

An Evaluation of the Efficacy, Safety, and Tolerability of Desvenlafaxine in the Long-term Treatment of Elderly Outpatients With Major Depressive Disorder

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ABSTRACT

Objective: To evaluate the safety and tolerability (primary) and efficacy (secondary) of desvenlafaxine (administered as desvenlafaxine succinate) treatment in elderly patients with major depressive disorder (MDD).

Methods: Outpatients ≥ 65 years of age with MDD received open-label, flexible-dose desvenlafaxine 100 or 200 mg/day for ≤ 6 months. Safety and tolerability were assessed; the primary efficacy measure was the 17-item Hamilton Rating Scale for Depression (HAM-D₁₇) total score.

Results: Safety analyses included 52 patients (mean age=72.9 years). The most frequently reported adverse events were mild or moderate nausea (40%), dizziness (25%), and headache (21%). Primary and secondary adverse events led to discontinuation of treatment for 18 (35%) patients. The most common adverse events cited as reasons for withdrawal were hypertension (10%) and nausea (10%). There were few clinically important changes in vital signs, laboratory assessments, or electrocardiograms. Treatment with desvenlafaxine reduced mean total HAM-D₁₇ scores through month 2; these improvements were maintained without dose escalation.

Conclusion: Desvenlafaxine was safe, well tolerated, and effective in elderly patients with MDD.

INTRODUCTION

Approximately 1 million Americans ≥ 65 years of age have major depressive disorder (MDD).^{1,2} MDD is the most commonly diagnosed affective disorder in this age group, with prevalence estimates as high as 9% in ambu-

FOCUS POINTS

- An estimated 1 million Americans ≥ 65 years of age have major depressive disorder (MDD); specific symptoms that may be associated with MDD in elderly patients include somatic complaints, insomnia, cognitive impairment, decreased productivity, and physical disability.
- In elderly patients with MDD, these symptoms can substantially impact psychosocial functioning and impair their ability to perform activities of daily living, which may result in an increased burden for family members and caregivers.
- Treatment with antidepressants can relieve symptoms of depression, reduce physical disability, and resolve functional impairment in elderly patients with MDD; however, treatment must be individualized to achieve an optimal therapeutic response, as elderly patients may be more sensitive to the effects of antidepressant therapies.
- Previous clinical trials have demonstrated the efficacy and safety of desvenlafaxine, a novel serotonin-norepinephrine reuptake inhibitor, in adult patients with MDD; however, the majority of these patients were < 65 years of age.
- The objectives of this study were to evaluate the safety, tolerability, and efficacy of desvenlafaxine for up to 6 months in elderly outpatients ≥ 65 years of age with MDD.

latory care settings.³ However, prevalence estimates of MDD among older adults in community settings vary widely, ranging from 0.9–19.4^{4,5} per 100 patients in the epidemiologic literature.⁶ Elderly individuals with MDD often present with symptoms such as insomnia, cognitive impairment, and somatic complaints; decreased productivity and physical disability also may be associated with late-life MDD.^{1,3,7} These factors can substantially impair an

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individual's ability to perform the basic activities of daily living, which may result in an increased burden for family members and caregivers.^{8,9}

Antidepressant therapy can improve symptoms of depression, reduce physical disability and stress, and reduce functional impairment in elderly patients with MDD.¹⁰ Unfortunately, underprescribing of antidepressants and prescription of inappropriate doses for elderly patients are relatively common in clinical practice.¹ For example, the American Psychiatric Association guidelines suggest that antidepressant treatment should be initiated at doses of 50% of the standard adult dose in elderly patients with MDD.⁷ Such modifications can potentially improve the safety and tolerability of antidepressants in this patient population, who may be more sensitive to the effects of antidepressants; however, treatment must be individualized and dose increases may be necessary to achieve an optimal therapeutic response.

Desvenlafaxine (administered as desvenlafaxine succinate), the major active metabolite of venlafaxine, is a novel serotonin-norepinephrine reuptake inhibitor (SNRI) approved for the treatment of MDD.¹¹⁻¹⁴ The efficacy and safety of desvenlafaxine has been demonstrated in clinical trials of adults with a diagnosis of MDD¹⁵⁻¹⁸; however, the majority of patients in these trials were <65 years of age. The primary objective of this study was to evaluate the safety and tolerability of desvenlafaxine for ≤6 months in elderly outpatients with MDD; efficacy was evaluated as a secondary objective.

METHODS

Study Design

This open-label, single-arm, multicenter study consecutively enrolled individuals ≥65 years of age with MDD at 14 outpatient clinical research centers in the United States from October 2004 to October 2005. The study protocol received institutional review board approval before the study began. Potential study participants, who were recruited by advertisement and from existing clinic populations, provided written, informed consent prior to having screening procedures performed. Patients who met inclusion criteria without meeting exclusion criteria entered a 10±4-day screening evaluation which included a medical and psychiatric history assessment. Patients who continued to meet the inclusion criteria and none of the exclusion criteria at baseline were enrolled in the study. Individuals who gave informed consent but failed to meet criteria at the screening or baseline visits were considered screening failures.

PATIENTS

Inclusion Criteria

Patients were outpatients ≥65 years of age with a primary diagnosis of MDD, based on *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition,¹⁹ criteria, single or recurrent episode, without psychotic features. Patients had to have had depressive symptoms for ≥30 days before the screening visit, a score of ≥24 on the Mini-Mental State Examination,²⁰ and a score ≥16 on the 17-item Hamilton Rating Scale for Depression (HAM-D₁₇)²¹ at screening and baseline.

Exclusion Criteria

Exclusion criteria included previous treatment within 90 days with, or known sensitivity to, venlafaxine; previous treatment with desvenlafaxine; suicide risk; dementia; current (ie, within the past 12 months) substance or alcohol abuse, posttraumatic stress disorder, obsessive-compulsive disorder, generalized anxiety disorder, panic disorder, or social anxiety disorder; personality disorder; lifetime diagnosis of bipolar disorder; history or presence of seizure disorder (other than childhood febrile seizure), clinically relevant hepatic or renal disease, gastrointestinal disease known to interfere with drug metabolism, neoplastic disorder (in past 2 years), raised intraocular pressure, or narrow-angle glaucoma; major acute illness during 90 days before screening; myocardial infarction within 180 days before screening; and use of prohibited medications.

Study Medication

On study days 1–7, study participants received desvenlafaxine 100 mg QD, which was increased on day 8 to 200 mg QD (administered as two 100 mg tablets). Patients who were unable to tolerate the 200 mg/day dose could resume taking the 100 mg/day dose at the discretion of the investigator. This flexible-dose regimen was administered for ≤6 months. At the end of the treatment period, a 7-day tapering to desvenlafaxine 100 mg/day was conducted for patients who were taking the 200 mg dose. This tapering regimen could be omitted or modified at the discretion of the investigator. A follow-up visit occurred 7 days after discontinuation of study medication.

Concomitant therapy with nonpsychopharmacologic drugs was permitted throughout the study if the drug was not a prohibited medication. Nonpsychopharmacologic drugs with psychotropic effects were permitted only if the patient had been receiving a stable dose of the drug and no dose changes were anticipated during the study.

SAFETY AND EFFICACY MEASURES

Safety

Safety and tolerability were assessed by recording spontaneously reported adverse events, patient discontinuations due to adverse events, standard 12 lead electrocardiogram (ECG), physical examination, vital signs (eg, pulse, blood pressure), and clinical laboratory parameters (eg, hematology, blood chemistry, urinalysis). Physical examinations were performed at screening, at 6 months after treatment initiation (day 180), or at early withdrawal. Laboratory parameters were assessed at screening; at 1, 3, and 6 months after treatment initiation (days 30, 90, and 180); or at early withdrawal. Study participants were asked to fast for 12 hours prior to testing. An ECG was performed at screening, baseline (day -1), at 3 and 6 months after treatment initiation (days 90 and 180), or at early withdrawal. Vital signs, weight, and adverse events (including date of occurrence, severity, and relationship to study medication) were recorded by study personnel at screening, baseline, biweekly office visits (days 7, 14, 30, 45, 60, 75, 90, 105, 120, 145, 150, 165, 180), taper visit (day 187), the follow-up visit (day 194), or early withdrawal. The taper visit could be omitted if the patient was not undergoing a tapering regimen. Reporting of adverse events was based on signs and symptoms spontaneously reported by the patient, those observed by the investigator, and responses to the nonspecific question: "How have you been feeling since your last visit?" Serious adverse events, posttreatment adverse events, and adverse events occurring during the taper regimen also were recorded.

Efficacy Measures

The primary efficacy measure, the mean total score on the HAM-D₁₇, was assessed at screening, baseline, and days 7, 14, 30, 60, 90, 120, 150, and 180 by trained raters. Secondary efficacy measures included clinical response to treatment ($\geq 50\%$ decrease from baseline in HAM-D₁₇ total score), rate of clinical remission (percentage of patients with HAM-D₁₇ total score ≤ 7), and health-related quality of life (QOL; measured by the Sheehan Disability Scale [SDS] total score), which were measured at days 90 and 180.²² The SDS is a patient-rated measure of functional impairment in three domains (family life/home responsibilities, social life, and work) on scales of 0–10, with a total score ranging from 0 (no disability) to 30 (extreme disability).

Statistical Analyses

Patients who received ≥ 1 dose of study medication comprised the safety population. Changes from baseline in safety parameters were summarized and mean changes

were analyzed using paired t-tests. No correction was made for multiplicity. Efficacy analyses were conducted using data from the intent-to-treat (ITT) population, which included patients who received ≥ 1 dose of study medication, had a baseline primary efficacy evaluation, and had ≥ 1 primary efficacy evaluation after the first dose of study medication. The primary efficacy end point, the mean score on the HAM-D₁₇, was summarized descriptively. The mean change from baseline in HAM-D₁₇ total score was analyzed by paired t-tests using the last observation carried forward (LOCF) and observed cases (OC) data. Clinical response and clinical remission (based on HAM-D₁₇ total score), and total and individual subscale scores of the SDS were summarized descriptively. A post-hoc analysis using paired t-tests was conducted to examine changes from baseline in specific HAM-D₁₇ items that might be relevant to elderly patients (items 4 [insomnia (early)], 5 [insomnia (middle)], 6 [insomnia (late)], 7 [work and activities], and 12 [somatic symptoms—gastrointestinal]) and SDS total scores. All statistical tests were two-sided with 5% level of significance.

RESULTS

Patient Demographics and Clinical Characteristics

Of 79 patients screened, 52 were enrolled. The mean age was 73 ± 5.5 years (range, 65–87 years), 28 patients (54%) were female, all patients were white, the mean duration of current MDD episode was 25 ± 29 months (range, 1–156 months), and the mean baseline HAM-D₁₇ score was 21.68. Patient characteristics were similar in the safety (n=52) and ITT (n=50) populations.

Patient Disposition

All 52 enrolled participants received desvenlafaxine treatment and were included in the safety analyses (Figure 1). Two individuals had no data recorded for HAM-D₁₇ at baseline or after the first dose of study medication and were not included in the ITT population. A total of 25 (46%) patients withdrew from the study (Figure 1).

SAFETY

Exposure to Study Medication

The mean daily dose of desvenlafaxine during the on-therapy period ranged from 173 ± 44 mg to 177 ± 42 mg during week 2 through month 6 of the study. The daily dose of

desvenlafaxine administered was reduced from 200 to 100 mg in seven (13%) patients during the on-therapy period due to adverse events. Thus, the majority of patients received desvenlafaxine 200 mg/day after the initial titration period (days 1–7). The dose-taper period was omitted for nine (17%) patients and shortened for two (4%) patients at the discretion of the investigator.

Adverse Events

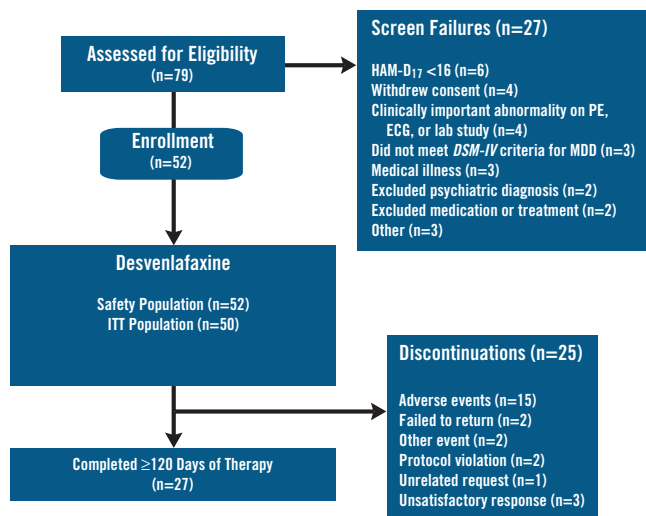
During the 6-month on-therapy period, adverse events were reported for 48 (92%) of the 52 patients. The most frequently occurring adverse events ($\geq 5\%$) were nausea (21 patients; [40%]); dizziness (13 patients; [25%]); dry mouth and headache (10 patients; [19%] for each); diarrhea and constipation (7 patients; [14%] for each); hyperhidrosis and decreased appetite (6 patients; [12%] for each); fatigue, increased blood pressure, and insomnia (5 patients; [10%] for each); upper respiratory tract infection, arthralgia, pollakiuria, erectile dysfunction, and hypertension (4 patients [8%] for each); and dyspepsia, vomiting, pyrexia, sedation, and abnormal dreams (3 patients [6%] for each). Most adverse events were mild or moderate in severity.

Primary and secondary adverse events led to discontinuation of treatment for 18 (35%) patients. Of these, 15 patients withdrew with adverse events cited as the primary reason. Most withdrawals due to adverse events occurred during

the first month of treatment. The most frequently reported adverse events leading to premature withdrawal were nausea (5 patients; 10%), hypertension (3 patients; 6%), and dizziness (3 patients; 6%). During the 14-day taper/post-study period (day 181–194), taper/post-study adverse events were reported by 25 (48%) patients, and the most frequently reported adverse events during this period were dizziness (6 patients; 12%) and vomiting (3 patients; 6%).

Two patients experienced three serious adverse events (SAEs). One 76-year-old patient who received desvenlafaxine 200 mg/day beginning on day 8 had clinically significant hypertension and a subarachnoid hemorrhage on day 39. This patient had hypertension at study baseline that progressively improved at the week 2 and month 1 assessments. She was subsequently hospitalized with dizziness, nausea, and blurred vision, at which time a subarachnoid hemorrhage and posterior communicating artery aneurysm were diagnosed by computed tomography scan. The patient reported having a history of falls with head trauma. The hypertension was considered possibly related to study medication; however, the subarachnoid hemorrhage was considered likely not related to treatment with desvenlafaxine. A 75-year-old patient with a history of hypertension, who received 200 mg/day desvenlafaxine beginning on day 8, experienced chest pain on day 79, for which she was hospitalized. Full diagnostic work-up did not reveal any etiology. The chest pain resolved 1 day after onset, and was considered likely not related to treatment with desvenlafaxine. Both individuals who experienced SAEs were withdrawn from the study.

FIGURE 1
PATIENT DISPOSITION



HAM-D₁₇=17-item Hamilton Rating Scale for Depression; PE=physical examination; ECG=electrocardiogram; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; MDD=major depressive disorder; ITT=intent to treat.

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Laboratory Parameters

At the final evaluation, statistically significant mean changes from baseline were observed for γ -glutamyl transpeptidase (GGT; +4.1 U/L), total protein (−1.6 g/dL), and urine specific gravity (+0.002) values ($P<.001$ for each comparison versus baseline). Mean changes in fasting lipid values at the final evaluation were not statistically significant (total cholesterol, −0.071 mmol/L; high-density lipoprotein cholesterol, −0.061 mmol/L; low-density lipoprotein cholesterol, −0.26 mmol/L; triglycerides, 0.035 mmol/L).

Among the patients with available laboratory results on therapy (n=42), 12 (29%) had laboratory values that met predefined criteria programmatically determined for potential clinical importance at any time on therapy. Five of these patients had values that were determined by the medical monitor to be clinically important compared with baseline values. These were an increase in total cholesterol of +2.15 mmol/L from baseline to 7.14 mmol/L at month 6; increase in serum glucose of +6.88 mmol/L to 15.71 mmol/L at month 6; increase in serum creatinine of +0.2 mg/dL to 1.4 mg/dL at month 6; increase in blood urea nitrogen of +10 mg/dL to 32 mg/dL at month 6; and elevated liver func-

tion tests at month 3 versus baseline (increases in aspartate aminotransferase of +38 mU/mL to 66 mU/mL, in alanine aminotransferase of +155 mU/mL to 186 mU/mL, and in GGT of +118 mU/mL to 133 U/L). There were no changes in serum sodium levels, or mean changes at any time point, and no patients met outlier criteria.

Vital Signs and Weight

Statistically significant mean changes at the final evaluation compared with baseline were noted for supine pulse (+3.2 beats/min; $P<.01$) and weight (-0.9 kg; $P<.05$). The final evaluation values for systolic and diastolic blood pressure showed mean reductions of -1.65 mm Hg and -0.35 mm Hg, respectively, which were not statistically significant compared with mean baseline values of 131.05±10.43 mm Hg and 77.54±6.80 mm Hg, respectively. No patients met the definition for a new onset of hypertension based on the criteria for sustained hypertension. Thirteen of 48 (27%) patients had vital sign measurements of potential clinical importance at any time during therapy. Changes in vital signs were considered to be clinically significant in two patients, both of whom had orthostatic hypotension. No patient was considered to have a clinically significant change in physical measurements from baseline to the end of study.

Electrocardiograms

At the final evaluation, the mean PR interval was significantly decreased compared with baseline (-4.00; $P<.05$); no other ECG assessments were statistically significant. No significant changes were observed for mean changes from baseline in heart rate, QT interval (uncorrected), or RR interval at any time during the study. Twelve of 35 (34%) patients had ECG changes of potential clinical importance on therapy. Three ECG findings in two patients were considered to be of clinical importance (bradycardia in one patient and increased frequency of premature ventricular contractions with couplets and increased Fridericia QT correction in the other). These two patients had medical histories that included ECG abnormalities.

Efficacy Measures

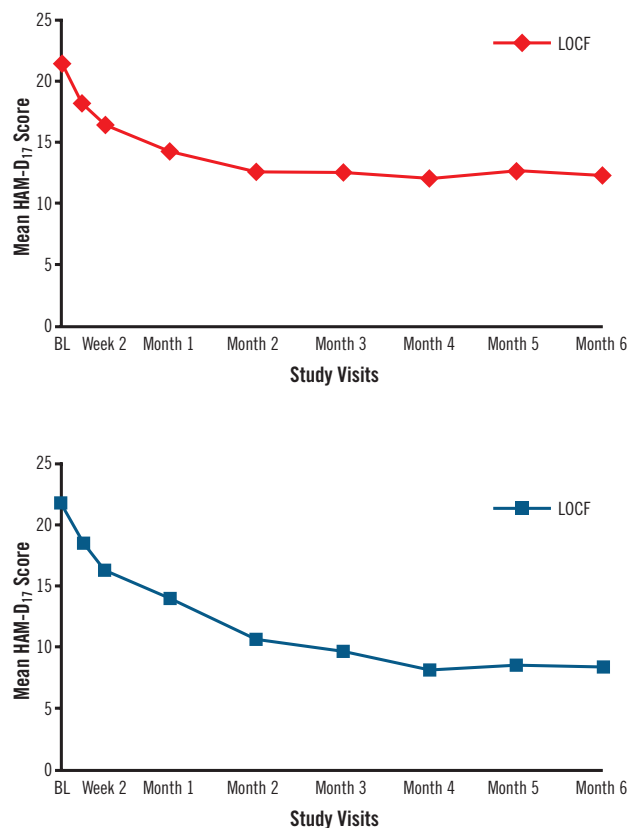
Following 3 months of treatment with desvenlafaxine, the mean total HAM-D₁₇ score (primary efficacy end point) decreased 9.20 points (LOCF) and 12.5 points (OC) from a baseline score of 21.68±3.20. This improvement was maintained for the duration of the study; the mean change from baseline at the final evaluation at month 6 was -9.28 points (LOCF) and -13.9 (OC), resulting in mean HAM-D₁₇ total scores of 12.40±7.19 (LOCF) and 8.30±5.72 (OC, 6 months), respectively (Figure 2).

Clinical response rates (based on HAM-D₁₇ total score) following treatment with desvenlafaxine were 6% (3/49; LOCF and OC) at week 1 and 42% (21/50; LOCF) and 63% (19/30; OC) at month 3. These increases in clinical response from baseline were maintained (40% [20/50] at month 6, LOCF; 65% [15/23] at month 6, OC) for the remainder of the study (Figure 3).

Rates of clinical remission (HAM-D₁₇ total score ≤7) following desvenlafaxine treatment were 2% (1/49; LOCF and OC) at week 1, and 28% (14/50; LOCF) and 39% (14/36; OC) at month 2. These remission rates were maintained (30% [15/50] at month 6; LOCF) or further improved from baseline (48% [11/23] at month 6; OC) for the duration of the study (Figure 3).

Treatment with desvenlafaxine resulted in clinically significant improvements from baseline in individual items of the HAM-D₁₇ considered of special concern for the elderly, including items 4, 5, 6 (early, middle, late insomnia) and 7

FIGURE 2
MEAN TOTAL HAM-D₁₇ SCORE OVER TIME, LOCF (A) AND OC (B): ITT POPULATION



HAM-D₁₇=17-item Hamilton Rating Scale for Depression; LOCF=last observation carried forward; OC=observed cases; ITT=intent to treat.

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(work and activities; $P < .001$ for each item versus baseline) and item 12 (somatic, gastrointestinal symptoms; $P = .0011$ versus baseline). Specifically, anhedonia, assessed by item 7, was significantly improved from baseline ($P < .001$ for both LOCF and OC; Figure 4).

Significant improvements from baseline were also noted in functional impairment as measured by SDS total scores (Figure 5); the mean change from baseline at the final evaluation was -5.50 ($P < .001$). Mean scores on individual domains (ie, family life/home, social life, and work) were improved substantially with desvenlafaxine treatment. The greatest improvement in individual domain score was a mean change from baseline of -2.07 for the social life component.

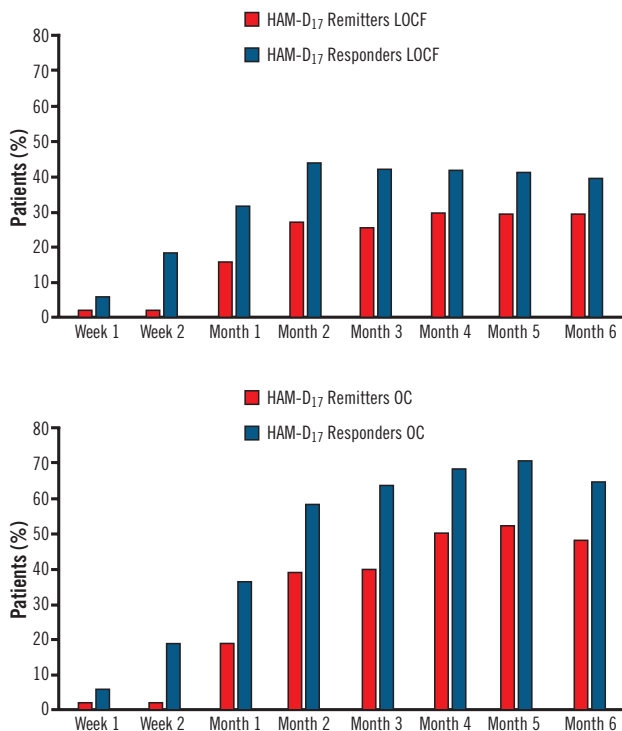
DISCUSSION

This study demonstrated that desvenlafaxine 100 and 200 mg/day was safe and well tolerated in individuals ≥ 65 years of age with MDD. Desvenlafaxine treatment was associated

with improvement in measures of depression and functional impairment that were sustained for up to 6 months. These findings are in agreement with previous multicenter, randomized, placebo-controlled trials that showed the safety and efficacy of desvenlafaxine 50, 100, 200, and 400 mg/day in the treatment of MDD.¹⁵⁻¹⁸ However, unlike this study, these were short-term (8-week) studies in adults of all ages. The current study expands upon the findings of previous short-term studies to establish the safety and sustained efficacy of desvenlafaxine over longer-term treatment (ie, 6 months) in the elderly population.

Adverse events observed in this study were generally mild or moderate in severity and were those commonly associated with SNRIs. The overall incidence of adverse events in this study (92%) was comparable to rates of 84% to 93% observed in controlled trials in general-aged, adult populations.^{17,18}

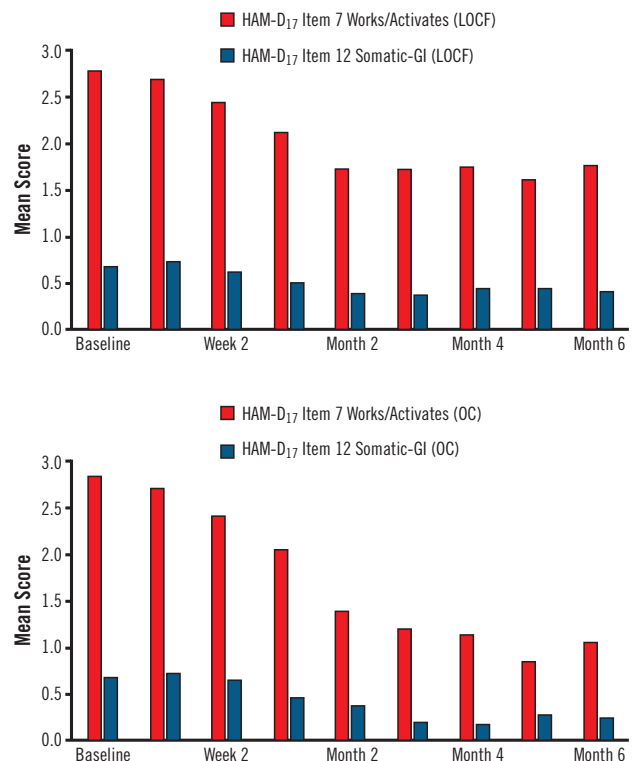
FIGURE 3
HAM-D₁₇ REMITTERS AND RESPONDERS USING LOCF (A) AND OC (B): ITT POPULATION



HAM-D₁₇=17-item Hamilton Rating Scale for Depression; LOCF=last observation carried forward; OC=observed cases; ITT=intent to treat.

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FIGURE 4
MEAN HAM-D₁₇ INDIVIDUAL ITEM SCORES: WORK/ACTIVITIES AND SOMATIC SYMPTOMS (GASTROINTESTINAL), LOCF (A) AND OC (B)



* $P < .001$ for item 7, final evaluation (LOCF) versus baseline using paired t-test.

† $P = .011$ for item 12, final evaluation (LOCF) versus baseline using paired t-test.

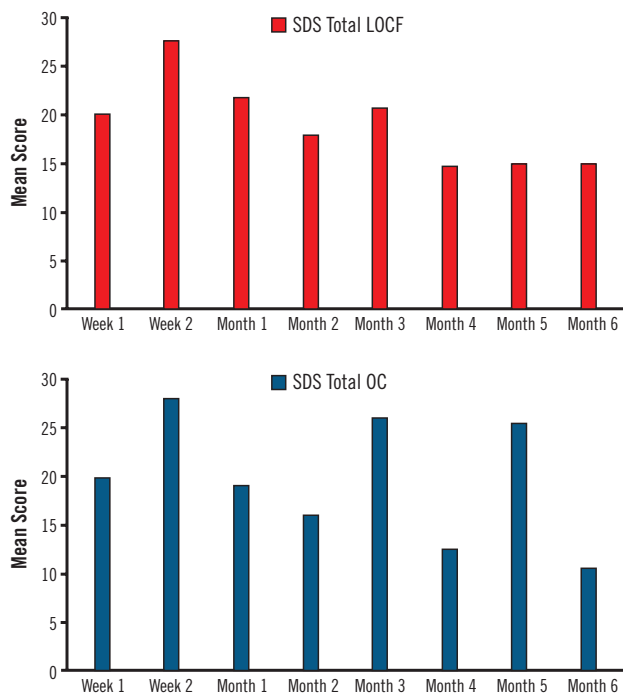
HAM-D₁₇=17-item Hamilton Rating Scale for Depression; LOCF=last observation carried forward; OC=observed cases.

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Most withdrawals due to adverse events in this study occurred during the first month of treatment. In addition, improvements from baseline at the end of the study in the HAM-D₁₇ insomnia and somatic symptoms-gastrointestinal individual items suggest that adverse events such as insomnia and nausea may occur less frequently with continued desvenlafaxine treatment. A pattern of decreasing incidence of adverse events over time has been observed in controlled studies with desvenlafaxine treatment of MDD,^{17,18} as well as treatment with other antidepressants,²³⁻²⁵ in the general-age adult population.

Physical disability, cognitive impairment, and sleep abnormalities are common complaints of elderly individuals with MDD.^{1,3,7} These symptoms can substantially impair an individual's health-related QOL.^{8,9} The Centers for Medicare and Medicaid Services examined the correlation between depression and mortality by conducting a national, cross-sectional survey of 141,589 Medicare managed-care plan participants aged ≥65 years.²⁶ Results demonstrated that a positive response to the question, "In the past year, have you had ≥2 weeks during which you felt sad, blue, or depressed or felt a loss of interest

FIGURE 5
MEAN SHEEHAN DISABILITY SCALE SCORE, LOCF (A), AND OC (B)



* $P < .001$, final evaluation (LOCF) versus baseline using paired t-test.

LOCF=last observation carried forward; OC=observed cases; SDS=Sheehan Disability Scale.

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or pleasure in things that you usually cared about or enjoyed?" was an independent health risk factor that increased the odds of death by 30% at follow-up. The current study demonstrates the significant improvement in psychosocial functioning, as measured by SDS total scores ($P < .001$ versus baseline at month 6), and substantial improvement in mean scores on individual domains of family life/home, social life, and work that resulted from treatment with desvenlafaxine. These findings suggest that the benefits of desvenlafaxine treatment may extend beyond relief of depressive symptoms and improve overall functional impairment in elderly patients with MDD.

Like other open-label antidepressant trials, some aspects of the study design limit the broader application of the results. The lack of control or comparator group does not allow the comparison of the efficacy and safety of desvenlafaxine versus placebo or other antidepressant treatment. The patient selection criteria excluded patients with substance abuse and significant comorbid psychiatric and medical illness, a patient population that may not accurately represent the general population of patients with MDD. This study also was limited by its small patient population. Furthermore, inclusion of the desvenlafaxine 200 mg/day dose may have contributed to the high withdrawal rate due to adverse events (35%) observed in the study. This study was designed prior to studies demonstrating the efficacy of the 50 mg/day dose, and although clinical studies have demonstrated the efficacy of desvenlafaxine 50 to 400 mg/day, no additional efficacy benefit has been observed for doses >50 mg/day.¹⁴ Thus, the doses of desvenlafaxine used in this study are higher than the current recommended therapeutic dose of 50 mg/day.

CONCLUSION

Desvenlafaxine is an SNRI approved for the treatment of MDD,¹¹⁻¹⁴ and multiple clinical studies have reported the safety and efficacy of desvenlafaxine 50, 100, 200, and 400 mg/day for the treatment of MDD.¹⁵⁻¹⁸ Results from this 6-month, multicenter, open-label study add to these studies and demonstrate that desvenlafaxine is safe and well tolerated, and sustains improvement in symptoms of depression in elderly patients ≥65 years of age with MDD. In addition, improvements in the individual HAM-D₁₇ items and SDS total scores suggest that the benefits of desvenlafaxine treatment may exceed improvement of depressive symptoms and reduce functional impairment in this elderly patient population. **PP**

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An Expert Panel Review of Clinical Challenges in Primary Care

L-Methylfolate, Methylcobalamine, and N-Acetylcysteine in the Treatment of Alzheimer's Disease Related Cognitive Decline

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