Speed of Improvement in Symptoms of Depression With Desvenlafaxine 50 mg and 100 mg Compared With Placebo in Patients With Major Depressive Disorder

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Abstract:
Purpose/Background: This post hoc analysis examined the time point at which clinically significant improvement in major depressive disorder (MDD) symptoms occurs with desvenlafaxine versus placebo.

Methods: Data were pooled from 9 short-term, double-blind, placebo-controlled studies in adults with MDD randomly assigned to desvenlafaxine 50 mg/d, 100 mg/d, or placebo. A mixed-effects model for repeated-measures analysis of change from baseline score was used to determine the time point at which desvenlafaxine treatment groups separated from placebo on the 17-item Hamilton Rating Scale for Depression and psychosocial outcomes. The association between early improvement and week 8 outcomes was examined using logistic regression analyses. Time to remission for patients with early improvement versus without early improvement was assessed using Kaplan-Meier techniques. Comparisons between groups performed with log-rank tests.

Results: In the intent-to-treat population (N = 4279 patients: desvenlafaxine 50 mg/d, n = 1714; desvenlafaxine 100 mg/d, n = 870; placebo, n = 1695), a statistically significant improvement on the 17-item Hamilton Rating Scale for Depression was observed with desvenlafaxine 50 mg/d at week 1 (P = 0.0129) and with desvenlafaxine 100 mg/d at week 2 (P = 0.0002) versus placebo. Early improvement was a significant predictor of later remission. Treatment assignment, baseline depression scale scores, and race were significantly associated with probability of early improvement. On several measures of depressive symptoms and function, desvenlafaxine 50 mg/d and 100 mg/d separated from placebo as early as week 1 and no later than week 4 in patients with MDD.

Implications/Conclusions: These findings suggest that clinicians may be able to use depression rating scale scores early in treatment as a guide to inform treatment optimization.

Key Words: desvenlafaxine, early improvement, major depressive disorder, time to remission

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Major depressive disorder (MDD) is a chronic and recurrent condition, with periods of partial or full remission interspersed with periods of clinical relapse. The ultimate treatment goal is remission, but multiple treatment trials may be required before remission is achieved. In the Sequenced Treatment Alternatives to Relieve Depression trial, for example, only 32.9% of patients achieved remission in their first treatment step. When patients do not achieve remission after an adequate antidepressant trial, the clinician must consider changes to treatment, such as increasing the dose, switching to a different antidepressant, or incorporating an adjunctive treatment. This decision should be made as rapidly as possible, as delays in effective MDD treatment are associated with poorer treatment outcomes and an earlier treatment switch is associated with a greater likelihood of a return to normal functioning.

Treatment guidelines recommend an antidepressant trial of up to 4 weeks or longer before considering a change in treatment. However, numerous trials and meta-analyses of MDD have shown that improvement in depressive symptoms or functional impairment as early as week 1 or 2 of treatment is predictive of a positive longer-term outcome. Among patients who do not show early improvement, however, approximately 4% to 31% ultimately achieve remission with continued treatment. The findings from analyses of early improvement antidepressant treatment raise important questions for the clinician treating individual patients: When should I expect to see initial improvement in symptoms with this antidepressant treatment? Is early improvement in depressive symptoms predictive of the duration of treatment needed to achieve remission? Are certain patients more likely to be early improvers versus late improvers? To address these critical questions, we conducted a post hoc meta-analysis of data from 9 clinical trials of desvenlafaxine 50 and 100 mg/d in patients with MDD. The key objective of this post hoc analysis was to assess the time point at which a statistically significant improvement was observed in depressive symptoms during treatment with desvenlafaxine or placebo. Additional objectives were to (1) examine the association between early improvement in symptoms of depression and later efficacy outcomes, including time to remission and (2) to explore associations between clinical characteristics and early response to treatment.
METHODS

Data Set

Individual MDD patient data were pooled from 9 phases 3 and 4, short-term, fixed-dose desvenlafaxine studies (Supplemental Digital Content 1, Supplemental Table 1, http://links.lww.com/JCP/A475). These represent all of the available short-term studies in patients with MDD that contained fixed-dose desvenlafaxine treatment arms (50 and/or 100 mg/d) conducted by the sponsor (Pfizer Inc.). Six studies had sites only in the United States, and 1 study each was carried out in the United States and Canada (NCT00824291), in the United States and Japan (NCT00798707), and in Europe and South Africa (NCT00300378). Each study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and consistent with the Principles of Good Clinical Practice and applicable regulatory requirements in each participating country.

All studies included in the meta-analysis were of similar design. Seven studies were of 8 weeks in duration, 1 study totaled 10 weeks in duration but had a week 8 primary end point, and 1 study continued for 12 weeks. The primary efficacy outcome for each study was the change from baseline in the 17-item Hamilton Rating Scale for Depression (HAM-D17) total score at week 8, with the exception of 1 study (NCT00824291), in which the primary end point was change from baseline in the HAM-D17 at week 12.

Treatment

In all 9 studies, patients were randomly assigned to receive fixed doses of desvenlafaxine or placebo (or duloxetine 60 mg/d comparator in NCT00384033) in a double-blind manner. Only data from the placebo and desvenlafaxine 50- and 100-mg/d treatment arms were included in the current analysis, representing the recommended therapeutic dosage in the United States (Pristiq package insert, 2016). Patients who were randomly assigned to treatment with desvenlafaxine 50 mg/d received the 50-mg/d dose beginning on study day 1. Those who were randomly assigned to treatment with desvenlafaxine 100 mg/d received desvenlafaxine 50 mg/d on study days 1 through 7 and began treatment with desvenlafaxine 100 mg/d on study day 8, with the exception of 1 study (NCT0072774), in which patients in the desvenlafaxine 100-mg/d group received 100 mg/d beginning on study day 1 with no titration. During the taper period (days 1 through 7 following the double-blind treatment period), patients taking desvenlafaxine 50 mg/d tapered to placebo, and patients taking desvenlafaxine 100 mg/d tapered to 50 mg/d, with the exception of 1 study in which patients tapered from desvenlafaxine 100 mg/d to placebo.

Patients

Each study enrolled adult outpatients with a diagnosis of MDD based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition or Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision criteria and depressive symptoms for at least 30 days before the screening. A minimum baseline HAM-D17 total score of 20 was required for inclusion in 7 studies; a minimum baseline Montgomery-Åsberg Depression Rating Scale (MADRS) score of 25 was required in 2 studies. Six of the studies enrolled men and women 18 years or older (in 1 study, patients from Japan were ≥20 years of age); 2 studies enrolled men and women 18 to 75 years of age. One study (NCT00824291) enrolled gainfully employed patients with a Sheehan Disability Scale (SDS) total score 10 or greater at both the screening and baseline visits. One study (NCT01121484) enrolled perimenopausal and postmenopausal women 40 to 70 years of age. All patients provided written informed consent before enrollment.

Study exclusion criteria ensured participants were medically stable patients with a principal diagnosis of MDD (excluding bipolar and psychotic depression). Patients were excluded if they had a current psychoactive substance abuse or dependence or comorbid psychiatric disorders. Clinically important screening abnormalities on physical examinations, vital signs, and electrocardiograms were exclusionary.

Outcome Measures

This pooled analysis assessed change from baseline for several outcome measures including HAM-D17 total score (9 studies), MADRS total score (7 studies), Clinical Global Impression Scale–Severity (CGI-S) and Clinical Global Impression Scale–Improvement (CGI-I) scores (9 studies), SDS total score (8 studies), and World Health Organization 5-item Well-being Index (WHO-5) score (6 studies). Remission was defined as a HAM-D17 total score of 7 or less. Treatment response was defined as a 50% reduction from baseline in HAM-D17 total score.

Statistical Analysis

All statistical analyses were performed using SAS 9.2 (SAS Institute Inc; Cary, NC) and using the full analysis set, which included all patients who received at least 1 dose of study medication. Dose groups were based on the patients’ assigned dose; the analysis of desvenlafaxine 100 mg/d included all data from patients assigned to the 100-mg dose, including data collected while patients were taking 50 mg/d in the titration period.

To assess the time point at which desvenlafaxine treatment groups statistically separated from placebo, a mixed-effects model for repeated-measures analysis was performed on the change from baseline score for each efficacy outcome. The model included terms for study, treatment, visit, and interaction between treatment and visit (weeks 1–8) and the respective baseline score.

Logistic regression analyses were performed on pooled data to assess the association between early improvement and week 8 remission. If missing, the last observation postbaseline and prior to week 8 was imputed; although NCT01121484 and NCT00824291 had week 10 and/or week 12 assessments, these were not used. Early improvement was defined as change of 20% or greater from baseline at week 2 in HAM-D17 total score. Adjusted odds ratios (ORs) for patients with early improvement versus without early improvement were extracted from the logistic regression models and represented by treatment group using forest plots. The analysis was also performed based on treatment response at week 8.

Logistic regression analyses of the probability of early improvement on HAM-D17 on baseline covariates were performed to examine features that predict early improvement. The logistic regression models included terms for treatment group, baseline HAM-D17 total score, age, race, sex and body mass index, and study.

Time to event was assessed for patients with early improvement versus without early improvement using Kaplan-Meier survival techniques for HAM-D17 remission. Comparisons between patients with early improvement versus without early improvement were performed using log-rank tests. Cox regression analyses were performed for each time-to-event variable. Cox regression models included terms for study, treatment group, early improvement
FIGURE 1. Adjusted mean changes from baseline in HAM-D17 total scores during the course of the study for pooled data from 9 desvenlafaxine studies of patients with MDD. *P = 0.013 desvenlafaxine 50 mg/d versus placebo. †P < 0.001 desvenlafaxine 50 mg/d and desvenlafaxine 100 mg/d versus placebo. A mixed-effects model for repeated-measures analysis was used to calculate adjusted means with SEs and *P values.

(continued...)

RESULTS

Patients

The intent-to-treat population of this post hoc analysis of data pooled from 9 desvenlafaxine studies included 4279 patients (desvenlafaxine 50 mg/d, n = 1714; desvenlafaxine 100 mg/d, n = 870; placebo, n = 1695). Demographic and baseline characteristics for these patients are summarized in Supplemental Digital Content 2, Supplemental Table 2 (http://links.lww.com/JCP/A476).

Efficacy Outcomes

Statistically significant improvements in HAM-D17 total scores were observed as early as week 1 with desvenlafaxine 50 mg/d versus placebo (P = 0.0129) and week 2 with desvenlafaxine 100 mg/d versus placebo (P = 0.0002) (Fig. 1, Table 1). Statistically significant separation from placebo was maintained through week 8 for both doses of desvenlafaxine (P < 0.0001) after their respective initial separations.

Results for other efficacy outcomes were generally consistent with those for the HAM-D17 total score (Table 1). On the CGI-S, both desvenlafaxine doses separated from placebo at week 2, and on the SDS (8 studies), separation from placebo occurred at weeks 2 and 4 for desvenlafaxine 50 and 100 mg/d, respectively. The MADRS and WHO-5 were not administered at week 1 in any study. Pooled data from the 7 studies utilizing the MADRS showed that both doses of desvenlafaxine separated from placebo at week 2. For the WHO-5 (6 studies), statistical separation from placebo was observed for desvenlafaxine 50 mg/d at week 2 and for desvenlafaxine 100 mg/d at week 4. For all outcomes, adjusted mean differences between desvenlafaxine groups and placebo were statistically significant at all time points subsequent to the first statistical separation through week 8.

A total of 952 (55.6%) of 1712 patients treated with desvenlafaxine 50 mg/d and 478 (55.2%) of 866 patients treated with desvenlafaxine 100 mg/d had early improvement in depression symptoms (≥20% decrease from baseline in HAM-D17 total score at week 2) compared with 803 (47.5%) of 1690 placebo-treated patients. Early improvement significantly predicted later remission, favoring early improvers over patients without early improvement, regardless of treatment assignment; in all treatment groups, remission rates were higher for those with early improvement compared with those without early improvement (Table 2). Among patients treated with desvenlafaxine 50 and
100 mg/d who had at least 20% improvement from baseline at week 2, the ORs for achieving HAM-D17 remission at week 8 were 4.93 (95% CI, 3.81–6.38) and 4.71 (95% CI, 3.36–6.58), respectively, compared with patients with less than 20% improvement (placebo, 4.77 [95% CI, 3.64–6.25]; all \( P < 0.0001 \); Fig. 2). Numbers needed to treat for benefit, calculated based on HAM-D17 remission rates for desvenlafaxine dose groups versus placebo, were substantially lower among patients with early improvement compared with patients without early improvement (Table 2). Odds ratios for HAM-D17 response are shown in Supplemental Digital Content 3, Supplemental Fig. 1 (http://links.lww.com/JCP/A477).

Kaplan-Meier curves illustrate the time to HAM-D17 remission for early improvers versus those without early improvement for each treatment group separately (Fig. 3, A–C). Cox analysis determined that the median time to remission was statistically significantly shorter for early improvers (56 days for desvenlafaxine 50- and 100-mg/d groups, 59 days for placebo) compared with patients who did not achieve early improvement (desvenlafaxine 50 mg/d: hazard ratio [HR], 4.12 [\( P < 0.0001 \)]; desvenlafaxine 100 mg/d: HR, 3.93 [\( P < 0.0001 \)]; placebo: HR, 4.71 [\( P < 0.0001 \)]). Median time to remission could not be calculated for those without early improvement because there were not enough patients with remission in this subgroup. Results were similar for time to response (Supplemental Digital Content 4, Supplemental Fig. 2, http://links.lww.com/JCP/A478).

Treatment assignment was significantly associated with probability of early improvement in HAM-D17 total score. Patients who received desvenlafaxine 50 mg/d had a significantly greater chance of early improvement compared with those who received placebo (OR, 1.43 [95% CI, 1.24–1.65]; \( P < 0.0001 \)). Results for desvenlafaxine 100 mg/d versus placebo were similar (OR, 1.35 [95% CI, 1.12–1.62]; \( P = 0.002 \)). In addition, a statistically significant association was observed between baseline depression scale scores and probability of early improvement; the OR for probability of early improvement as a function of continuous baseline HAM-D17 total score was 0.98 (95% CI, 0.95–1.0; \( P = 0.03 \)), with lower baseline depression scale scores associated with greater probability of early improvement. Race (ie, Asian, black, or other) was the only baseline demographic characteristic assessed for which there was a statistically significant association with probability of early improvement. Specifically, the OR for black versus white was 0.82 (95% CI, 0.68–0.99; \( P = 0.04 \)); for “other” versus white, the OR was 1.62 (95% CI, 1.14–2.32; \( P = 0.008 \)); and for Asian versus white, the OR was 0.86 (95% CI, 0.63–1.19; \( P = 0.37 \)). There was no significant association between age, sex, or body mass index and probability of early improvement.

**DISCUSSION**

This post hoc meta-analysis of data from 9 short-term, fixed-dose clinical trials of desvenlafaxine addressed important questions

### TABLE 2. Early Improvement* as a Predictor of Remission at Week 8

| HAM-D17 Remission Rates | OR1 (95 CI%), Early Improvement vs No Early Improvement | \( P \), Early Improvement vs No Early Improvement |
|-------------------------|-----------------------------------------------------|---------------------------------------------|
|                         | Patients With Early Improvement | Patients Without Early Improvement |
|                         | Percentage | NNT | Percentage | NNT | OR† | 95 CI% | \( P \) |
| Placebo                 | 33.1% | 9.5% | 9.5% | 4.77 (3.64–6.25) | \( <0.0001 \) |
| Desvenlafaxine 50 mg/d  | 40.2% | 15 | 11.7% | 46 | 4.93 (3.81–6.38) | \( <0.0001 \) |
| Desvenlafaxine 100 mg/d | 44.4% | 9 | 15.0% | 19 | 4.71 (3.36–6.58) | \( <0.0001 \) |

A logistic regression model with terms for treatment, early improvement in HAM-D17, study, and interaction between treatment and early improvement was used to calculate OR, 95% CI, and \( P \) values.

*Decrease of 20% from baseline in HAM-D17 total score at week 2.

†Odds ratios comparing the odds of remission for patients with HAM-D17 improvement at week 2 with the odds of remission for those who did not improve at week 2.

NNT indicates number needed to treat.
Title: Speed of Desvenlafaxine Response

Abstract:

Treatment guidelines state that antidepressant medications should be given an “adequate trial,” which is generally considered to be use of an adequate antidepressant dose for 4 to 8 weeks in duration.2 If improvement in symptoms (commonly defined in clinical trials as ≥20% change from baseline in depression scale scores3) is not observed at 2 to 4 weeks, a dose increase is recommended.4 Meta-analyses have shown that the onset of antidepressant effect can occur as early as 1 to 2 weeks of treatment,32,33 and the current analysis indicates that the mean time course of treatment effect with desvenlafaxine 50 and 100 mg/d in a clinical trial population is consistent with that of other antidepressant drugs examined. In meta-analyses of data from clinical trials of duloxetine, HAM-D17 total scores separated from placebo at week 2,32 and analyses of HAM-D17 Maier subscale showed a significant difference from placebo at week 1 for duloxetine and escitalopram.32,33 In an analysis of 20 selective serotonin reuptake inhibitor trials, a significant difference versus placebo on various rating scale scores was observed at week 1.34 Although knowledge of mean time course of response to a specific antidepressant treatment may be useful in managing patient expectations and monitoring early improvement, it is important to bear in mind that patients will show individual patterns of response. A 2-week time frame is commonly used for assessing early improvement in clinical trial populations, but a substantial number of patients who do not meet criteria for early improvement at week 2 may nonetheless go on to achieve remission with no change in treatment.35

In the current analysis, early improvement in symptoms of depression (≥20% reduction from baseline in HAM-D17 total score at week 2) was significantly associated with both a greater probability of remission at week 8 and shorter time to remission. Patients who had a 20% or greater reduction in depressive symptoms (as measured by HAM-D17 total score) after 2 weeks of treatment, regardless of treatment assignment, had approximately 5 times greater odds of achieving remission at week 8 compared with patients who did not show 20% improvement at week 2. Previously published studies for antidepressant treatment of MDD have reported that patients with early improvement on the HAM-D17, MADRS, or Beck Depression Inventory are more likely than those without early improvement to be responders or remitters later in treatment.13,14 In the current analysis, early improvement was predictive of later treatment outcome among patients treated with either active treatment or placebo. Few previously published analyses of the association between early improvement and later depression outcomes have included placebo groups. In a meta-analysis of 41 antidepressant trials, the positive predictive value of early improvement was similar for predicting remission in placebo and active treatment groups, but for predicting response, positive predictive value seemed to be lower for the placebo group.9 In the current analysis, greater numbers of desvenlafaxine-treated patients versus placebo-treated patients met the early improvement threshold, and numerically greater proportions of early improvers treated with desvenlafaxine versus placebo went on to achieve response and remission. However, the odds of remission after early improvement did not differ significantly between treatment groups. The association between early improvement and time to response has also been previously examined, and—as in this analysis—early improvement in depressive symptoms was associated with shorter time to response.10 This analysis extends that finding to demonstrate that early improvement significantly predicts time to remission.

To our knowledge, this is the first analysis of data from randomized controlled trials that examined the clinical and demographic features that might be associated with early improvement in depressive symptoms. In an open-label study that assessed relationships between brain-derived neurotrophic factor (BDNF) concentrations and response to duloxetine treatment, higher baseline BDNF concentrations were observed in patients who showed improvement in symptoms at week 2, although BDNF concentrations at baseline did not differ in eventual remitters versus nonremitters.13 The influence of baseline demographic or clinical characteristics was not examined in that trial. In a naturalistic study of female inpatients receiving cognitive-behavioral therapy, most of whom also received psychoactive medications, early improvers were older than those without early improvement and were less likely to have comorbid disorders.14 However, after controlling for age, severity of depressive symptoms, and...
treatment duration, early improvement in depressive symptoms predicted remission regardless of whether patients had, or did not have, medical comorbidities. In the current analysis, other than assignment to desvenlafaxine treatment, the only baseline factors that were predictors of early response to treatment were baseline depression scale scores and race.

The main limitations of this analysis are related to its post hoc nature and the fact that the studies included were not designed to assess the speed of improvement in depressive symptoms. Indeed, these findings are limited by the timing of the assessments because the earliest time point available for assessment of improvement was 1 week. Furthermore, the value of the week 1 assessment for the desvenlafaxine 100-mg/d group was limited by the use of the 50-mg titration dose during the first week. Although the patients assigned to 100 mg/d may not have received the full 100-mg/d dose before the week 1 assessment, however, they did receive the 50-mg dose over that period, which showed statistical separation at week 1. In addition, although the studies analyzed were similar in design, there were differences among them in planned treatment duration and population characteristics. The examination of predictors of early improvement was limited to the inclusion of only those demographic and clinical characteristics that were collected in the pooled studies and thus available for analysis. Finally, inclusion and exclusion criteria in all studies were designed to select a patient population that was generally healthy with a primary diagnosis of MDD. Given that clinically significant comorbid conditions are common in patients with MDD,56 these results may not generalize to a wider MDD patient population.

CONCLUSIONS

Statistically significant improvements from baseline in depressive symptoms were observed as early as 1 week after treatment initiation with desvenlafaxine 50 or 100 mg/d versus placebo. Early improvement in HAM-D17 total score at week 2 predicted remission at week 8 and was associated with a shorter time to remission. In addition, lower baseline depression scale scores were associated with a significantly greater probability of early improvement. These findings suggest that clinicians may be able to use depression rating scale scores early in treatment as a guide to inform later treatment with desvenlafaxine.

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