimenopausal, $P = .003$; postmenopausal, $P < .001$). Response (58.6%) and remission (38.2%) rates were significantly higher for desvenlafaxine compared with placebo (31.6% [$P < .001$] and 22.4% [$P = .008$], respectively). In all, 19/256 (7.4%) desvenlafaxine-treated patients and 4/125 (3.2%) placebo-treated patients discontinued due to adverse events. Treatment-emergent adverse events were reported by 94/125 (75.2%) placebo-treated patients and 218/256 (85.2%) desvenlafaxine-treated patients.

Conclusions: Short-term treatment with desvenlafaxine was effective and generally well tolerated in perimenopausal and postmenopausal women with MDD.

Trial Registration: clinicaltrials.gov Identifier: NCT00369343

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Corresponding author: *Susan G. Kornstein, MD, Mood Disorders Institute and Institute for Women's Health, PO Box 980710, Department of Psychiatry, Richmond, VA 23209-0710 (skornstein@mcvh-vcu.edu).*

The risk for major depressive disorder (MDD) is greater in women than in men,[1] and the risk for depression is reported to increase during the menopausal transition.[2,3] In longitudinal cohort studies assessing the association between perimenopause and depression, women entering menopause were twice as likely to develop new-onset depression compared with women in the same age range (36–45 years and 35–47 years, respectively, at enrollment) who remained premenopausal[2] and compared with their own premenopausal status.[3] Despite the vulnerability of women in the menopausal transition, however, few studies have evaluated the efficacy of treatments for depression in the perimenopausal and postmenopausal patient population.

The efficacy of estrogen for treating perimenopausal or postmenopausal women with depression has been assessed in 4 randomized, placebo-controlled studies.[4–7] Perimenopausal women with MDD, dysthymic disorder, or minor depression (n = 50) treated with 100 μg transdermal 17β-estradiol had statistically significantly greater improvement in Montgomery-Asberg Depression Rating Scale (MADRS) scores after 12 weeks compared with the placebo group ($P < .01$).[4] Women with perimenopause-associated MDD or minor depression (n = 34) had significantly greater improvement in Hamilton Depression Rating Scale (HDRS) scores after 3-week treatment with 0.05 mg/d transdermal 17β-estradiol compared with placebo ($P = .02$).[5] Two placebo-controlled studies found no improvement in HDRS scores with transdermal estrogen compared with placebo in postmenopause: one study assessed estradiol, 50 μg twice weekly for 3 months, in postmenopausal women with MDD (n = 64),[6] and the other administered 0.1 mg/d estradiol transdermally for 8 weeks in postmenopausal women with MDD, dysthymic disorder, or minor depression (n = 57).[7] Because of the paucity of evidence for the efficacy of estrogen for perimenopausal and postmenopausal depression, together with the increased risk for breast cancer, coronary heart disease, stroke, and dementia with long-term estrogen (plus progestin) use,[8–10] estrogen is generally not recommended for treating depression in perimenopausal or postmenopausal women.[11,12] Antidepressants are considered the first-line treatment for this population.[13]

Little is known, however, about the efficacy of antidepressants in perimenopausal and postmenopausal women. Antidepressant efficacy has been prospectively assessed in perimenopausal or postmenopausal women in small, open-label studies only. Perimenopausal women with MDD (n = 20)

had significant improvement in HDRS scores compared with baseline ($P < .001$) in an 8-week open-label trial of the selective serotonin reuptake inhibitor (SSRI) escitalopram.[14] Escitalopram also showed superior efficacy compared with estrogen/progestin therapy (decrease in median MADRS scores; $P = .03$) in an 8-week, open-label trial of perimenopausal and postmenopausal women (n = 40) with depressive disorders.[15] In a 12-week study of citalopram for depressive disorders, median MADRS scores for 22 perimenopausal and postmenopausal women improved significantly compared with baseline ($P < .05$).[16] Perimenopausal women (n = 16) treated with the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine had significant improvement compared with baseline in HDRS scores ($P < .001$) in an 8-week, open-label trial,[17] and postmenopausal women (age 40–60 years; n = 20) had a significant median decrease from baseline in MADRS scores ($P < .001$) after 8 weeks of duloxetine treatment.[18] Duloxetine efficacy also was demonstrated for women 40 to 55 years old and for women over 55 years in a post hoc analysis of pooled data from 347 women enrolled in two 9-week, double-blind, placebo-controlled MDD trials (change from baseline in HDRS scores compared with placebo, $P < .001$ and $P < .05$, respectively).[19] To date, however, no large, randomized, placebo-controlled trials have prospectively assessed the efficacy of antidepressants specifically in perimenopausal or postmenopausal women with MDD.

The SNRI desvenlafaxine (administered as desvenlafaxine succinate) has demonstrated efficacy for treating MDD in adults in 4 short-term, placebo-controlled studies.[20–24] The objective of this large, multicenter, randomized, double-blind, placebo-controlled trial was to evaluate the short-term efficacy and safety of desvenlafaxine in perimenopausal and postmenopausal women with MDD.

METHOD

This phase 3b, multicenter, randomized, double-blind, placebo-controlled trial was conducted at 37 outpatient study sites in the United States from September 2006 to June 2008. The study protocol received institutional review board approval before the study began and was conducted according to the US Food and Drug Administration Code of Federal Regulations (21 CFR, Part 50) and in accordance with the ethical principles in the Declaration of Helsinki. It was consistent with Good Clinical Practice and applicable regulatory requirements. Written informed consent was obtained from all subjects before enrollment.

Patients

Perimenopausal and postmenopausal women aged 40 to 70 years meeting *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition,[25] criteria for MDD, single or recurrent episode, without psychotic features and with depressive symptoms for at least 30 days before the screening visit, were enrolled. Postmenopausal status was defined by 12 months of spontaneous amenorrhea or 6 months postsurgical bilateral oophorectomy (with or without hysterectomy). Perimenopausal status was defined by the presence of any of the following within 6 months of baseline: an absolute change of 7 days or more in menstrual cycle length; a change in menstrual flow amount (2 or more flow categories, eg, from light or moderately light to moderately heavy or heavy) or duration (absolute change of 2 or more days); and periods of amenorrhea lasting at least 3 months. Eligible participants had screening and baseline MADRS[26] total scores ≥ 22 and had no more than a 5-point improvement in total score from screening to baseline.

Patients were excluded if they had ever received treatment with desvenlafaxine; had known hypersensitivity to venlafaxine; had significant risk of suicide based on clinical judgment; were pregnant or breastfeeding; had current (within 12 months) psychoactive substance abuse or dependence, manic episodes, posttraumatic stress disorder, obsessive-compulsive disorder, or clinically important personality disorder or a lifetime diagnosis of bipolar or psychotic disorder; had depression associated with the presence of an organic mental disorder; had a history of seizure disorder; had clinically important medical disease (including uncontrolled hypertension or unstable angina); had formal cognitive-based or interpersonal therapy within 30 days before baseline; or had used prohibited treatments. Prohibited treatments included hormone products within 4 weeks to 6 months before baseline (depending on route of administration of the hormone); antidepressants, anxiolytics, sedative hypnotics (other than zaleplon, eszopiclone, or zolpidem), serotonin precursors, psychotropic drugs or nonpsychotropic drugs with psychotropic effects, or herbal products intended to treat anxiety, insomnia, or depression within 7 days before baseline; and electroconvulsive therapy or formal psychotherapy within 6 months before baseline.

Study Design

Patients were randomly assigned to receive placebo or desvenlafaxine (100–200 mg/d) using a 1:2 allocation in an 8-week, flexible-dose trial followed by a 6-month, open-label extension period. (At the time this study was initiated, the 50-mg/d dose was not yet approved by the US Food and Drug Administration as an effective dose, and therefore a 50-mg/d treatment arm was not included in the study design.) Randomization was performed through a central computerized randomization/enrollment system. Participants, investigators, and monitors were blind to treatment assignment. After a screening phase of up to 4 weeks, desvenlafaxine was dosed at 50 mg/d from day 1 to 7 and 100 mg/d from day 8 to 14. From day 15, patients received desvenlafaxine 100 or 200 mg/d, at the discretion of the investigator. Patients who could not tolerate desvenlafaxine 200 mg/d had their dose decreased to 100 mg/d. After day 7, 100 mg/d was the minimum dose maintained during the course of the study. Patients who withdrew early or elected not to continue in the open-label extension had their dosage tapered over 7 to 14 days (depending on study drug dosage) during a 3-week,

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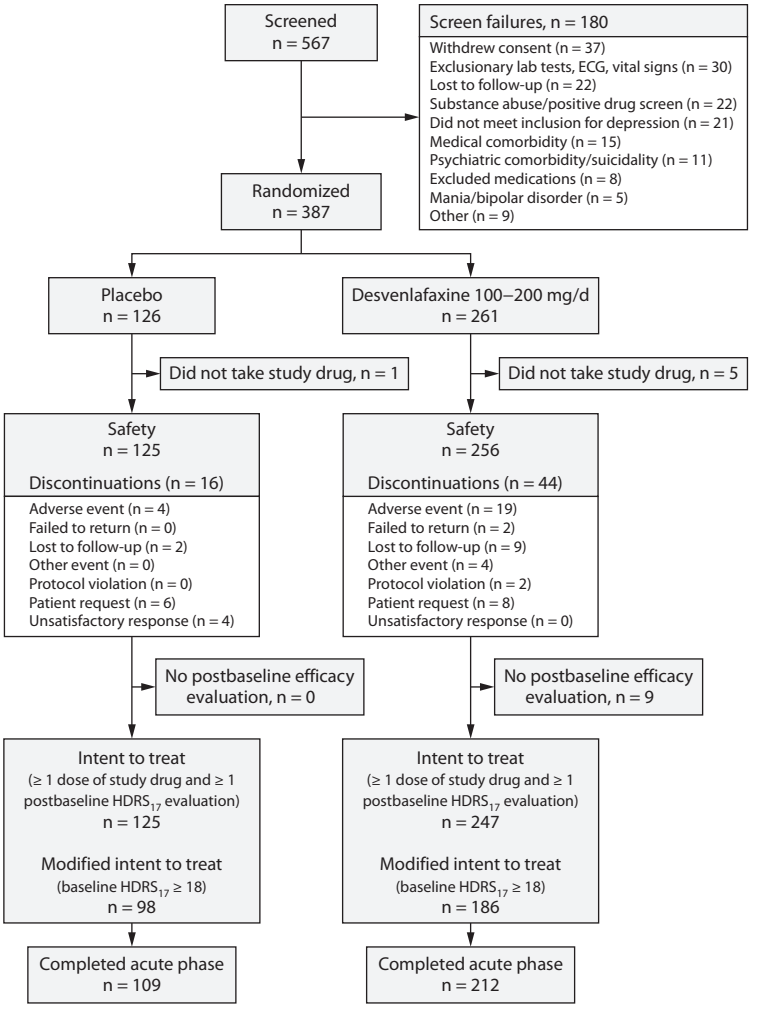
follow-up period. This article reports the analysis of data from the 8-week, double-blind phase only; results from the open-label extension phase will be reported elsewhere.

Efficacy, Safety, and Tolerability Assessments

The primary efficacy variable was change from baseline in 17-item HDRS ($HDRS_{17}$)[27] total score. Secondary measures included the Clinical Global Impressions-Improvement (CGI-I) and Clinical Global Impressions-Severity of Illness (CGI-S) scales,[28] MADRS total score, the Hamilton Anxiety Rating Scale (HARS),[29] Quick Inventory of Depressive Symptomatology–Self-Report,[30] the Sheehan Disability Scale (SDS),[31] the Menopause Rating Scale (MRS),[32] the 5 Dimension Health State EuroQol (EQ-5D),[33] and the Visual Analog Scale–Pain Intensity.[34] Response rates based on $HDRS_{17}$ (≥ 50% reduction in total score), CGI-I (CGI-I scores 1 or 2), and MADRS (≥ 50% reduction in total score) and remission rate based on $HDRS_{17}$ (total score ≤ 7) were assessed. The MRS, EQ-5D, and SDS were administered at baseline, week 4, and week 8. All other primary and secondary efficacy assessments were made at baseline (except CGI-I) and at weeks 1, 2, 3, 4, 6, and 8.

Safety assessments, including monitoring of adverse events (AEs) and discontinuations due to AEs, recording of concomitant medications, and measurement of weight and vital signs (supine blood pressure, resting pulse rate), were collected during the study. Patients received a physical examination and a single 12-lead electrocardiogram recording was made at screening only. Laboratory evaluations were performed at screening and week 8. Laboratory determinations included hematology, blood chemistry, lipid profile, urinalysis, and free thyroxine index including total thyroxine and triiodothyronine uptake. Follow-up evaluations were scheduled weekly for 3 weeks after the end of treatment.

Figure 1. Study Flow Diagram



Abbreviations: ECG = electrocardiogram, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale.

Statistical Analysis

The sample size estimates[35] were based on the primary efficacy variable, the $HDRS_{17}$ total score. Calculations used a standard deviation of 8 units, based on the estimates of variability obtained from earlier phase 3 studies of desvenlafaxine. A sample size of 300 patients (200 desvenlafaxine: 100 placebo) was estimated to be sufficient to provide 90% power to detect a significant difference of 3 units between the desvenlafaxine and the placebo treatment groups with an α of 5%. Primary efficacy analyses were based on a modified intent-to-treat population (mITT), defined as patients who took at least 1 dose of study drug, had at least 1 postbaseline $HDRS_{17}$ evaluation, and had a baseline $HDRS_{17}$ score ≥ 18. Approximately 345 subjects were to be randomly assigned to treatment to compensate for subjects who failed to qualify for the mITT analysis.

A mixed-effects model for repeated-measures (MMRM) analysis was used as the primary analysis model for all of the continuous end points. The model used baseline value as a covariate and included factors for site, week, treatment, and the interaction of treatment by week. Because of the number of investigative sites with few subjects, data from individual sites were pooled to form centers with a greater number of subjects; each pooled center was referred to as a site for the purposes of the analysis. Post hoc MMRM analyses of $HDRS_{17}$ total score for the perimenopausal and postmenopausal subgroups were conducted based on the ITT population (took ≥ 1 dose of study drug, had ≥ 1 postbaseline $HDRS_{17}$ evaluation). Analysis of covariance (ANCOVA) with treatment, site, and baseline $HDRS_{17}$ total score as covariates was performed using the last-observation-carried-forward (LOCF) data as a secondary analysis. The CGI-I was analyzed as a categorical variable using the Cochran-Mantel-Haenszel (CMH) test with treatment as a factor, and adjusted for site.

Table 1. Demographics and Baseline Characteristics, ITT Population

Characteristic	Placebo (n = 125)	Desvenlafaxine (n = 247)
Age, y		
Mean ± SD	53 ± 7	52 ± 6
Range	40–68	40–70
Menopausal status, n (%)		
Perimenopause	37 (30)	84 (34)
Postmenopause	88 (70)	163 (66)
Weight, kg		
Mean ± SD	81 ± 20	82 ± 20
Range	46–158	46–152
Race, %		
White	85	81
Black	13	15
Other	2	4
Duration of current MDD episode		
Mean ± SD, mo	22 ± 57	19 ± 38
Patients, %		
< 24 mo	81	85
24 to < 60 mo	13	8
60 to < 120 mo	3	4
≥ 120 mo	3	2
Baseline score, mean ± SD (mITT population)		
$HDRS_{17}$ total	21.0 ± 4.3	20.6 ± 4.2
MADRS total	30.58 ± 4.81	30.59 ± 4.36
HARS total	17.51 ± 4.34	18.17 ± 4.78
CGI-S	4.59 ± 0.69	4.55 ± 0.61
QIDS-SR	14.85 ± 3.89	14.41 ± 3.97
VAS-PI overall pain	3.95 ± 2.70	3.41 ± 2.43

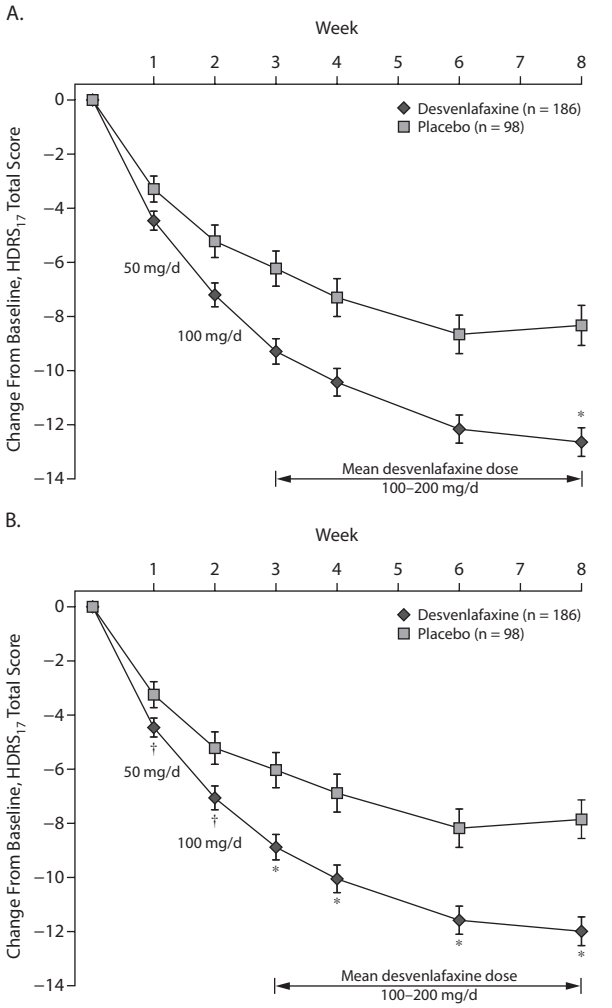
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HARS = Hamilton Anxiety Rating Scale, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, ITT = intent-to-treat, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, mITT = modified intent-to-treat, QIDS-SR = Quick Inventory of Depressive Symptomatology–Self-Report, VAS-PI = Visual Analog Scale–Pain Intensity.

A logistic regression model with baseline as covariate, and using treatment and site as factors, was used to analyze rates of response and remission using LOCF data.

RESULTS

A total of 387 subjects were randomly assigned to treatment, and 381 patients took at least 1 dose of the double-blind study drug and were included in the safety population; 44/256 (17.2%) desvenlafaxine-treated patients and 16/125 (12.8%) placebo-treated patients discontinued during the double-blind period (Figure 1). The ITT population (≥ 1 dose of study drug, ≥1 postbaseline $HDRS_{17}$ evaluation) included 372 patients who had at least 1 postbaseline $HDRS_{17}$ evaluation (Table 1). Of those, only 284 patients met the mITT criteria as per the protocol for the primary efficacy analysis. In all, 321 patients completed the double-blind treatment phase. Baseline demographic and clinical characteristics for the ITT population (desvenlafaxine, n = 247; placebo, n = 125) are shown in Table 1. There were no significant differences between treatment groups in any demographic characteristic at baseline. The mean desvenlafaxine dose ranged from to 162 to 175.8 mg/d after the 2-week titration period.

Figure 2. Adjusted Mean Change From Baseline in $HDRS_{17}$ Total Score: (A) Primary Efficacy Analysis (MMRM) Results (week 8 evaluation in the mITT population) and (B) ANCOVA Analysis Using LOCF Data



*$P < .001$, desvenlafaxine vs placebo.
†$P < .05$, desvenlafaxine vs placebo.
Abbreviations: ANCOVA = analysis of covariance, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, LOCF = last observation carried forward, mITT = modified intent to treat, MMRM = mixed-effects model for repeated measures.

Efficacy

In the primary efficacy analysis (MMRM), there was a significantly greater reduction in $HDRS_{17}$ total scores from baseline to week 8 for desvenlafaxine-treated patients (adjusted mean change, −12.64) compared with placebo-treated patients (−8.33, $P < .001$; Figure 2A). Statistically significant separation from placebo was observed for desvenlafaxine-treated patients as early as week 1 ($P = .044$), when patients were receiving the 50-mg/d dose, in the ANCOVA analysis using LOCF data (Figure 2B). Statistically significant improvement from baseline for the desvenlafaxine group was sustained through week 8 (week 2, $P = .013$; weeks 3–8, $P < .001$). In a subgroup analysis of the ITT perimenopausal and postmenopausal groups, significant reductions

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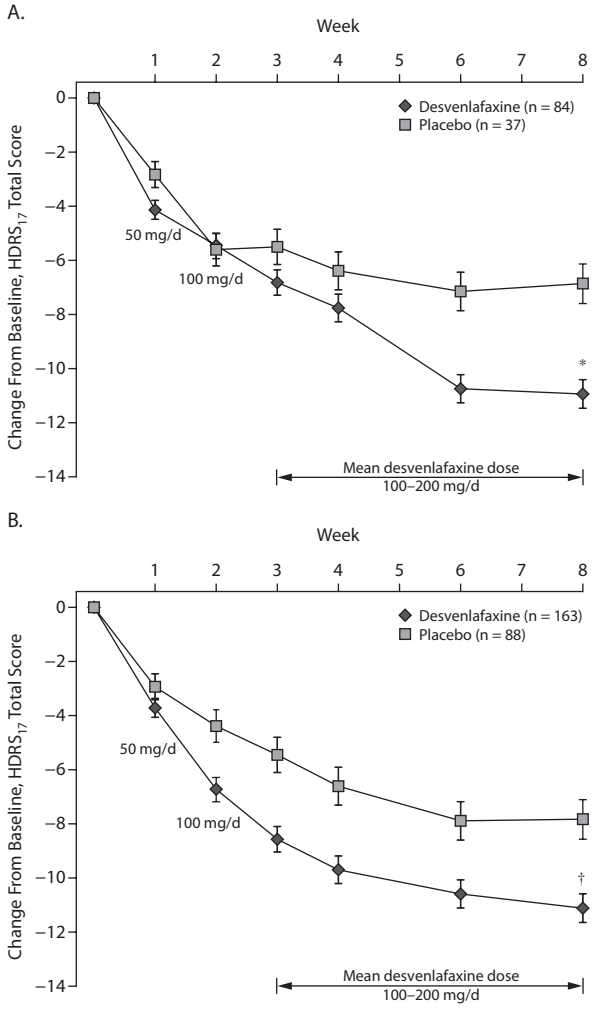
Figure 3. Change From Baseline in $HDRS_{17}$ Total Scores (MMRM) in the ITT Population in (A) Perimenopausal Women and (B) Postmenopausal Women



*$P = .003$, desvenlafaxine vs placebo.
†$P < .001$, desvenlafaxine vs placebo.
Abbreviations: $HDRS_{17}$ = 17-item Hamilton Rating Scale for Depression, ITT = intent to treat, MMRM = mixed-effects model for repeated measures.

in $HDRS_{17}$ total scores for desvenlafaxine compared with placebo were observed at week 8 in the MMRM analysis for both perimenopausal women (adjusted mean change, −10.96; $P = .003$; Figure 3A) and postmenopausal women (adjusted mean change, −11.09; $P < .001$; Figure 3B). The treatment effect of desvenlafaxine (adjusted mean difference from placebo) was −4.07 (95% CI, −6.77 to −1.37) for perimenopausal women and −3.27 (95% CI, −5.07 to −1.47) for the postmenopausal group.

The desvenlafaxine treatment group had statistically significant improvement compared with placebo on all secondary efficacy measures at week 8 (Table 2). Desvenlafaxine-treated patients (mITT population, MMRM) had significantly lower CGI-I scores at week 8 compared with placebo-treated women (2.00 vs 2.82; $P < .001$); a significantly higher percentage (126/186 [67.7%]) of women in the desvenlafaxine group scored 1 (very much improved) or 2 (much improved) compared with placebo (40/97 [41.2%]; CMH test, mITT population, LOCF; $P < .001$).

Desvenlafaxine-treated patients (mITT population) had significantly higher rates of response based on $HDRS_{17}$ total scores (109/186 [58.6%]), MADRS total scores (114/186 [61.3%]), and CGI-I scores (126/186 [67.7%]) at week 8, compared with placebo (31/98 [31.6%], 32/98 [32.7%], and 40/97 [41.2%], respectively; all comparisons, $P < .001$). $HDRS_{17}$ remission rates were significantly higher for the desvenlafaxine group (71/186 [38.2%]) compared with placebo at week 8 (22/98 [22.4%]; $P = .008$).

Safety

A total of 19/256 (7.4%) desvenlafaxine-treated patients and 4/125 (3.2%) placebo-treated patients discontinued due to AEs during the double-blind period (Figure 1). The AE cited most commonly by patients discontinuing due to an AE was hypertension; 5 desvenlafaxine-treated patients (0 placebo-treated patients) discontinued due to hypertension.

Adverse Events

Treatment-emergent AEs were reported by 218/256 (85.2%) patients in the desvenlafaxine group and 94/125 (75.2%) patients receiving placebo. Most AEs were mild or moderate in severity. The most common treatment-emergent AEs (reported by ≥ 5% of desvenlafaxine-treated patients and at ≥ 2 times placebo rate) were dry mouth, 24% (placebo, 10%); somnolence, 15% (placebo, 7%); constipation, 14% (placebo, 6%); hypertension, 7% (placebo, 2%); sweating, 7% (placebo, 2%); dyspepsia, 6% (placebo, 2%); and anorexia, 6% (placebo, < 1%). Incidence of treatment-emergent nausea in the desvenlafaxine group (43/256 [16.8%]) was less than twice the placebo rate (15/125 [12.0%]). Serious AEs were reported by 3 desvenlafaxine-treated patients (chest pain and hypertension [1 patient]; medication error and psychotic depression [1 patient]; infection), and 2 placebo-treated patients (cerebrovascular disorder; skin carcinoma). Two patients, 1 in the desvenlafaxine group and 1 in the placebo group, reported suicidal ideation during the double-blind phase. No deaths were reported during the study or within 30 days after its conclusion.

Laboratory Assessments

A total of 335 patients had at least 1 laboratory assessment during the double-blind period, and, of those, 125 (37.3%) had laboratory values of potential clinical importance. Common laboratory values of potential clinical importance included a decrease in bicarbonate ≥ 4 mmol/L or out of normal range in 17 desvenlafaxine-treated patients (14 placebo); uric acid levels > 0.4758 mmol/L in 4 desvenlafaxine-treated patients (1 placebo); and total fasting cholesterol levels ≥ 7.758 mmol/L in 7 desvenlafaxine-treated patients (1 placebo) and fasting triglycerides levels ≥ 3.7 mmol/L in 9 desvenlafaxine-treated patients (1 placebo). Laboratory values of potential clinical importance also included positive urine tests for

Table 2. Adjusted Mean Change From Baseline at Week 8 in the mITT Population (primary efficacy analysis) and Rates of Response and Remission

Efficacy Variable	Placebo (n = 98)	Desvenlafaxine (n = 186)	Effect Size (95% CI)	*P* Value
Primary variable (MMRM)				
$HDRS_{17}$ total score, mean (SE)	−8.33 (0.74)	−12.64 (0.53)	−0.65 (−0.92 to −0.37)	< .001
Secondary variables (MMRM)				
CGI-I score, mean (SE)[a]	2.82 (0.13)	2.00 (0.10)	−0.67 (−0.94 to −0.39)	< .001
MADRS total score, mean (SE)	−11.77 (1.04)	−18.21 (0.75)	−0.68 (−0.96 to −0.41)	< .001
HARS total score, mean (SE)	−5.89 (0.62)	−8.62 (0.44)	−0.49 (−0.76 to −0.22)	< .001
CGI-S score, mean (SE)	−1.27 (0.14)	−2.07 (0.10)	−0.64 (−0.91 to −0.36)	< .001
EQ-5D, mean (SE)	0.06 (0.02)	0.18 (0.02)	0.52 (0.25 to 0.79)	< .001
MRS, mean (SE)	−6.11 (0.73)	−8.84 (0.53)	−0.41 (−0.68 to −0.14)	.003
SDS score, mean (SE)	−4.32 (0.75)	−8.84 (0.53)	−0.68 (−0.95 to −0.40)	< .001
QIDS-SR, mean (SE)	−4.72 (0.50)	−7.27 (0.36)	−0.56 (−0.83 to −0.29)	< .001
VAS-PI overall pain, mean (SE)	−0.65 (0.20)	−1.67 (0.15)	−0.55 (−0.82 to −0.27)	< .001
$HDRS_{17}$ response rate (LOCF), %[b]	32	59		< .001[c]
$HDRS_{17}$ remission rate (LOCF), %[d]	22	38		.008[c]
MADRS response rate (LOCF), %[e]	33	61		< .001[c]
CGI-I response rate (LOCF), %[f]	41	68		< .001[c]

[a]Reported as total score, week 8.
[b]$HDRS_{17}$ response: ≥ 50% reduction in $HDRS_{17}$ total score.
[c]Logistic regression *P* value.
[d]$HDRS_{17}$ remission: $HDRS_{17}$ total score ≤ 7.
[e]MADRS response: ≥ 50% reduction in MADRS total score.
[f]CGI-I response: CGI-I scores of 1 or 2.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, EQ-5D = 5 Dimension Health State EuroQol, HARS = Hamilton Anxiety Rating Scale, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, mITT = modified intent-to-treat, MMRM = mixed-model repeated-measures, MRS = Menopause Rating Scale, QIDS-SR = Quick Inventory of Depressive Symptomatology–Self-Report, SDS = Sheehan Disability Scale, VAS-PI = Visual Analog Scale–Pain Intensity.

protein albumin (40 desvenlafaxine, 7 placebo), acetone/ketones (17 desvenlafaxine, 5 placebo), and hemoglobin (23 desvenlafaxine, 6 placebo). Eleven desvenlafaxine-treated patients had clinically important laboratory findings during the double-blind period: 8 patients, increased urine protein; 1 patient, elevated liver function test; 1 patient, increased fasting glucose; and 1 patient, decreased hematocrit and hemoglobin.

Statistically significant mean changes from baseline to week 8 were observed in desvenlafaxine-treated patients compared with placebo for alkaline phosphatase (+5.3 mU/mL; placebo, −1.0 mU/mL; $P < .001$), total bilirubin (−1.34 μmol/L; placebo, −0.5 μmol/L; $P = .007$), γ-glutamyl transpeptidase (+8.1 mU/mL; placebo, +1.9 mU/mL; $P = .013$), total cholesterol (+0.099 mmol/L; placebo, −0.243 mmol/L; $P = .006$), and low-density lipoprotein cholesterol (+0.068 mmol/L; placebo, −0.196 mmol/L; $P = .014$). There was a statistically significant increase from baseline in alanine aminotransferase/serum glutamic pyruvic transaminase (+1.8 mU/mL; $P < .05$) at week 8; the change was not statistically significant compared with placebo (−0.1 mU/mL). The baseline used for comparison was the last value at either the screening visit or the baseline visit.

Vital Signs

A total of 97/377 (26%) patients in the safety population had hypertension at baseline. Fifteen (15/248 [6%]) desvenlafaxine-treated patients (5/125 [4%] placebo) had treatment-emergent changes in vital sign results of potential clinical importance. Of those, 4 desvenlafaxine-treated patients (0 placebo) had potentially clinically significant increases in supine diastolic blood pressure (≥ 15 mm Hg and value ≥ 105 mm Hg), and 7 desvenlafaxine-treated patients (2 placebo) had a decrease in weight of 7% of body weight or more. Clinically important vital sign results were reported in 5 desvenlafaxine-treated patients: 2 patients had clinically important increased diastolic blood pressure, and 1 patient each had increased systolic blood pressure, increased systolic and diastolic blood pressure, and decreased weight. At week 8, desvenlafaxine-treated patients had statistically significant increases from baseline compared with placebo in pulse rate (+2.64 bpm; placebo, −0.30 bpm; $P = .013$) and supine diastolic blood pressure (+1.77 mm Hg; placebo, −0.70 mm Hg; $P = .012$). Desvenlafaxine treatment was associated with a small but statistically significant mean decrease in weight from baseline (−0.76 kg) compared with placebo (−0.07 kg; $P = .014$) at week 8.

DISCUSSION

This study is the first randomized, double-blind, placebo-controlled trial to prospectively assess the efficacy of an antidepressant in the perimenopausal and postmenopausal population. In this trial, flexible-dose (100 to 200 mg/d) desvenlafaxine demonstrated short-term efficacy, safety, and tolerability in perimenopausal and postmenopausal women with MDD. Desvenlafaxine-treated patients achieved significantly greater improvement compared with placebo on the primary outcome measure, $HDRS_{17}$ total score, and all secondary efficacy end points, including CGI-I, MADRS, HARS, CGI-S, and response and remission rates. Statistical separation from placebo was observed as early as week 1 and was sustained through all 8 weeks of treatment for $HDRS_{17}$, CGI-I, MADRS, HARS, and CGI-S scores using ANCOVA on LOCF data. In a subgroup analysis, desvenlafaxine significantly improved $HDRS_{17}$ total scores compared with placebo for both perimenopausal and postmenopausal groups.

The safety and tolerability of desvenlafaxine in perimenopausal and postmenopausal women were consistent with the results of other desvenlafaxine trials.[20–23,36–38] The rate of discontinuations due to AEs was low for desvenlafaxine

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(7.4%; placebo, 3.2%), and most AEs were mild to moderate in severity. Incidence of treatment-emergent nausea, which was among the most common treatment-emergent AE in most,[20–22,36–38] but not all,[23] previous desvenlafaxine trials, was low compared with placebo in this study (desvenlafaxine 16.8%; placebo, 12.0%). Desvenlafaxine treatment was associated with a small but significant mean increase in diastolic blood pressure (< 2 mm Hg; $P < .05$), consistent with previously published studies of desvenlafaxine at similar doses,[20,37,39] and treatment-emergent hypertension was reported in 17/256 (7%) patients. In an integrated analysis of safety data from 9 double-blind, placebo-controlled trials of desvenlafaxine for MDD, mean increases in diastolic blood pressure were dose-related, with no significant difference compared with placebo for the FDA-recommended desvenlafaxine dose of 50 mg/d.[39] Desvenlafaxine treatment was not associated with weight gain in perimenopausal and postmenopausal women in this study. No new safety findings were observed in this patient population. In previous MDD trials, desvenlafaxine doses higher than 50 mg/d were associated with an increase in discontinuations due to AEs, with no increase in efficacy.[24]

It is unclear if the results of this trial are specific to desvenlafaxine or will generalize to other SNRIs or to antidepressants of other drug classes. Results from several studies suggest that antidepressant response to some drugs may in fact vary with sex and age or menopausal status,[40–45] and 2 studies in natural practice clinical settings suggest that some SSRIs (citalopram, sertraline, paroxetine, or fluoxetine) may be less effective in postmenopausal women compared with premenopausal or perimenopausal women,[41] or in older women (≥ 50 years) compared with younger women (≤ 44) where age is a surrogate for menopausal status.[44] Results consistent with those findings were reported in a pooled analysis of 8 randomized, controlled MDD trials examining age and sex effects on antidepressant efficacy.[40] For patients treated with fluoxetine, paroxetine, or fluvoxamine, $HDRS_{17}$ remission rates were significantly lower for women 50 years or older (28%) compared with women younger than 50 years (36%) and compared with both older (35%) and younger (36%) men. Several studies have reported that the efficacy of antidepressant drugs (particularly SSRIs) was enhanced by the administration of estrogen in depressed perimenopausal or postmenopausal women,[46–49] suggesting that SSRI efficacy is affected by changing hormone levels related to menopause (although other studies found no effect of added estrogen[50,51]). In contrast, no age or sex effects were observed in patients treated with the SNRIs venlafaxine[40] or duloxetine.[19,52] Those results suggest that other SNRIs, at least, might effectively treat MDD in perimenopausal and postmenopausal women. However, additional randomized controlled trials of perimenopausal and postmenopausal women with MDD will be necessary to establish efficacy of other antidepressants or demonstrate the superiority of one drug or class over another in this population.

Vasomotor symptoms (VMS), including hot flushes and night sweats, contribute significantly to the risk of depression in the menopausal transition,[2,3] and treating VMS together with depressive symptoms may improve outcomes for many perimenopausal and postmenopausal women with MDD. Both SSRIs and SNRIs have demonstrated efficacy for alleviating VMS associated with menopause.[53–58] In randomized, placebo-controlled trials, desvenlafaxine 100 mg/d reduced the number and severity of hot flushes in postmenopausal women with moderate to severe VMS.[56–58] Changes in frequency of hot flushes were not measured in the current study, but desvenlafaxine-treated patients had significant improvement compared with placebo on the MRS scale (see Table 2), which includes a rating of hot flushes and sweating. Future studies designed to assess the contribution of a reduction in hot flushes to the improvement in depressive symptoms in this population should include climacteric and quality-of-life scales.

CONCLUSIONS

Short-term treatment with flexible-dose desvenlafaxine was associated with significant improvement on all primary and secondary end points in this large, placebo-controlled study of perimenopausal and postmenopausal women with MDD. Treatment with desvenlafaxine was generally safe and well tolerated in this patient population, with an AE profile consistent with other SNRIs.

Drug names: citalopram (Celexa and others), desvenlafaxine (Pristiq), duloxetine (Cymbalta), fluoxetine (Prozac, Sarafem, and others), fluvoxamine (Luvox and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), zaleplon (Sonata and others), zolpidem (Ambien, Zolpimist, and others).

Author affiliations: Department of Psychiatry and Institute for Women's Health, Virginia Commonwealth University, Richmond (Dr Kornstein); and Pfizer Inc, formerly Wyeth Research, Collegeville, Pennsylvania (Ms Jiang, Drs Reddy and Guico-Pabia, and Mr Musgnung).

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