A Randomized, Double-Blind, Placebo-Controlled Trial of Desvenlafaxine Succinate in Adult Outpatients With Major Depressive Disorder

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Objective: This study evaluated the efficacy and tolerability of desvenlafaxine succinate (desvenlafaxine) in the treatment of major depressive disorder (MDD).

Method: In this 8-week, multicenter, randomized, double-blind, placebo-controlled trial, adult outpatients (aged 18–75 years) with a primary diagnosis of MDD (DSM-IV criteria) were randomly assigned to treatment with desvenlafaxine (100–200 mg/day) or placebo. The primary outcome measure was the 17-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$) score at final on-therapy evaluation. The Clinical Global Impressions-Improvement scale (CGI-I) was the key secondary measure. Other secondary measures included the Montgomery-Asberg Depression Rating Scale (MADRS), Clinical Global Impressions-Severity of Illness scale, Visual Analog Scale–Pain Intensity (VAS-PI) overall and subcomponent scores, and $HAM\text{-}D_{17}$ response and remission rates. The study was conducted from June 2003 to May 2004.

Results: Of the 247 patients randomly assigned to treatment, 234 comprised the intent-to-treat population. Following titration, mean daily desvenlafaxine doses ranged from 179 to 195 mg/day. At endpoint, there were no significant differences in scores between the desvenlafaxine (N = 120) and placebo (N = 114) groups on the $HAM\text{-}D_{17}$ or CGI-I. However, the desvenlafaxine group had significantly greater improvement in MADRS scores ($p = .047$) and in VAS-PI overall pain ($p = .008$), back pain ($p = .006$), and arm, leg, or joint pain ($p < .001$) scores than the placebo group. The most common treatment-emergent adverse events (at least 10% and twice the rate of placebo) were nausea, dry mouth, constipation, anorexia, somnolence, and nervousness.

Conclusion: Desvenlafaxine was generally safe and well tolerated. In this study, it did not show significantly greater efficacy than placebo on the primary or key secondary efficacy endpoints, but it did demonstrate efficacy on an alternate depression scale and pain measure associated with MDD.

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Major depressive disorder (MDD) is a serious illness, with an estimated 16.6% lifetime prevalence in the United States.[1] The disease frequently follows a chronic course, and despite the substantial increase over the past decade in the proportion of individuals with depression who received treatment,[2] MDD is still associated with significant personal, societal, and economic burden. It is estimated that the cost of depression in 2003 was $83.1 billion, including $26.1 billion (31%) in direct medical costs, $5.4 billion (7%) in suicide-related mortality costs, and $51.5 billion (62%) in workplace costs.[2] Depressive symptoms are also found in up to 36% of all medically ill patients,[3] and comorbidity of MDD with medical illnesses has been found to significantly increase the morbidity, mortality, and costs of medical illnesses.[4–6] In light of the considerable burden that still remains with MDD, there continues to be a need for novel and effective treatment options.

Desvenlafaxine succinate (desvenlafaxine) is the succinate salt of the major metabolite of venlafaxine, *O*-desmethylvenlafaxine,[7,8] and preclinical in vitro and in vivo models suggest that it may have efficacy in the treatment of depression.[9] Like venlafaxine, desvenlafaxine selectively inhibits neuronal uptake of serotonin (5-HT) and norepinephrine (NE) and has little affinity for muscarinic, cholinergic, histamine H_1, and α_1-adrenergic receptors.[10] Desvenlafaxine is well absorbed following oral administration, with a mean terminal-phase elimination half-life of approximately 9 to 11 hours[11] and a consistent

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pharmacokinetic profile of intraindividual and interindividual exposure.[11] Elimination occurs primarily by phase 2 metabolism to form a glucuronide conjugate metabolite, and by renal excretion of unchanged desvenlafaxine.[11] Desvenlafaxine is not metabolized by the cytochrome P450 (CYP) pathway, and in vitro data suggest that it is associated with minimal inhibition of CYP enzymes.[12] It is also minimally bound (30%) to plasma proteins at therapeutic concentrations (data on file, Wyeth Research).

Desvenlafaxine is expected to have antidepressant efficacy comparable to that of venlafaxine extended release (ER). Previous fixed-dose trials have shown desvenlafaxine to be effective in the treatment of patients with MDD.[13,14] Here, we report the results of a phase 3 trial that compared the antidepressant efficacy, safety, and tolerability of desvenlafaxine (100 to 200 mg/day) versus placebo in patients with MDD.

METHOD

This study was conducted at multiple centers in the United States. Institutional review boards approved the protocol before the study 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 (FDA) 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. The study was conducted from June 2003 to May 2004.

Patients

Inclusion criteria. Male and female outpatients aged 18 to 75 years were eligible for this study if they had a primary diagnosis of MDD. At screening, a psychiatric assessment was performed by the investigator using a modified Mini-International Neuropsychiatric Interview (MINI),[15] and a diagnosis of MDD—single or recurrent episode without psychotic features—was confirmed according to *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) criteria. Patients must have also had depressive symptoms for at least 30 days before the screening visit, and, at screening and baseline, a 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. Sexually active women were required to use a medically acceptable form of contraception (oral contraceptives, injectable or implantable methods, intrauterine devices, or properly used barrier contraception).

Exclusion criteria. Reasons for exclusion from the study included the following: previous treatment with desvenlafaxine, treatment with venlafaxine or venlafaxine ER within 90 days, or known hypersensitivity to venlafaxine or venlafaxine ER; potential suicide risk; current (within 12 months from baseline) psychoactive substance abuse or dependence (including alcohol); manic episodes, posttraumatic stress disorder, obsessive-compulsive disorder, or clinically important personality disorder; current generalized anxiety disorder, panic disorder, or social anxiety disorder that the investigator considered primary based on the modified MINI assessment[15]; Covi Anxiety Scale[18] total score greater than the Raskin Depression Scale[18] total score at baseline; Covi Anxiety Scale score > 3 on any single item or a total score > 9 at baseline; depression associated with 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; use of prohibited treatments; and, for women, pregnancy, breast-feeding, or planning to become pregnant during the study.

Study Design

This multicenter, phase 3 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. 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 study medication. Patients who finished the study 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 instructed to take 1 tablet daily (desvenlafaxine 100 mg or placebo) on days 1 through 14. From day 15 onward, the dose was increased to 200 mg (2 tablets) per day. The dose could be decreased to the original dosage of 1 tablet per day only for safety and tolerability reasons. Patients continued taking active treatment or placebo through day 56 or early withdrawal. Patients receiving desvenlafaxine 200 mg/day (2 tablets) had their dose decreased to 100 mg (1 tablet) for 7 days. For patients receiving desvenlafaxine 100 mg (1 tablet), their dose was discontinued and they received placebo (1 tablet) for 7 days. Patients assigned to receive placebo continued receiving it for 7 days. All patients were evaluated for a final visit 7 days after discontinuing all treatments.

The 7-day taper period was recommended; however, if a patient experienced safety and/or tolerability issues, alterations to taper were permitted and were left to the discretion of the physician. Patients who completed the 8-week, double-blind study period and continued in the long-term, open-label study did not have their doses tapered or have follow-up evaluations.

Efficacy and Safety Measures

Efficacy measures. The primary efficacy measure, the HAM-D_{17}, was administered at each visit. The key secondary efficacy measure, the Clinical Global Impressions-Improvement scale (CGI-I),[17] was administered at all postbaseline visits. Other secondary outcome measures included the CGI-S, administered at each visit, and the Montgomery-Asberg Depression Rating Scale[19] (MADRS), Covi Anxiety Scale, Sheehan Disability Scale[20] (SDS), World Health Organization 5-item Well Being Index (WHO-5),[21] and Visual Analog Scale–Pain Intensity (VAS-PI),[22] which were administered at baseline and on study days 14, 28, and 56.

Safety measures. Safety evaluations included assessment of vital signs and weight, recording of adverse events (AEs) and concomitant treatments, and review of treatment compliance; these evaluations were performed at each visit. A physical examination and laboratory determinations were performed by the investigator at screening and day 56; a 12-lead ECG was performed at screening, baseline, and day 56. The Discontinuation-Emergent Signs and Symptoms checklist[23] was administered at baseline and day 56 (for patients who did not enter the long-term, open-label extension study). During the study, investigators reported serious adverse events (SAEs). Subsequently, the sponsor's medical monitor reviewed the clinical report forms, laboratory test results, vital signs results, and ECG results, as well as any relevant correspondence to identify any other patients with SAEs or reportable events, such as pregnancies or overdoses, that had not been already categorized as an SAE, regardless of whether the event was considered to be associated with the use of the study drug.

All laboratory, vital signs, and ECG data for individual patients during the double-blind period were screened against reference criteria that, if exceeded, would be considered of potential clinical importance. The criteria were specified by the sponsor, or in some cases, by the FDA, based on experience with venlafaxine trials. For cholesterol, both the FDA's and the sponsor's criteria were applied to the data. QTc criteria were based on guidance from the European Agency for the Evaluation of Medicinal Products. The remaining patients who were identified by the screening criteria were considered to have had results that were not clinically important. The potentially clinically important results were isolated or transient occurrences, were associated with tests performed in patients who had not fasted, were unrelated to adverse events or discontinuations, or were inconsistent with the rest of the clinical picture.

Statistical Analysis

The primary efficacy outcome measure was the change from baseline in the HAM-D_{17} total score at the final on-therapy (FOT) evaluation, for the intent-to-treat (ITT) population. The FOT evaluation for the ITT population was also the primary endpoint used for all efficacy analyses and health outcomes assessments. This "modified" last-observation-carried-forward (LOCF) endpoint was defined as the last assessment performed on the patient, regardless of the number of days on therapy. The FOT evaluation could occur more than 3 days after day 56, which permitted inclusion of a greater number of patients in the FOT analysis than the more strictly defined week 8 LOCF evaluation, which required that the final visit take place within 3 days of day 56 (although both the FOT and LOCF analyses carried forward data from the last postbaseline visit for patients who withdrew from the study, prior to day 52).

For efficacy, an observation made after the first full dose of double-blind study medication was treated as an on-therapy observation. Analyses for each visit were performed on the ITT population, defined as all randomly assigned patients who had a baseline primary efficacy evaluation, 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 study medication. The LOCF method was used to impute a value for patients who had missing values at a given endpoint by carrying forward the last recorded postbaseline observation, for the outcome measured. An observed-cases analysis was also performed for each outcome, which included only data from patients with no missing data for the analysis at a given week (e.g., for week 8, a visit within the window of study day 52 through day 59). The patients included in the week 8 observed-cases analysis were considered efficacy completers. Safety analyses were performed on the safety population, consisting of all randomly assigned patients who received at least 1 dose of medication. Safety completers were those who had a duration of therapy of 53 or more days (56 ± 3 days).

Analysis of variance (ANOVA) was used to test for comparability of treatment groups with respect to age, weight, and baseline scores of the HAM-D_{17} and CGI-S. The χ^2 test or Fisher exact test was used to compare the distribution of nominal attributes (e.g., ethnic origin and gender).

The primary endpoint was the change from baseline on the HAM-D_{17} score at the FOT evaluation, which was tested using analysis of covariance (ANCOVA) with treatment and site as factors and baseline HAM-D_{17} score as covariate. The assumptions of the ANCOVA models were checked at the final evaluation based on the primary

efficacy variable. If assumptions of parallelism and homogeneity of variance were not met, a nonparametric ANCOVA based on ranks was performed.

The CGI-I score was the key secondary efficacy variable. Mean scores on the CGI-I were analyzed using ANOVA with treatment and site as factors. A treatment-by-site interaction term was added to the primary and key secondary efficacy analysis models to explore the possibility of qualitative or quantitative treatment-by-site interaction. If the interaction was significant ($p \leq .10$), an assessment of the magnitude and direction of the interaction term was made.

Other secondary variables included MADRS total score, CGI-S, and the overall pain score and each subcomponent score of the VAS-PI. Health outcome assessments included the SDS and the WHO-5. These measures were evaluated using ANCOVA on changes from baseline, with treatment and site as the main factors and baseline severity as the covariate in the primary model. Two additional secondary variables were response rate based on HAM-D_{17} total score and remission, defined as a score on the HAM-$D_{17} \leq 7$. Response on the HAM-D_{17} was defined as a decrease of 50% or more in the total score from baseline. Response rate on the HAM-D_{17} was analyzed with the logistic regression model, with treatment and site as factors and baseline score as a covariate. HAM-D remission rates were analyzed using logistic regression.

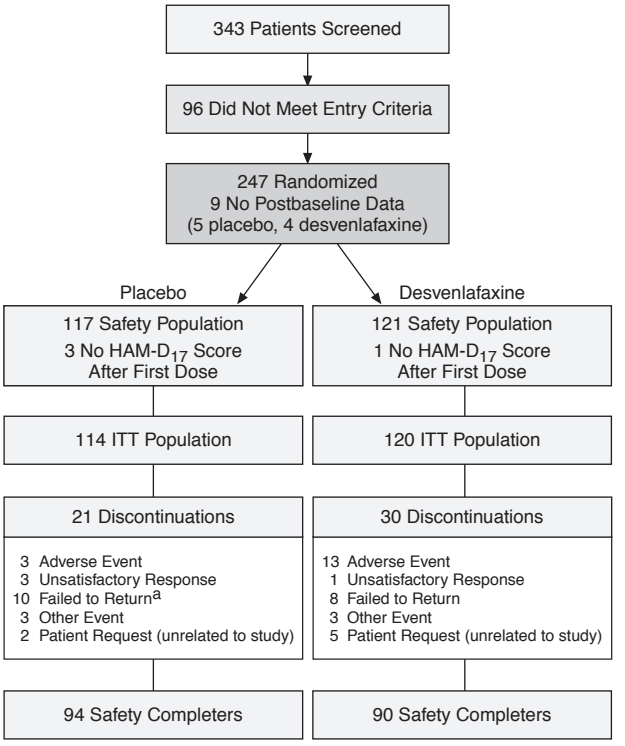
Ancillary efficacy variables included the HAM-D_6 depression subscale[24] (HAM-D_{17} items 1, 2, 7, 8, 10, and 13), the Covi Anxiety Scale, response rates based on the MADRS, response rates based on the CGI-I, and response rates based on the SDS. The HAM-D_6 total score and the Covi Anxiety Scale were evaluated using ANCOVA on changes from baseline with treatment and site as the main factors and baseline severity as the covariate in the primary model. No corrections were made for the multiple efficacy measures of depression used in the study.

Health outcomes assessments included the SDS and WHO-5. The total and individual subscale scores of the SDS and the WHO-5 score were analyzed using an ANCOVA model at each time point with treatment and site as main effects and baseline score as the covariate.

Patients who had CGI-I scores of 1 or 2 were classified as responders. Response rates were analyzed using logistic regression with treatment and site as factors. A second model included an additional term to the possibility of a treatment-by-site interaction. Response on the MADRS, defined as a 50% or greater decrease on the total score from baseline, and on the SDS, defined as a score of 1 ("no complaints, normal activity") or 2 ("symptoms mild, but not interfering with normal work or social activities"), was analyzed using logistic regression, with treatment and site as factors and baseline score as covariate.

If there was a significant difference between desvenlafaxine and placebo groups for ANCOVA analysis on the primary efficacy variable, the HAM-D_{17}, the RANDOM effect mixed model, and/or the ETRANK method[25] were used to correct for missing data.

Figure 1. Study Flowchart



[a]One patient failed to return for the final efficacy evaluation after remaining in the study long enough to be considered a completer and was not included in any efficacy analysis of completers.
Abbreviations: HAM-D_{17} = 17-item Hamilton Rating Scale for Depression, ITT = intent-to-treat.

Sample size estimates were based on the primary efficacy variable, the HAM-D_{17} total score. Based on experience with venlafaxine ER, a standard deviation of 8 units was selected for use in calculations in order to demonstrate that the active treatment group, desvenlafaxine, was significantly different from the placebo group with a mean difference of 3.5 units or more.[26] A sample size of 111 patients per group was sufficient to declare a mean difference of 3.5 units between the desvenlafaxine and placebo groups statistically significant at the 5% level with a power of approximately 90%. To compensate for patients who failed to qualify for the ITT analysis (5% of all patients), 120 patients were randomly assigned to each group.

RESULTS

Patients

Of 343 patients who were screened, 96 did not meet entry criteria, and 247 patients enrolled in the study (Figure 1): 122 were randomly assigned to receive placebo and

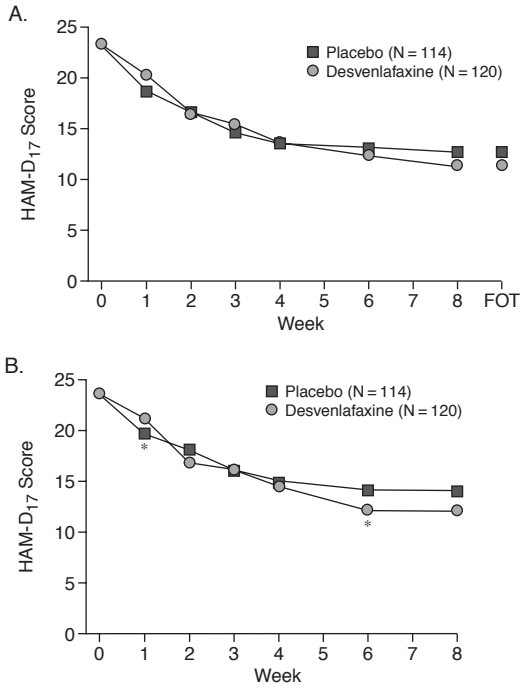
Table 1. Demographic and Baseline Characteristics (ITT population)

Characteristic	Placebo (N = 114)	Desvenlafaxine (N = 120)
Age, y		
Mean	39.3	41.9
SD	12.9	12.5
Range	18.0–73.0	20.0–70.0
Gender, N (%)		
Female	74 (65)	67 (56)
Male	40 (35)	53 (44)
Ethnic origin, N (%)		
Asian	1 (< 1)	4 (3)
Black	14 (12)	9 (8)
Hispanic	14 (12)	11 (9)
Native American	0	1 (< 1)
White	85 (75)	95 (79)
Height, cm[a]		
Mean	167.7	170.1
SD	9.7	10.2
Range	147.3–193.0	147.3–190.5
Weight, kg[b]		
Mean	81.9	83.8
SD	19.9	22.9
Range	42.2–130.8	43.6–215.4
Duration of current episode, mo[c]		
Mean	21.9	26.5
SD	39.1	47.4
Range	1.4–240.9	1.2–421.9
Current episode duration groups, N (%)		
< 6 mo	42 (37)	27 (23)
6 to < 12 mo	20 (18)	32 (27)
12 to < 24 mo	31 (27)	30 (25)
24 to < 60 mo	12 (11)	18 (15)
60 to < 120 mo	2 (2)	8 (7)
≥ 120 mo	7 (6)	5 (4)
Baseline HAM-D_{17} total[c]		
Mean	23.7	23.7
SD	2.5	3.3
Range	19.0–31.0	5.0–32.0
Global severity (CGI-S)[c]		
Mean	4.4	4.4
SD	0.5	0.5
Range	4–6	3–6
Global severity (CGI-S), by groups score, N (%)		
3	0	1 (1)[d]
4	72 (63)	71 (59)
5	41 (36)	46 (38)
6	1 (1)	2 (2)

[a]Placebo N = 113, desvenlafaxine N = 119.
[b]Placebo N = 113, desvenlafaxine N = 120.
[c]Placebo N = 114, desvenlafaxine N = 120.
[d]Although minimum CGI-S score of 4 was an inclusion criterion, 1 subject was not considered a major violator. The subject had a prestudy score and a baseline score of 4. The subject returned 7 days later without having taken any medication; the CGI-S score at that time was 3, and the subject began medication the next day.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D_{17} = 17-item Hamilton Rating Scale for Depression, ITT = intent-to-treat.

125 were randomly assigned to receive desvenlafaxine. Nine patients had no data after baseline. The remaining 238 patients who completed the prestudy period and took randomly assigned desvenlafaxine or placebo under double-blind conditions were included in all safety analyses. Three patients in the placebo group and 1 patient in the desvenlafaxine group, included in the safety population, had no HAM-D_{17} score after the first dose of their assigned treatment (protocol violations). These patients were excluded from the ITT population, which, as a result, consisted of 234 patients. Fifty-five patients from the safety population discontinued treatment during the double-blind period (including the 4 patients with protocol violations mentioned above): 24 (21%) patients treated with placebo and 31 (26%) patients treated with desvenlafaxine. There were no significant differences between treatment groups on demographic or baseline clinical characteristics (Table 1).

Figure 2. Adjusted Mean HAM-D_{17} Scores for the ITT Population, LOCF/FOT (A) and for Observed Cases (B)

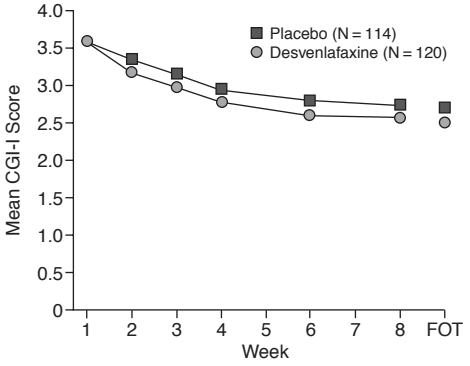


*p < .05, desvenlafaxine vs. placebo.
Abbreviations: FOT = final on-therapy, HAM-D_{17} = 17-item Hamilton Rating Scale for Depression, ITT = intent to treat, LOCF = last observation carried forward.

Efficacy Evaluation

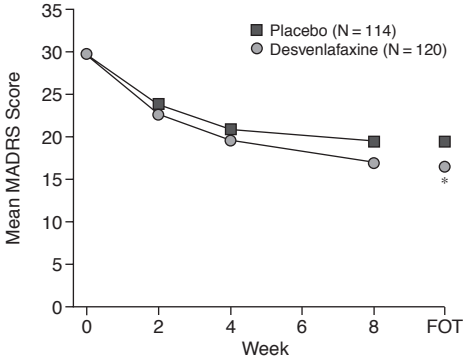
Primary efficacy measure. At the FOT evaluation, the adjusted mean score on the primary outcome measure, the HAM-D_{17} total score, was 14.1 for the desvenlafaxine group and 15.1 for the placebo group (Figure 2A), a difference between groups that was not statistically significant (p = .277). For the observed-cases analysis, the adjusted mean score on the primary outcome measure, the HAM-D_{17} total score, was 12.2 for the desvenlafaxine group and 14.2 for the placebo group (Figure 2B), a difference between groups that was not statistically significant (p = .067). However, the difference between the 2 groups was statistically significant at week 1 (p = .021)

Figure 3. Adjusted Mean CGI-I Scores (ITT population, LOCF/FOT)



Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, FOT = final on-therapy, ITT = intent to treat, LOCF = last observation carried forward.

Figure 4. Adjusted Mean MADRS Scores (ITT population, LOCF/FOT)

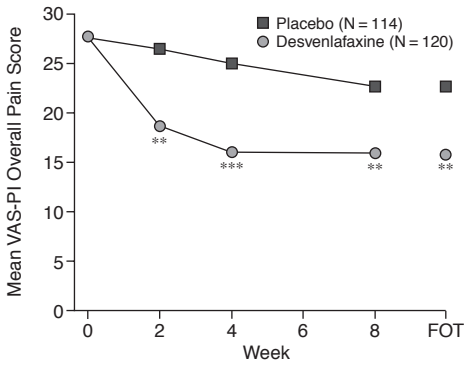


*p < .05, desvenlafaxine vs. placebo.
Abbreviations: FOT = final on-therapy, ITT = intent to treat, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale.

in favor of placebo and at week 6 (p = .042) in favor of desvenlafaxine.

Secondary efficacy measures. Mean scores on the key secondary outcome measure, the CGI-I, were 2.5 for the desvenlafaxine group and 2.7 for the placebo group, a difference that was not statistically significant at the study endpoint (Figure 3). Mean improvement at the final evaluation (LOCF) was significantly greater in the desvenlafaxine group than in the placebo group on the MADRS (p = .047) (Figure 4), VAS-PI overall pain (p = .008) (Figure 5), VAS-PI back pain (p = .006), and VAS-PI arm, leg, or joint pain (p < .001). There were no significant differences at endpoint between treatment groups for the changes from baseline on the remaining continuous secondary efficacy measures. There were no significant differences between the desvenlafaxine

Figure 5. Adjusted Mean VAS-PI Overall Scores (ITT population, LOCF/FOT)[a]



[a]Desvenlafaxine-treated patients also showed significantly greater improvement than placebo-treated patients in VAS-PI back pain (p < .01) and arm, leg, or joint pain scores (p < .001) at the final evaluation.
**p < .01, desvenlafaxine vs. placebo.
***p < .001, desvenlafaxine vs. placebo.
Abbreviations: FOT = final on-therapy, ITT = intent to treat, LOCF = last observation carried forward, VAS-PI = Visual Analog Scale–Pain Intensity.

groups in the percentages of patients who experienced HAM-D_{17} response (43% vs. 34%), HAM-D_{17} remission (23% vs. 20%), MADRS response (45% vs. 35%), CGI-I response (51% vs. 45%), or SDS response (33% vs. 25%).

Results of analyses of observed cases data were largely consistent with those of the LOCF analyses; statistically significant differences were seen for the MADRS; VAS-PI overall pain, back pain, and arm/leg or joint pain; HAM-D_6; and 1 item of the SDS (Table 2). Additionally, among completers the HAM-D_{17} response rate was significantly greater for the desvenlafaxine group than for the placebo group (54.9% vs. 37.9%, p = .031).

Safety Evaluation

Dosing. Following the initial titration period (days 1 to 14), mean daily doses of desvenlafaxine for the ITT population ranged from 179.0 to 195.3 mg. For completers, mean daily doses of desvenlafaxine after the initial titration period ranged from 182.4 to 195.2 mg.

Treatment-emergent adverse events. Treatment-emergent adverse events (TEAEs) were reported by 112 patients (93%) taking desvenlafaxine and 93 patients (79%) taking placebo. The most common TEAEs (at least 10% and twice the rate of placebo) were nausea, dry mouth, constipation, anorexia, somnolence, and nervousness. The incidence of nausea was 30% in the desvenlafaxine group and 9% in the placebo group (Table 3). The nausea severity was mild or moderate in all except 4 cases.

Discontinuations due to treatment-emergent adverse events. During the double-blind period, 3 (3%) patients in the placebo group and 13 (11%) patients in the

Table 2. Adjusted Mean Scores for Secondary Efficacy Endpoints at the Final Visit

Outcome Measure	Self-Report (SR) or Clinician Administered (CA)	Score Range (worst–best)	Baseline (N = 234)	ITT Population Final On-Therapy[a] Placebo (N = 114)	ITT Population Final On-Therapy[a] Desvenlafaxine (N = 120)	Completers Week 8 Placebo (N = 87)	Completers Week 8 Desvenlafaxine (N = 82)
CGI-I	CA	7–1	…	2.7	2.5	2.6	2.3
MADRS	CA	60–0	29.6	19.5	16.8*	18.7	14.9*
CGI-S	CA	7–1	4.4	3.3	3.1	3.2	2.9
VAS-PI	SR						
Overall pain		100–0	27.9	22.6	15.6**	17.7	11.0*
Stomach pain		100–0	17.3	13.1	11.3	10.8	8.6
Back pain		100–0	28.0	20.5	13.1**	17.5	11.4*
Chest pain		100–0	11.8	11.5	8.6	9.8	5.3
Arm, leg, or joint pain		100–0	29.2	21.6	13.3***	18.6	11.7*
HAM-D_6	CA	22–0	12.9	8.3	7.5	8.0	6.7*
Covi Anxiety Scale	CA	15–3	6.0	5.2	4.9	5.1	4.7
SDS	SR						
Work		10–0	6.0	4.2	4.0	4.1	3.5
Social		10–0	6.8	4.9	4.4	4.6	4.1
Family		10–0	6.7	4.7	4.5	4.4	4.0
Work/social		10–0	4.0	3.2	3.0	3.2	2.8*
WHO-5	SR	25–0	6.6	11.3	12.2	11.7	13.0

[a]Evaluation no later than 3 days after patient took last full dose that could occur more than 3 days after the scheduled week 8 final visit (last observation carried forward).
*p < .05.
**p < .01.
***p < .001.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D_6 = 6-item Hamilton Rating Subscale for Depression, HAM-D_{17} = 17-item Hamilton Rating Scale for Depression, ITT = intent-to-treat, MADRS = Montgomery-Asberg Depression Rating Scale, SDS = Sheehan Disability Scale, VAS-PI = Visual Analog Scale–Pain Intensity, WHO-5 = 5-item World Health Organization Well-Being Index.

desvenlafaxine group withdrew from the study due to TEAEs. Insomnia (3%) was the most frequent reason for discontinuation of treatment in desvenlafaxine-treated patients. Due to adverse events, 12 of 45 (27%) patients in the desvenlafaxine group and 2 of 39 (5%) patients in the placebo group eliminated the taper period entirely and were abruptly discontinued from the study.

No deaths occurred in this study or immediately afterward. Two patients were reported to have had SAEs: 1 patient had worsening of depression during screening and was not enrolled, and 1 patient treated with placebo had severe anemia caused by menometrorrhagia. None of the SAEs were considered related to treatment. In addition, 1 patient reported an event while receiving desvenlafaxine (unintended pregnancy).

Twelve patients (6 each in the placebo and desvenlafaxine groups) were considered to have had adverse events of clinical interest or clinically important laboratory value, vital sign, or ECG results that were not included as SAEs.

None of these 12 patients discontinued treatment because of the identified adverse events. Among the 6 patients in the desvenlafaxine group who had AEs or results of clinical interest or importance, 1 male patient experienced suicidal ideation, which was judged by the medical monitor to be unrelated to the medication; 2 male patients experienced urinary hesitation, judged to be possibly related to the medication; and 1 female patient had orthostatic hypotension, another had increased cholesterol and low-density lipoprotein (LDL), and a third had weight loss, none of which were categorized in relation to the medication.

Mean laboratory test results. Significant differences were noted between treatment groups in the adjusted mean changes from baseline at the week 8 or FOT evaluation for γ-glutamyltransferase (GGT) ($p < .001$), alkaline phosphatase ($p < .001$), fasting total cholesterol ($p < .01$), fasting high-density lipoprotein (HDL) ($p < .01$), and fasting LDL ($p < .05$). In each case, patients receiving desvenlafaxine had a greater mean change from baseline than patients receiving placebo, with significant changes from baseline ($p < .05$) at the week 8 or FOT evaluation among those receiving desvenlafaxine for all tests, except creatinine, fasting HDL cholesterol, and fasting triglycerides.

In addition, there were significant differences between treatment groups ($p < .05$) in the adjusted mean changes from baseline at the week 8 or FOT evaluation for 7 other laboratory tests (chloride, bicarbonate, phosphorus, uric acid, free thyroxine index, total thyroxine, and hematocrit). A significant ($p < .05$) change from baseline was noted at the week 8 or FOT evaluation among desvenlafaxine-treated patients for sodium, chloride, bicarbonate, calcium, phosphorus, uric acid, total bilirubin, albumin, free thyroxine index, total thyroxine, and monocytes. These statistically significant changes from base-

Table 3. Treatment-Emergent Adverse Events Reported by ≥ 5% of Patients in Any Treatment Group During the Double-Blind Period (excluding taper), N (%) of Patients

Adverse Event	Placebo (N = 117)	Desvenlafaxine (N = 121)
Any adverse event	93 (79)	112 (93)**
Body as a whole	57 (49)	66 (55)
Abdominal pain	7 (6)	7 (6)
Asthenia	8 (7)	13 (11)
Back pain	7 (6)	4 (3)
Flu syndrome	8 (7)	6 (5)
Headache	36 (31)	37 (31)
Infection	7 (6)	10 (8)
Pain	9 (8)	7 (6)
Digestive system	45 (38)	82 (68)***
Anorexia	2 (2)	16 (13)***
Constipation	7 (6)	20 (17)*
Diarrhea	8 (7)	14 (12)
Dry mouth	14 (12)	31 (26)**
Dyspepsia	5 (4)	9 (7)
Nausea	10 (9)	36 (30)***
Vomiting	2 (2)	8 (7)
Musculoskeletal system	15 (13)	15 (12)
Arthralgia	4 (3)	8 (7)
Myalgia	7 (6)	4 (3)
Nervous system	43 (37)	66 (55)**
Abnormal dreams	6 (5)	6 (5)
Anxiety	6 (5)	6 (5)
Dizziness	14 (12)	19 (16)
Hostility	6 (5)	4 (3)
Insomnia	13 (11)	21 (17)
Nervousness	5 (4)	13 (11)
Somnolence	7 (6)	14 (12)
Tremor	0	8 (7)**
Respiratory system	16 (14)	23 (19)
Upper respiratory infection	7 (6)	2 (2)
Yawn	0	8 (7)**
Skin and appendages		
Sweating	4 (3)	9 (7)
Urogenital system		
Abnormal sexual function	2 (1 [1%] for women; 1 [2%] for men)[a]	3 (0 [0%] for women; 3 [6%] for men)[b]

[a]N = 42 among men; N = 75 among men.
[b]N = 53 among men.
*p < .05.
**p < .01.
***p < .001.

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

Measure	N	Baseline Mean	Mean Change From Baseline	p Value (desvenlafaxine vs placebo)[a]
Supine pulse rate, bpm				
Placebo	113	67.85	1.72*	NS
Desvenlafaxine 100 mg	110	68.54	2.80***	
Systolic BP, supine, mm Hg				
Placebo	113	119.75	–1.59	< .001
Desvenlafaxine 100 mg	110	118.47	3.76***	
Diastolic BP, supine, mm Hg				
Placebo	113	75.57	–0.91	.003
Desvenlafaxine 100 mg	110	75.63	1.85**	
Weight, kg				
Placebo	112	82.16	0.36	< .001
Desvenlafaxine 100 mg	110	85.19	–0.74**	

[a]Comparison based on adjusted mean changes from baseline using analysis of covariance with baseline as covariate.
*p < .05 vs. baseline mean.
**p < .01 vs. baseline mean.
***p < .001 vs. baseline mean.
Abbreviations: BP = blood pressure, NS = nonsignificant.

line were not considered to be clinically important by the medical monitor.

Aspartate aminotransferase increased by 1.6 U/L at both the week 8 and FOT evaluations ($p < .05$), and alanine aminotransferase increased by 3.9 and 4.2 U/L at the week 8 and FOT evaluations, respectively ($p < .01$), among patients treated with desvenlafaxine. Both GGT and alkaline phosphatase were significantly ($p < .001$) increased at week 8 in the desvenlafaxine group by 5.8 mU/L, whereas the placebo group had decreases of 1.3 and 0.6 mU/L, respectively, for GGT and alkaline phosphatase (p = NS); the FOT evaluation results were also significantly elevated in the desvenlafaxine group. Total bilirubin was significantly decreased at both the week 8 and FOT evaluations in the desvenlafaxine group ($p < .05$). Total cholesterol/lipids increased significantly ($p < .05$) from baseline by 0.22882 mmol/L at week 8 and 0.19025 mmol/L at the FOT evaluation for the desvenlafaxine group compared with a decrease of 0.10528 mmol/L at week 8 and 0.11968 mmol/L at the FOT evaluation for the placebo group (p = NS). HDL cholesterol increased from baseline by 0.03566 mmol/L at week 8 and 0.03658 mmol/L at the FOT evaluation for the desvenlafaxine group (p = NS) compared with a decrease of 0.05948 mmol/L at week 8 and 0.06531 mmol/L at the FOT evaluation for the placebo group ($p < .01$). LDL cholesterol increased from baseline at 8 weeks by 0.17085 mmol/L ($p < .05$) for the desvenlafaxine group compared to a decrease of 0.04350 mmol/L for the placebo group (p = NS).

Vital signs and weight. Mean changes from baseline to the FOT evaluation in vital signs and weight are summarized in Table 4. Mean increases in supine systolic blood pressure in the desvenlafaxine group were statistically significant compared with baseline and compared with mean changes in the placebo group at all weeks and the FOT evaluation, except for week 2. Mean changes in supine diastolic blood pressure in the desvenlafaxine group were statistically significant compared with baseline and compared with mean changes in the placebo group at all weeks and the FOT evaluation, except week 6. Mean decreases in weight in the desvenlafaxine treatment group were statistically significant compared with baseline and with mean increases in the placebo group, at all weeks, and the FOT evaluation.

Electrocardiogram. A statistically significant increase from baseline in mean heart rate was observed in the desvenlafaxine group at the FOT evaluation (4.27 bpm; $p < .01$); a significant decrease from baseline was observed in the placebo

group (–2.27 bpm; $p < .01$). There were statistically significant differences in heart rate between desvenlafaxine group and the placebo group ($p < .001$).

A decrease in the mean QT interval was observed in the desvenlafaxine group at the FOT evaluation (–4.27 ms; p = NS), which was significantly different ($p < .01$) from the mean increase (4.90 ms) observed in the placebo group ($p < .05$ vs. baseline). Corrected QT intervals (Bazett [QTcB] and Fridericia [QTcF] corrections and a correction based on the population correction factor [QTcN]) were also evaluated, and there were no statistically significant differences between the desvenlafaxine and placebo groups.

DISCUSSION

In this phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial conducted in outpatients with a primary diagnosis of MDD, the primary and key secondary efficacy endpoints did not show significant differences between the placebo group and the desvenlafaxine group in the ITT population. No significant differences between the placebo group and the desvenlafaxine group at the FOT evaluation were observed for HAM-D_{17} total score or CGI-I score.

These results are somewhat surprising in light of findings of desvenlafaxine efficacy in MDD in 2 fixed-dose trials.[13,14] However, previous research has shown that nearly half of antidepressant studies fail to show a statistical difference from placebo[27] and that multiple factors may influence outcomes. For example, antidepressant dose schedule may influence trial outcome,[28] and it is possible that the failure to show a significant difference between desvenlafaxine and placebo on the primary outcome measure in this trial may be related to the titrated-dose design. Additional data suggest that the pretreatment severity of depression affects outcomes, which may be related to a greater magnitude of improvement among antidepressant-treated patients with more severe depression than those with less severe depression.[29] Relatively low mean baseline HAM-D scores, such as the one seen in this study (23.7), have been associated with smaller effect sizes and a lower frequency of statistically significant separation from placebo compared with higher scores (e.g., 26 or more).[30,31]

Desvenlafaxine was significantly different from placebo at the final evaluation on the MADRS total score. Although this was a secondary efficacy measure in this study, the MADRS is as sensitive an instrument as the HAM-D for assessing antidepressant efficacy.[32]

Desvenlafaxine was associated with significantly greater improvement than placebo at the final evaluation on VAS-PI overall pain, VAS-PI back pain, and VAS-PI arm, leg, or joint pain. While psychic or emotional symptoms are the core feature of MDD, painful physical symptoms contribute significantly to depression-related disability.[33] These symptoms are the primary presenting complaint for many patients, especially in the primary care setting,[34] where more than two thirds of depressed patients report only physical symptoms during medical evaluation.[35] Both 5-HT and NE have been implicated in the psychic and somatic symptoms of depression, including pain.[36,37] Antidepressants that increase neurotransmission of both 5-HT and NE, including some tricyclic antidepressants[38,39] and the serotonin-norepinephrine reuptake inhibitors venlafaxine[40–42] and duloxetine,[43,44] have demonstrated efficacy in the treatment of painful symptoms in patients with depression as well as in chronic pain patients without depression. Evidence suggests that descending serotonergic and noradrenergic pathways mediate pain through neurons in the spinal cord.[36,37] It is, therefore, possible that antidepressants that simultaneously modulate central and peripheral serotonergic and noradrenergic activity may have greater efficacy than antidepressants that only modulate serotonergic activity in treating pain symptoms associated with MDD.

Desvenlafaxine was generally safe and well tolerated. No patient receiving desvenlafaxine had an SAE. Desvenlafaxine treatment was associated with few clinically important changes in laboratory test results, vital signs, or ECG assessments. One patient had a clinically important increase in total cholesterol/lipids and a decrease in LDL cholesterol, 1 patient had a clinically important weight loss, and 1 patient had clinically important orthostatic hypotension. Impairment in sexual functioning and weight gain, 2 adverse effects that often limit patient compliance with marketed antidepressants, were not strongly manifest, although longer trials might yield different results.

Desvenlafaxine (100 to 200 mg/day) did not differ significantly from placebo in this study on the primary or key secondary endpoints, although some secondary measures reflected significant improvement compared with placebo. It is difficult to account for the divergent findings between rating scales, and interpretation of the study results is limited by the lack of correction for the multiple assessments of depression used in the study. Nonetheless, desvenlafaxine was generally safe and well tolerated overall, and we believe that these results, considered alongside those of other clinical trials of desvenlafaxine, are sufficiently suggestive of antidepressant and associated anti-pain activity for desvenlafaxine to warrant further study.

Drug names: duloxetine (Cymbalta), venlafaxine (Effexor and others).

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