A Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Desvenlafaxine Succinate in the Treatment of Major Depressive Disorder

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Objective: This study evaluated the efficacy and safety of desvenlafaxine succinate extended-release in major depressive disorder (MDD).

Method: Adult outpatients with DSM-IV–defined MDD were randomly assigned to desvenlafaxine 100 mg/day (N = 114), 200 mg/day (N = 116), or 400 mg/day (N = 113) or placebo (N = 118) for 8 weeks. Efficacy variables included change from baseline in the 17-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$, the primary efficacy measure), Clinical Global Impressions-Improvement scale (CGI-I), Montgomery-Asberg Depression Rating Scale, Clinical Global Impressions-Severity of Illness scale (CGI-S), rates of response (≥ 50% decrease from baseline $HAM\text{-}D_{17}$ score) and remission ($HAM\text{-}D_{17}$ score ≤ 7), and Visual Analog Scale–Pain Intensity overall score. The study was conducted from November 2003 to November 2004.

Results: At the final on-therapy evaluation, the mean $HAM\text{-}D_{17}$ scores for desvenlafaxine 100 mg/day (12.75) and 400 mg/day (12.50) were significantly lower than for placebo (15.31; p = .0038 and p = .0023, respectively); for desvenlafaxine 200 mg/day, the mean score was 13.31 (p = .0764). CGI-I and Montgomery-Asberg Depression Rating Scale results were significant for all groups; CGI-S results were significant with 100 mg/day and 400 mg/day. Response rates were significantly greater for desvenlafaxine 100 mg/day (51%) and 400 mg/day (48%) versus placebo (35%; p = .017 and p = .046, respectively); the response rate for desvenlafaxine 200 mg/day was 45% (p = .142). Remission rates were significantly greater for desvenlafaxine 400 mg/day (32%) versus placebo (19%; p = .035); remission rates were 30% for desvenlafaxine 100 mg/day (p = .093) and 28% for desvenlafaxine 200 mg/day (p = .126). Visual Analog Scale–Pain Intensity results were significant for desvenlafaxine 100 mg/day versus placebo (p = .002), but not for the higher doses. The most commonly reported adverse events were nausea, insomnia, somnolence, dry mouth, dizziness, sweating, nervousness, anorexia, constipation, asthenia, and abnormal ejaculation/orgasm.

Conclusions: Desvenlafaxine is effective and well tolerated in the short-term treatment of MDD.

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The disease burden associated with major depressive disorder (MDD) is substantial and increasing.[1] Recent data from the National Comorbidity Survey Replication (NCS-R) estimate the lifetime prevalence of MDD at 16.6%[2] and the 1-year prevalence at 6.7%.[3] Additional data from the NCS-R revealed that just over half (52%) of patients with MDD had sought mental health care treatment within the previous year to relieve their symptoms.[4] A greater proportion of patients (32.5%) sought treatment in a primary care setting than in a psychiatric setting (20.6%). Despite the number of antidepressants available, there is a variable degree of response to individual agents, and the majority of patients treated in clinical trials do not achieve remission.[5] Thus, there remains a need for new, effective antidepressant treatment options.

Desvenlafaxine, or *O*-desmethylvenlafaxine, is the major active metabolite of the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine.[6,7] Like venlafaxine, desvenlafaxine selectively inhibits neuronal uptake of serotonin and norepinephrine and has little affinity for muscarinic, cholinergic, histamine H_1, and α_1-adrenergic receptors.[8] Desvenlafaxine has been shown to be active in preclinical in vitro and in vivo models used to predict antidepressant efficacy.[9] Desvenlafaxine is well absorbed following oral administration of desvenlafaxine succinate,

with a mean terminal-phase elimination half-life of approximately 9 to 11 hours.[10] The pharmacokinetic profile of desvenlafaxine provides consistent intra- and interindividual exposure.[10] Elimination of desvenlafaxine is primarily by phase II metabolism to form a glucuronide conjugate metabolite and by renal excretion of unchanged desvenlafaxine.[10] Desvenlafaxine is not metabolized by the cytochrome P450 pathway, and in vitro data suggest that desvenlafaxine is associated with minimal inhibition of cytochrome P450 enzymes.[11] In addition, desvenlafaxine has lower protein binding than some other antidepressants. Therefore, desvenlafaxine is expected to have a low risk of drug-drug interactions, an important potential benefit since patients with MDD have high rates of comorbid medical illness and treatment.[12]

In this article, we report the results of a phase III trial that compared the antidepressant efficacy, safety, and tolerability of 3 fixed doses of desvenlafaxine succinate extended-release (hereafter, "desvenlafaxine") and placebo. Because antidepressants that affect both serotonergic and noradrenergic neurotransmission have been shown to relieve painful symptoms in depression as well as in nondepressive chronic pain conditions,[13–15] we additionally examined the impact of desvenlafaxine treatment on pain symptomatology in subjects with major depression.

METHOD

The study was conducted at 25 centers in the United States. The study was reviewed by both central and local institutional review boards, depending on the study site, before recruitment of subjects started. Protocol amendments were approved while the study was in progress and before the data were unblinded. The study was conducted in conformity with the U.S. Food and Drug Administration Code of Federal Regulations (21CFR, Part 50) and the Declaration of Helsinki and its amendments, and was consistent with Good Clinical Practice and the applicable regulatory requirements. Participants provided written informed consent before enrollment, and the study was conducted from November 2003 to November 2004.

Patients

Entry criteria were designed to include subjects with at least moderate severity MDD and to exclude subjects with comorbidity that could decrease the specificity of the antidepressant efficacy findings. Criteria were also designed to exclude subjects for whom participation in protocol treatment would pose excess risk compared to potential benefit.

Male and female outpatients aged 18 to 75 years were eligible for this study. Eligible participants had a primary diagnosis of MDD—single or recurrent episodes without psychotic features—according to the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV), and they had depressive symptoms for at least 30 days before the screening visit. The following were required at screening and baseline: 17-item Hamilton Rating Scale for Depression[16] ($HAM\text{-}D_{17}$) total score ≥ 20; HAM-D item 1 (depressed mood) score ≥ 2, and Clinical Global Impressions-Severity of Illness scale (CGI-S)[17] score ≥ 4. All sexually active female participants were on medically acceptable contraception: oral contraceptives, injectable or implantable methods, intrauterine devices, or barrier contraception.

Reasons for excluding patients from the study were previous treatment with desvenlafaxine, treatment with venlafaxine or venlafaxine extended-release (ER) within 90 days, or known hypersensitivity to venlafaxine or venlafaxine ER; potential suicide risk; women who were pregnant, breast-feeding, or planning to become pregnant during the study; current (within 12 months from baseline) psychoactive substance abuse or dependence (including alcohol), manic episodes, bipolar or psychotic disorder, posttraumatic stress disorder, obsessive-compulsive disorder, generalized anxiety disorder, panic disorder, or social anxiety disorder that the investigator considered primary based on a modified Mini-International Neuropsychiatric Interview assessment[18]; clinically important personality disorder; Covi Anxiety Scale[19] total score greater than the Raskin Depression Scale[19] total score at baseline; Covi Anxiety Scale score > 3 on any single item or a total score > 9 at baseline; a mental disorder due to a general medical condition or neurologic disorder; history of a seizure disorder; clinically important medical disease; gastrointestinal disease or surgery known to interfere with the absorption or excretion of drugs; neoplastic disorder (except basal or squamous cell carcinoma of the skin) within 2 years; presence of raised intraocular pressure or history of narrow angle glaucoma; myocardial infarction within 180 days before screening; clinically important abnormalities on screening physical examinations, electrocardiogram (ECG), or laboratory analyses; or use of prohibited treatments.

Study Design

This multicenter, phase III trial employed a randomized, double-blind, placebo-controlled, parallel-group design. Following an initial screening of 6 to 14 days, eligible patients received up to 8 weeks of treatment, followed by a tapering period of 2 additional weeks. Study visits occurred weekly for the duration of the study including the tapering period. Taper was recommended, but could be omitted, extended, or shortened at the discretion of the investigator. A follow-up visit was completed approximately 7 days after the last dose of test article. All patients who completed the study, regardless of treatment group, had the option of enrolling in a long-term,

open-label extension study; those who enrolled did not have their doses tapered.

Treatment

Patients were randomly assigned at baseline to 1 of 3 fixed doses (100, 200, or 400 mg/day) of desvenlafaxine or placebo. On study days 1 to 3, patients in each desvenlafaxine group received treatment with 100 mg of desvenlafaxine. The dose was increased on day 4 to 200 mg for patients in the 200-mg and 400-mg groups, and on day 8 to 400 mg for patients in the 400-mg group. The assigned maintenance dose of desvenlafaxine was maintained until day 56 or early withdrawal. During the taper period, doses were reduced to the next lowest dose at weekly intervals; patients who had received 100 mg did not have their doses tapered.

Efficacy and Safety Assessments

The primary efficacy assessment, the HAM-D_{17}, was administered at each visit. The secondary efficacy assessments were the Clinical Global Impressions-Improvement scale (CGI-I), administered at all post-baseline visits; the CGI-S, administered at each visit; and the Montgomery-Asberg Depression Rating Scale (MADRS),[20] Covi Anxiety Scale, Sheehan Disability Scale,[21] World Health Organization 5-item Well Being Index (WHO-5),[22] and Visual Analog Scale–Pain Intensity,[23] which were administered at baseline and on study days 14, 28, and 56. For the HAM-D, MADRS, and CGI scales, only certified raters (i.e., those who met education and experience criteria and who demonstrated proficiency following trial-specific training) evaluated patients.

Safety evaluations included assessment of vital signs and weight, recording of adverse events and concomitant treatments, and review of treatment compliance; these evaluations were performed at each visit. A physical examination and laboratory determinations were performed at screening and day 56; a 12-lead ECG was performed at screening, baseline, and day 56. The Discontinuation-Emergent Signs and Symptoms (DESS)[24] checklist was administered at baseline and day 56 (for patients who did not enter into the long-term open-label extension study).

Statistical Analysis

Sample size estimates were based on the HAM-D_{17} total score, which was the primary efficacy variable. Based on experience with venlafaxine ER, a standard deviation of 8 units was selected for use in the calculations. A sample size of 111 patients per group was determined to be sufficient to declare a statistically significant mean difference between desvenlafaxine treatment and placebo treatment of 3.5 units at the 5% level with a power of approximately 90%. To compensate for patients who failed to qualify for the intent-to-treat (ITT) analysis (5% of all patients), 120 patients were randomly assigned to each group.

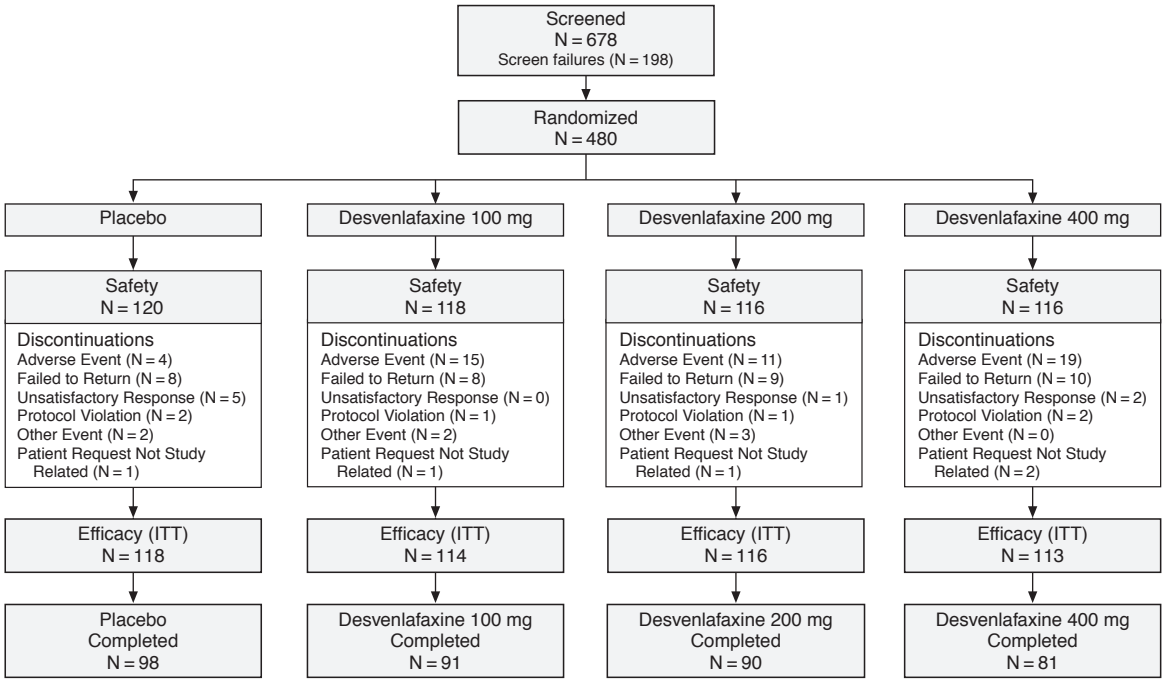
One-way analysis of variance (ANOVA), χ^2 tests, or Fisher exact tests were used to compare groups on applicable demographic and pretreatment clinical variables. Efficacy analyses were performed on the ITT study group: patients who took at least 1 dose of double-blind study medication and had at least 1 primary efficacy evaluation after the first dose of double-blind test medication. Analyses were performed at each evaluation period, and the last-observation-carried-forward (LOCF) method was used to account for the results of patients who discontinued early.

The primary endpoint for all efficacy variables was the final on-therapy evaluation. The primary efficacy variable was change from baseline on the HAM-D_{17} total score, and the key secondary efficacy variable was the CGI-I score. Other secondary efficacy variables included scores on the MADRS, CGI-S, and Visual Analog Scale–Pain Intensity and rates of response (defined as a decrease of $\geq 50\%$ in the total HAM-D_{17} score from baseline) and remission (defined as HAM-D_{17} score ≤ 7). Additional definitions of response (based on MADRS or CGI-I score) and scores on other assessment scales were analyzed as ancillary efficacy variables.

Changes from baseline on all efficacy measures, except CGI-I scores, were evaluated using analysis of covariance with treatment and site as factors and baseline score as covariate. A sequential testing strategy, in which HAM-D_{17} was tested first followed by the CGI-I, was applied to the CGI-I. Mean CGI-I scores were assessed using ANOVA with treatment and site as the factors. Dunnett's multiple comparisons procedure was used to address multiplicity associated with testing the 3 desvenlafaxine treatment groups against placebo for the primary and secondary efficacy variables. Response and remission rates were analyzed with a categorical data analysis method. For the response analysis, HAM-D_{17} and MADRS scores were analyzed with a logistic regression model with treatment, site, and baseline score as factors; CGI-I response rates were analyzed with a logistic regression model with treatment and site as factors. Statistical significance was declared at the .05 level.

Two additional prespecified efficacy analyses were also performed for the primary efficacy variable: the mixed effect model and ETRANK.[25] The mixed effect model analyzes all data, taking into account the correlation between observations. For the mixed effect model, an autoregression of the first order [AR(1)] covariance structure was used to model the within-subject correlation, and change from baseline on the HAM-D_{17} was analyzed as the response, with treatment, week, baseline scores, and a term for interaction between treatment and week of therapy as explanatory variables. Site was modeled as

Figure 1. Analysis Population



Abbreviation: ITT = intent to treat.

a random effect. ETRANK uses a randomization technique to analyze incomplete repeated-measures data when the pattern of withdrawal is treatment related. The method uses the observed full data set (without imputing or estimating the missing data) and creates efficient scoring systems that are either categorical time-related ranks or the observed levels. These were used to generate an empirical significance level with timepoint descriptive statistics.

Safety analyses included all randomized patients who took at least 1 dose of double-blind test medication. Adverse events, treatment-emergent adverse events, laboratory evaluations, vital signs, weight, and 12-lead ECG evaluation data were summarized. The DESS analysis was used to evaluate a summation of symptoms at first appearance or upon exacerbation during the tapering period. This analysis was performed at each weekly tapering visit and at the follow-up visit. The DESS scores were evaluated on the basis of dose and test medication. Each subject's DESS scores were grouped with those of other patients taking the same dose of the test medication on day 56. Statistical between-group differences for the DESS totals were determined by t tests.

RESULTS

Patients

A total of 480 patients were randomly assigned to receive study medication. Of these, 470 (98%) were evaluated for safety (10 patients had no data after baseline), and 461 (96%) were included in the ITT population and evaluated for efficacy; 19 patients were excluded from the ITT population because they did not take test medication (N = 9) or did not have a primary efficacy evaluation (HAM-D_{17}) on therapy (N = 10) (Figure 1). Overall, 110 patients (23%) withdrew from the study during the double-blind period: 22 (18%) from the placebo group, 27 (23%) from the desvenlafaxine 100-mg group, 26 (22%) from the desvenlafaxine 200-mg group, and 35 (30%) from the desvenlafaxine 400-mg group. Adverse events were the most common reasons for withdrawal in the desvenlafaxine treatment groups, and failure to return (7%) and unsatisfactory response (4%) were the most common reasons for discontinuations in the placebo group. There were no significant differences among the treatment groups on pretreatment demographic and clinical characteristics (Table 1).

Efficacy Evaluation

Primary efficacy measure. At 3 weeks, the mean HAM-D_{17} score for desvenlafaxine 100 mg (14.8, 95% CI = 13.8 to 15.9) was significantly lower than for placebo (16.8, 95% CI = 15.8 to 17.8) and remained significantly lower through the final on-therapy visit (Figure 2). At 6 weeks, the mean HAM-D_{17} score for desvenlafaxine 400 mg (12.8, 95% CI, 11.5–14.0) was significantly lower than for placebo (15.5, 95% CI = 14.3 to 16.7) and

Table 1. Demographic and Baseline Characteristics: Intent-to-Treat Population

Characteristic	Placebo (N =118)	Desvenlafaxine 100 mg (N = 114)	Desvenlafaxine 200 mg (N = 116)	Desvenlafaxine 400 mg (N = 113)
Age, mean (SD), y	40.0 (12.8)	40.4 (12.1)	40.7 (12.8)	39.0 (12.6)
Sex, N (%)				
Female	80 (68)	74 (65)	71 (61)	61 (54)
Male	38 (32)	40 (35)	45 (39)	52 (46)
Ethnic origin, N (%)				
White	86 (73)	88 (77)	75 (65)	84 (74)
Black	11 (9)	11 (10)	16 (14)	10 (9)
Hispanic	18 (15)	10 (9)	19 (16)	14 (12)
Asian	2 (2)	3 (3)	2 (2)	3 (3)
Native American	0 (0)	0 (0)	2 (2)	0 (0)
Arabic	1 (< 1)	1 (< 1)	0 (0)	0 (0)
Other	0 (0)	1 (< 1)	2 (2)	2 (2)
Weight, mean (SD), kg	81.7 (20.3)	85.1 (20.2)	83.0 (22.7)	83.7 (21.1)
Duration of current episode, mean (SD), mo	24.0 (51.2)	27.8 (58.3)	26.1 (55.1)	20.8 (29.3)
Baseline HAM-D_{17} total score, mean (SD)	23.1 (2.5)	23.2 (2.5)	22.9 (2.5)	23.0 (2.2)
Baseline CGI-S score, mean (SD)	4.4 (0.6)	4.3 (0.5)	4.3 (0.5)	4.3 (0.5)
Baseline Visual Analog Scale–Pain Intensity score, mean				
Overall	27.9	28.1	22.0	25.7
Stomach pain	17.9	18.0	13.4	17.7
Back pain	27.1	30.9	24.0	24.7
Chest pain	10.1	10.6	9.6	8.7
Arm, leg, and joint pain	27.2	26.7	25.3	24.7

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D_{17} = 17-item Hamilton Rating Scale for Depression.

remained significantly lower through the final on-therapy visit. At the final on-therapy evaluation, the adjusted mean change from baseline in the HAM-D_{17} total score was significantly greater in the desvenlafaxine 100-mg (–10.60; p = .0038) and desvenlafaxine 400-mg (–10.74; p = .0023) groups than in the placebo group (–7.65); the mean change for the desvenlafaxine 200-mg treatment group (–9.63) was not significantly different from that of the placebo group (p = .0764). Significantly greater reductions from baseline on the HAM-D_{17} total score compared with placebo were observed for the desvenlafaxine 100-mg treatment group at weeks 3 (p = .0226), 4 (p = .0497), 6 (p = .0028), and 8 (p = .0016); for the desvenlafaxine 200-mg treatment group at week 6 (p = .0500); and for the desvenlafaxine 400-mg treatment group at weeks 6 (p = .0060) and 8 (p = .0008).

Key secondary efficacy measure. At the final on-therapy evaluation, mean CGI-I scores were 2.3 for the desvenlafaxine 100-mg (p = .0008), 2.5 for the desvenlafaxine 200-mg (p = .0462), and 2.4 for the desvenlafaxine 400-mg (p = .0129) groups and 2.8 for the placebo group. In the desvenlafaxine 100-mg and 400-mg treatment groups, mean CGI-I scores were significantly lower compared with those of the placebo group at weeks 3, 4, 6, and 8.

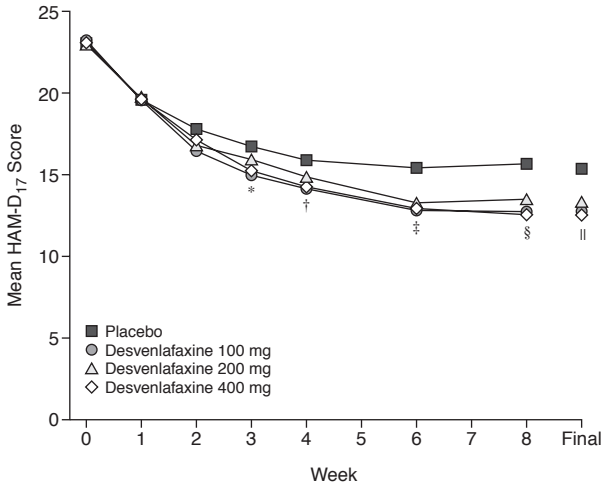
Other secondary efficacy variables. Mean changes from baseline to the final on-therapy evaluation for secondary efficacy variables and quality of life measures are summarized in Table 2.

Rates of HAM-D_{17} response and remission at the final on-therapy evaluation and findings from categorical data analyses are presented in Figure 3. Logistic regression analysis of HAM-D_{17} response and remission rates produced similar results. At the final on-therapy evaluation, the adjusted odds ratios for response, relative to placebo, were 2.158 (95% CI = 1.25 to 3.73) in the desvenlafaxine 100-mg (p = .0060), 1.603 (95% CI = 0.93 to 2.76) in the desvenlafaxine 200-mg (p = .089), and 1.917 (95% CI = 1.11 to 3.32) in the desvenlafaxine 400-mg (p = .020) groups. For remission, the adjusted odds ratios relative to placebo were 1.868 (95% CI = 0.99 to 3.52) in the desvenlafaxine 100-mg (p = .053), 1.734 (95% CI = 0.92 to 3.26) in the desvenlafaxine 200-mg (p = .088), and 2.202 (95% CI = 1.17 to 4.14) in the desvenlafaxine 400-mg (p = .014) groups.

Improvement in pain over time is presented as changes from baseline in Visual Analog Scale–Pain Intensity scores in Table 2. As shown, those receiving desvenlafaxine 100 mg showed significantly greater improvement in overall pain compared with placebo (–13.9 vs. –5.9; p = .002). The highly significant improvement in arm, leg, and joint pain subscale may account for a portion of the magnitude of improvement in overall pain score for this treatment group.

Secondary analysis of efficacy. The results of the additional prespecified analyses of HAM-D_{17} total scores for the 100-mg and 400-mg doses were similar to the final on-therapy evaluation. Doses of desvenlafaxine 100 mg and 400 mg were significantly different from placebo as measured by the primary variable for the mixed effect model (p < .001 for both doses) and ETRANK analyses (p < .001 for both doses). The results for desvenlafaxine

Figure 2. HAM-D_{17} Mean Scores by Week and at Final On-Therapy Evaluation



*p = .0226 desvenlafaxine 100 mg vs. placebo.
†p = .0497 desvenlafaxine 100 mg vs. placebo.
‡p = .0028 desvenlafaxine 100 mg vs. placebo, p = .0500 desvenlafaxine 200 mg vs. placebo, p = .0060 desvenlafaxine 400 mg vs. placebo.
§p = .0016 desvenlafaxine 100 mg vs. placebo, p = .0008 desvenlafaxine 400 mg vs. placebo.
‖p = .0038 desvenlafaxine 100 mg vs. placebo, p = .0023 desvenlafaxine 400 mg vs. placebo.
Abbreviation: HAM-D_{17} = 17-item Hamilton Rating Scale for Depression.

200 mg were also significantly different from placebo for the mixed effect model and ETRANK analyses (p = .004 and p < .001, respectively).

Safety Evaluation

Adverse events. Treatment-emergent adverse events were reported by 106 patients (90%) in the desvenlafaxine 100-mg group, 108 (93%) in the desvenlafaxine 200-mg group, 101 (87%) in the desvenlafaxine 400-mg group, and 101 (84%) in the placebo group. The treatment-emergent adverse events with an incidence in any of the desvenlafaxine treatment groups of at least 5% and twice the rate of placebo are listed in Table 3. Of these, the most common were nausea, insomnia, somnolence, dry mouth, dizziness, sweating, nervousness, anorexia, constipation, asthenia, and abnormal ejaculation/orgasm. Nausea occurred at the highest frequency (35%, 31%, and 41% in desvenlafaxine 100-mg, 200-mg, and 400-mg groups, respectively, compared with 8% in the placebo group). Among patients who discontinued due to adverse events, nausea was the most common adverse event cited as the reason for discontinuation among desvenlafaxine-treated patients: 7 (6%) in the desvenlafaxine 100-mg, 3 (3%) in the desvenlafaxine 200-mg, and 6 (5%) in the desvenlafaxine 400-mg groups, compared with 2 (2%) in the placebo group. Nausea was reported most frequently during the first week of treatment (incidence 22%–31% in desvenlafaxine treatment groups) and became less frequent over time. Likewise, the majority of discontinuations due to nausea occurred during the first 2 weeks of treatment; 1 patient discontinued due to nausea during week 3 and 1 during week 4.

Four patients had serious adverse events, including 1 death. One patient, who was assigned to treatment with desvenlafaxine 100 mg, died from a completed suicide on study day 5. It is not known whether this patient had taken any of the medication that was dispensed at the baseline visit. Three additional participants were reported to have serious adverse events (1 patient each with dystonia secondary to promethazine use [desvenlafaxine 400 mg], suicide attempt [desvenlafaxine 400 mg], and chest pain [placebo]) that were assessed by the investigators as probably not related or definitely not related to the study drug. One of these participants discontinued from the study because of a serious adverse event (suicide attempt).

The DESS checklist analysis was used to evaluate symptoms that occurred during the taper period. Because most patients entered the open-label extension trial and did not have a taper period, too few patients were included in the DESS checklist analysis to provide meaningful interpretations of the results. Overall, the DESS checklist was administered to 87 patients during the taper period: 19 patients in the placebo group, 20 patients in the desvenlafaxine 100-mg group, 28 patients in the desvenlafaxine 200-mg group, and 20 patients in the desvenlafaxine 400-mg group. In the desvenlafaxine treatment groups, the most commonly reported adverse events (incidence in ≥ 5% and at least twice that of placebo) emerging during the taper period were nausea (6%), abnormal dreams (5%), and infection (5%). The most frequently occurring taper-emergent adverse events (reported by at least 5% of subjects) in the placebo group were headache (9%) and anxiety (9%).

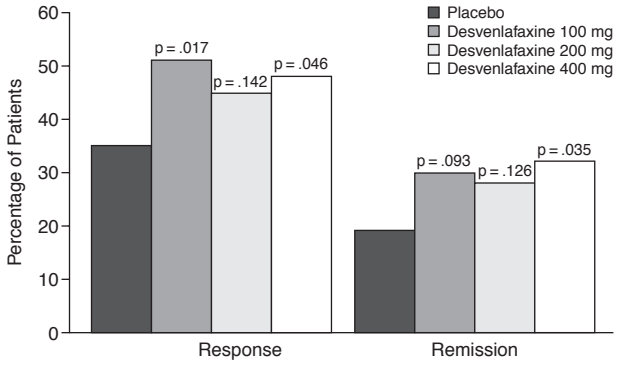
Laboratory evaluations. Statistically significant changes in mean values from baseline to the final on-therapy evaluation were observed in the desvenlafaxine treatment groups for the following laboratory evaluations: alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (GGT), bilirubin, alkaline phosphatase, fasting total cholesterol, and fasting triglycerides. In addition, there were significant differences between at least 1 desvenlafaxine treatment group and the placebo group in the adjusted mean changes from baseline at the final on-therapy evaluation for ALT, AST, GGT, bilirubin, alkaline phosphatase, fasting total cholesterol, and fasting low-density lipoprotein (LDL) cholesterol. Four desvenlafaxine-treated patients were determined to have clinically important laboratory abnormalities: 1 patient in the desvenlafaxine 100-mg group had increased ALT (≥ 3 × upper limit of normal

Table 2. Secondary Efficacy Endpoints, LOCF Analysis: Final On-Therapy Evaluation

Efficacy Variable	N	Change From Baseline	Difference in Adjusted Means (95% CI)	p Value vs Placebo
MADRS total score				
Placebo	118	–9.9		
Desvenlafaxine 100 mg	114	–13.6	3.9 (1.3 to 6.4)	.004
Desvenlafaxine 200 mg	116	–13.5	3.7 (1.3 to 6.2)	.005
Desvenlafaxine 400 mg	113	–15.2	5.7 (3.1 to 8.3)	< .001
CGI-S score				
Placebo	118	–1.0		
Desvenlafaxine 100 mg	114	–1.5	0.5 (0.2 to 0.8)	.002
Desvenlafaxine 200 mg	116	–1.3	0.3 (0.0 to 0.6)	.056
Desvenlafaxine 400 mg	113	–1.5	0.6 (0.2 to 0.9)	< .001
VAS-PI				
Overall pain				
Placebo	115	–5.9		
Desvenlafaxine 100 mg	111	–13.9	8.0 (2.9 to 13.1)	.002
Desvenlafaxine 200 mg	112	–5.4	2.6 (–3.0 to 8.3)	.357
Desvenlafaxine 400 mg	110	–10.1	5.2 (–0.4 to 10.8)	.069
Stomach pain				
Placebo	115	–5.2		
Desvenlafaxine 100 mg	111	–8.6	3.4 (–1.7 to 8.5)	.194
Desvenlafaxine 200 mg	111	–6.0	3.9 (–1.0 to 8.7)	.122
Desvenlafaxine 400 mg	110	–6.8	1.5 (–4.2 to 7.1)	.611
Back pain				
Placebo	115	–7.6		
Desvenlafaxine 100 mg	111	–14.1	4.6 (–0.9 to 10.1)	.102
Desvenlafaxine 200 mg	112	–10.3	4.4 (–1.1 to 9.9)	.120
Desvenlafaxine 400 mg	110	–10.2	3.8 (–1.8 to 9.4)	.188
Chest pain				
Placebo	115	–2.4		
Desvenlafaxine 100 mg	111	–4.4	1.3 (–2.6 to 5.2)	.524
Desvenlafaxine 200 mg	112	–2.4	0.6 (–3.3 to 4.5)	.763
Desvenlafaxine 400 mg	110	–3.3	2.0 (–1.6 to 5.7)	.278
Arm, leg, joint pain				
Placebo	115	–5.5		
Desvenlafaxine 100 mg	111	–14.3	9.0 (4.0 to 14.0)	< .001
Desvenlafaxine 200 mg	112	–8.3	4.1 (–1.5 to 9.8)	.155
Desvenlafaxine 400 mg	110	–11.4	6.7 (1.2 to 12.3)	.019
SDS				
Total				
Placebo	115	–5.6		
Desvenlafaxine 100 mg	111	–8.6	3.3 (1.2 to 5.4)	.003
Desvenlafaxine 200 mg	112	–7.5	2.1 (0.1 to 4.2)	.042
Desvenlafaxine 400 mg	110	–8.7	3.2 (1.2 to 5.2)	.002
Work				
Placebo	108	–1.7		
Desvenlafaxine 100 mg	111	–2.3	3.4 (2.9 to 3.9)	.018
Desvenlafaxine 200 mg	112	–1.7	3.9 (3.4 to 4.4)	.330
Desvenlafaxine 400 mg	108	–1.7	3.9 (3.4 to 4.4)	.266
Social life/leisure activities				
Placebo	115	–1.7		
Desvenlafaxine 100 mg	111	–2.8	1.1 (0.3 to 1.8)	.004
Desvenlafaxine 200 mg	112	–2.6	0.8 (0.1 to 1.5)	.023
Desvenlafaxine 400 mg	110	–3.2	1.4 (0.7 to 2.1)	< .001
Family life/home responsibilities				
Placebo	115	–1.8		
Desvenlafaxine 100 mg	111	–2.7	1.1 (0.5 to 1,8)	.001
Desvenlafaxine 200 mg	112	–2.4	0.8 (0.1 to 1.4)	.029
Desvenlafaxine 400 mg	110	–2.8	1.1 (0.5 to 1.8)	.001
Work/social disability				
Placebo	115	–0.6		
Desvenlafaxine 100 mg	110	–0.9	0.3 (0.1 to 0.6)	.019
Desvenlafaxine 200 mg	111	–0.8	0.2 (0.0 to 0.5)	.102
Desvenlafaxine 400 mg	109	–1.0	0.4 (0.1 to 0.7)	.004
WHO-5				
Placebo	115	4.4		
Desvenlafaxine 100 mg	110	6.7	–2.2 (–3.7 to –0.7)	.004
Desvenlafaxine 200 mg	112	6.2	–1.9 (–3.3 to –0.5)	.008
Desvenlafaxine 400 mg	110	6.8	–2.6 (–4.1 to –1.2)	< .001

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, SDS = Sheehan Disability Scale, VAS-PI = Visual Analog Scale–Pain Intensity, WHO-5 = World Health Organization 5-item Well Being Index.

Figure 3. HAM-D_{17} Response[a] and Remission[b] Rates at Final On-Therapy Evaluation



[a]≥ 50% reduction in HAM-D_{17} total score.
[b]HAM-D_{17} total score ≤ 7.
Abbreviation: HAM-D_{17} = 17-item Hamilton Rating Scale for Depression.

[ULN]), 1 in the desvenlafaxine 200-mg group had increased fasting glucose (≥ 11.10 mmol/L), 1 in the desvenlafaxine 400-mg group had increased total cholesterol (increase ≥ 1.29 mmol/L and value ≥ 6.75 mmol/L) and LDL cholesterol (increase ≥ 1.29 mmol/L and value ≥ 4.91 mmol/L), and 1 in the desvenlafaxine 400-mg group had increased ALT, AST (≥ 3 × ULN), GGT (determined by the medical monitor), and alkaline phosphatase (≥ 3 × ULN).

Vital signs and weight. Mean changes from baseline to the final on-therapy evaluation in vital signs and weight are summarized in Table 4. Mean increases in pulse rates in the desvenlafaxine 400-mg group were statistically significant compared with baseline and were significantly greater compared with the changes in the placebo group at all evaluations, and were significantly greater than those in the desvenlafaxine 100-mg group at weeks 2 through 8 and the final on-therapy observation.

Mean increases in supine systolic blood pressure (BP) in the desvenlafaxine 200-mg and 400-mg groups were statistically significant compared with baseline and compared with mean changes in the placebo group at all weeks and the final on-therapy evaluation. In the desvenlafaxine 100-mg group, significant differences compared with the placebo group were observed at weeks 1, 6, and 8 and the final on-therapy evaluation. No patients experienced sustained changes in supine systolic pressure that were considered of potential clinical importance.

Mean changes in supine diastolic BP in the desvenlafaxine 200-mg and 400-mg groups were statistically significant compared with baseline and compared with mean changes in the placebo group at all weeks and the final on-therapy evaluation. In the desvenlafaxine 100-mg group, significant differences compared with the placebo group were observed at weeks 4, 6, and 8. Four patients (4%) in the desvenlafaxine 400-mg group, 1 (< 1%) each in the placebo and desvenlafaxine 200-mg groups, and none in the desvenlafaxine 100-mg group had sustained, treatment-emergent increases in supine diastolic BP ≥ 10 mm Hg from baseline to an on-therapy value of ≥ 90 mm Hg for at least 3 visits. One patient in the placebo group, 1 in the desvenlafaxine 200-mg group, and 2 in the desvenlafaxine 400-mg group had increased diastolic BP (i.e., increase ≥ 15 mm Hg and value ≥ 105 mm Hg), and 1 patient in the desvenlafaxine 400-mg group had orthostatic hypotension (systolic decrease ≥ 30 mm Hg and diastolic decrease ≥ 15 mm Hg from supine to first standing).

Mean changes in weight in all desvenlafaxine treatment groups were statistically significant compared with baseline and with mean changes in the placebo group at all weeks and the final on-therapy evaluation. The mean decreases in weight in the desvenlafaxine 400-mg group were statistically significant compared with those observed in the desvenlafaxine 100-mg group at weeks 2 through 8 and the final on-therapy observation, and compared with those in the desvenlafaxine 200-mg group at weeks 2, 4, 6, and 8 and the final on-therapy observation. One patient in the desvenlafaxine 100-mg group had clinically important weight loss (i.e., ≥ 7%); anorexia was reported as an adverse event for this patient.

Electrocardiogram. A statistically significant (defined as $p < .05$) increase from baseline in mean heart rate was observed in the desvenlafaxine 400-mg treatment group at the final on-therapy evaluation (4.70 bpm); a significant decrease from baseline was observed in the placebo group (–2.70 bpm). There were statistically significant differences in heart rate between each of the desvenlafaxine treatment groups and the placebo group. Decreases in mean PR interval at the final on-therapy evaluation in the desvenlafaxine 200-mg (–3.16 ms) and 400-mg (–5.41 ms) treatment groups were statistically significant compared with baseline and placebo, and for the desvenlafaxine 400-mg group compared with the desvenlafaxine 100-mg group. A statistically significant decrease from baseline in the mean QRS interval was observed in the desvenlafaxine 400-mg treatment group at the final on-therapy evaluation (–1.54 ms); this decrease was significantly different from the mean increases observed in the desvenlafaxine 100-mg (0.75 ms), desvenlafaxine 200-mg (0.66 ms), and placebo (1.80 ms) groups.

A statistically significant decrease in the mean QT interval was observed in the desvenlafaxine 400-mg treatment group at the final on-therapy evaluation (–7.64 ms), which was significantly different from the mean increases observed in the other desvenlafaxine groups and in the placebo group. Corrected QT intervals (Bazett [QTcB] and Fridericia [QTcF] corrections and a correction based on the population correction factor [QTcN])

Table 3. Treatment-Emergent Adverse Events by Treatment Group[a]

Adverse Event	Placebo (N = 120)	Desvenlafaxine 100 mg (N = 118)	Desvenlafaxine 200 mg (N = 116)	Desvenlafaxine 400 mg (N = 116)
Nausea	10 (8)	41 (35)	36 (31)	47 (41)
Insomnia	10 (8)	26 (22)	21 (18)	35 (30)
Somnolence	10 (8)	24 (20)	25 (22)	30 (26)
Dry mouth	12 (10)	20 (17)	22 (19)	29 (25)
Sweating	4 (3)	12 (10)	19 (16)	24 (21)
Dizziness	7 (6)	20 (17)	18 (16)	22 (19)
Nervousness	5 (4)	6 (5)	10 (9)	17 (15)
Anorexia	3 (3)	14 (12)	14 (12)	16 (14)
Constipation	3 (3)	14 (12)	10 (9)	16 (14)
Abnormal ejaculation/orgasm	1 (< 1)	2 (2)	7 (6)	13 (11)
Asthenia	6 (5)	8 (7)	13 (11)	12 (10)
Impotence[b]	1 (3)	3 (7)	3 (7)	5 (9)
Anorgasmia	0 (0)	4 (3)	3 (3)	9 (8)
Tremor	1 (< 1)	5 (4)	11 (9)	9 (8)
Vomiting	4 (3)	6 (5)	8 (7)	8 (7)
Abnormal vision	2 (2)	6 (5)	7 (6)	8 (7)
Mydriasis	1 (< 1)	3 (3)	2 (2)	8 (7)
Abnormal dreams	4 (3)	7 (6)	7 (6)	8 (7)
Tachycardia	2 (2)	4 (3)	3 (3)	6 (5)
Vasodilatation	0 (0)	2 (2)	6 (5)	5 (4)
Taste perversion	2 (2)	1 (< 1)	1 (< 1)	6 (5)
Yawn	0 (0)	3 (3)	6 (5)	2 (2)

[a]Events reported by at least 5% of subjects at twice the rate of placebo in any treatment group during the double-blind period, excluding taper. Data reported as N (%) of subjects.
[b]Based on the number of men in each treatment group: placebo, N = 40; desvenlafaxine 100 mg, N = 42; desvenlafaxine 200 mg, N = 45; and desvenlafaxine 400 mg, N = 53.

Table 4. Vital Signs and Weight: Final On-Therapy Evaluation

Variable	N	Baseline Mean	Mean Change From Baseline	p Value vs Baseline	p Value vs Placebo[a]
Supine pulse rate, bpm					
Placebo	116	69.67	0.15	NS	
Desvenlafaxine 100 mg	109	68.89	–0.03	NS	NS
Desvenlafaxine 200 mg	112	69.47	1.06	NS	NS
Desvenlafaxine 400 mg	112	67.16	4.19	< .001	≤ .05[b]
Systolic BP, supine, mm Hg					
Placebo	116	118.36	0.23	NS	
Desvenlafaxine 100 mg	109	117.80	2.96	< .01	≤ .05
Desvenlafaxine 200 mg	112	117.22	3.62	< .001	≤ .05
Desvenlafaxine 400 mg	112	118.86	4.05	< .001	≤ .05
Diastolic BP, supine, mm Hg					
Placebo	116	75.68	0.44	NS	
Desvenlafaxine 100 mg	109	75.86	2.21	< .01	NS
Desvenlafaxine 200 mg	112	75.07	2.84	< .001	≤ .05
Desvenlafaxine 400 mg	112	75.55	3.41	< .001	≤ .05
Weight, kg					
Placebo	116	81.38	–0.07	NS	
Desvenlafaxine 100 mg	109	84.43	–0.85	< .001	≤ .05
Desvenlafaxine 200 mg	112	83.50	–0.99	< .001	≤ .05
Desvenlafaxine 400 mg	112	83.89	–1.82	< .001	≤ .05[c]

[a]Comparison based on adjusted mean changes from baseline using analysis of covariance with baseline as the covariate. Significant ($p \leq .05$) differences between groups are shown only if the overall comparison was significant.
[b]$p \leq .05$ vs. desvenlafaxine 100 mg.
[c]$p \leq .005$ vs. desvenlafaxine 100 mg and vs. desvenlafaxine 200 mg.
Abbreviation: BP = blood pressure, bpm = beats per minute.

were also evaluated. The mean QTcB showed a dose-dependent increase from baseline at the week 8 evaluation (4.64 ms, 6.66 ms, and 7.25 ms in the 100-mg, 200-mg, and 400-mg groups, respectively). These increases were significantly different from the mean change for the placebo group; significant differences from placebo were also observed at the final on-therapy evaluation for the desvenlafaxine 200-mg and 400-mg treatment groups. There were not dose-dependent increases from baseline in QTcF and QTcN; however, there were small but statistically significant differences from baseline in the desvenlafaxine 100-mg and 200-mg groups. No significant differences in QTcF intervals were observed between any of the active treatment groups and the placebo group. The

mean increase in QTcN in the desvenlafaxine 200-mg treatment group at week 8 (5.25 ms) was statistically significant compared with the increase in the placebo group (2.43 ms).

DISCUSSION

In this randomized, double-blind, 8-week trial in adult outpatients with MDD, treatment with desvenlafaxine in daily doses of 100 mg and 400 mg was associated with statistically significant improvement compared with placebo on the primary efficacy measure, HAM-D_{17} total score, the key secondary efficacy measure, CGI-I score, and other secondary efficacy measures. The desvenlafaxine 200-mg dose trended toward significance on the HAM-D_{17} at the final on-therapy evaluation (LOCF analysis; $p = .0764$). At the final on-therapy evaluation, the mean CGI-I score for the desvenlafaxine 200-mg group was statistically significantly different from the placebo group ($p = .0462$). The mean change in CGI-S score was –1.0 for the placebo group, –1.5 for the desvenlafaxine 100-mg ($p = .002$), –1.3 for the desvenlafaxine 200-mg ($p = .056$), and –1.5 for the desvenlafaxine 400-mg ($p < .001$) groups. The mean change from baseline in the MADRS total score was –9.9 for the placebo group, –13.9 for the desvenlafaxine 100-mg ($p = .004$), –13.5 for the desvenlafaxine 200-mg ($p = .005$), and –15.5 for the desvenlafaxine 400-mg ($p < .001$) groups. The desvenlafaxine 200-mg dose group was comparable to the 100-mg and 400-mg dose groups as measured by the CGI-I, CGI-S, and MADRS scores.

Rates of response (45%–51%) and remission (28%–32%) associated with desvenlafaxine treatment in this study were generally consistent with those observed in trials of short-term antidepressant treatment.[26,27] The lack of a statistically significant difference between the desvenlafaxine 200-mg and placebo groups on the primary outcome measure is interesting in light of the significant differences seen with the 100-mg and 400-mg doses. Considering that approximately half of clinical antidepressant studies (particularly for fixed-dose studies)[28] fail to show a significant difference between the active agent and placebo, this finding may be related to type II error, rather than indicative of a true lack of efficacy. In support of this interpretation, the desvenlafaxine 200-mg group demonstrated statistically significant differences from placebo on the key secondary outcome measure (CGI-I, as well as MADRS) and both measures of overall functioning (Sheehan Disability Scale, WHO-5). Significant improvements versus placebo were observed with desvenlafaxine at all doses on total scores of the Sheehan Disability Scale and the WHO-5 at the final study evaluation.

Although this fixed-dose study provided an opportunity to explore the potential for dose-response effects with regard to efficacy, there was no statistical evidence of such an effect. However, these effects can be difficult to detect, particularly in light of the variability in response that is common in clinical trials of antidepressants. Additional studies may be useful to further evaluate potential dose-response effects and better characterize the clinical effects of treatment with different doses of desvenlafaxine.

Desvenlafaxine treatment was generally well tolerated in this patient population, particularly at the 100-mg dose that demonstrated broad symptom efficacy. The adverse events reported in the study and rates of discontinuation due to adverse events[29] were consistent with those observed during treatment with other SNRIs. The most common adverse events (incidence ≥ 10% in any desvenlafaxine treatment group) were nausea, insomnia, somnolence, dry mouth, sweating, dizziness, nervousness, anorexia, constipation, asthenia, and abnormal ejaculation/orgasm. Most were mild or moderate in severity and transient. The incidence of nausea ranged from 31% to 41% across the doses, and nausea was the primary adverse event leading to discontinuation. However, the greatest incidence of nausea occurred during the first week of treatment, becoming less frequent by week 2 and thereafter.

Pain was measured using a visual analog scale similar to that employed in several studies that evaluated the response of pain symptoms to antidepressant treatment.[30,31] Treatment with desvenlafaxine was associated with improvement in some painful symptoms at the 100-mg dose, but for overall pain scores, neither the 200-mg nor the 400-mg dose group was significantly different from placebo. This result was surprising in light of data that suggest analgesia increases with increasing noradrenergic activity.[32] Greater attrition at higher doses early in the study may have made it difficult to measure dose-response effects. In other studies of antidepressants that evaluated the effects of antidepressant therapy on pain in patients with MDD, the extent of pain improvement correlated with mean baseline pain scores.[30,33,34] Because pain was not a consideration for inclusion in this study, most patients did not have high levels of pain at baseline, and the ability to detect pain improvements was limited. Thus, the detection of significant improvement in some pain symptoms in this patient population may indicate that greater benefit will be observed in those with more severe pain. More data regarding this effect are needed for clarity.

Desvenlafaxine treatment was associated with few clinically important changes in laboratory tests, vital signs, weight, and ECG assessments. Statistically significant mean changes in laboratory values, including bilirubin, ALT, AST, and cholesterol, associated with desvenlafaxine treatment did not appear to be clinically important. The occurrence of sustained increases in supine diastolic blood pressure (≥ 10 mm Hg from baseline to an on-therapy value of ≥ 90 mm Hg for ≥ 3 visits), as well as mean increases in pulse and BP and mean

decreases in weight associated with desvenlafaxine treatment, suggest the presence of a dose-response effect. Several small but statistically significant mean changes from baseline in ECG parameters were observed in the desvenlafaxine treatment groups, most of which are attributable to the increases observed in mean heart rate. The QTcB showed a dose-dependent increase from baseline, although the QTcF and QTcN did not. The differences between the QTcB and the QTcF or QTcN are probably due to the increasing heart rate associated with increasing doses of desvenlafaxine, which leads to an overcorrection by the Bazett formula.

CONCLUSIONS

In this 8-week study, desvenlafaxine was effective in treating a broad range of symptoms associated with MDD. Treatment with desvenlafaxine was well tolerated, particularly at the 100-mg dose, with an adverse event profile consistent with other SNRIs. Given its predictable pharmacokinetics and low potential for drug-drug interactions, further evaluation of the efficacy of desvenlafaxine in MDD and other central nervous system–related disorders is warranted. The preliminary evidence for impact on pain symptoms should be further assessed in additional studies in MDD and in subjects selected for the presence of pain symptoms. Additional research to evaluate long-term efficacy and safety may help to establish the potential role of this compound in treatment of MDD.

Drug names: promethazine (Promethegan and others), venlafaxine (Effexor and others).

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