Early identification of likely responders to an antidepressant strategy may guide clinical treatment decisions, minimize the use of ineffective treatments, and ultimately improve adherence and treatment outcomes in depressed patients. 

**Methods**
Data were pooled from double-blind, fixed-dose studies in adult patients with a diagnosis of MDD based on DSM-IV or DSM-IV-TR. Patients were randomly assigned to desvenlafaxine or placebo. Primary end points were early improvement from baseline (weeks 2, 3, and 4) and was statistically significant for both (\(P < 0.0001\)).

**Results:**
A negative predictive value (those who did not remit at week 8 nor improve at week 3/those who did not remit at week 8) was significantly higher than those who did not show a positive change from baseline HAM-D17 at week 2 (50.2% vs 30.5%, \(P < 0.0001\)).

**Conclusions:**
Values at these early time points may have a clinically meaningful predictive role in determining outcomes with this antidepressant agent.

**Results:**
Analysis of the holdout sample showed comparable predictive performance. The highest PPVs (75% at week 2; 79% at week 3) for week 8 treatment success were associated with the minimal acceptable improvement: \(≥45\%\) decrease from baseline HAM-D17.

**Conclusions:**
Later treatment success could be early identified (week 8) with high predictability across the definitions; multivariate analysis with adjustments for confounders was conducted, showing that early identification remained a strong predictor of treatment success with these adjustments.

**Results:**
A total of 724 patients who were randomly assigned to treatment, took at least 1 dose of study drug, and had a baseline HAM-D ≤ 32 were included in the analysis for evaluating efficacy and tolerability of the 2 treatment groups (desvenlafaxine 10 mg/d and placebo).

**Conclusions:**
Later identification of likely responders to observed antidepressant strategy may guide clinical treatment decisions, minimize the use of ineffective treatments, and ultimately improve adherence and treatment outcomes in depressed patients.

**References:**

**Figure 1:**
- Rates of Treatment Success at Week 8 According to Early Improvement With Placebo

**Table 1:**
Baseline Demographics

**Table 2:**
Baseline Demographics

**Table 3:**
Response and Remission at End Point (Week 8, LOCF) by Age Groups

**Table 4:**
Operating Characteristics of Early Improvement in HAM-D 17 to Predict Later Treatment Success

**Table 5:**
Multivariate Logistic Regression Predicting Treatment Success at End Point

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**References:**

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**Disclosures:**
Claudio N. Soares, History and/or similar conflicts: Pfizer, Lundbeck, Astellas, Bristol-Myers-Squibb, Merck Pharmacueticals, Research Grants: 01 grants, Pfizer, Cymbalta. Speaker honoraria from other funds: Pfizer, Lundbeck, Astellas. Developed educational lectures/advisory boards: Pfizer, Astellas.
Rana S. Fayyad, Cedric O’Gorman, and Christine J. Guico-Pabia are Pfizer employees.
Predictors of Response and Remission With Desvenlafaxine 50 mg/d: A Pooled Analysis of Randomized, Placebo-Controlled Studies in Patients With Major Depressive Disorder

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McMaster University & St. Joseph’s Healthcare, Hamilton, Ontario; Ontario; Toronto, New York, NY; Pfizer Inc, Collegeville, PA

Objectives
The primary aim of this post hoc pooled analysis was to determine whether early improvement during treatment (±) in the model for patients with major depressive disorder (MDD). In this study, data on age, gender, baseline depressive and functional measures, duration of current episode, as well as improvements of depressive scores at earlier time points were used for predicting minimally acceptable improvement at end point, according to the following definitions:

- Response (≥50% decrease in baseline HAM-D score, 12 secondary efficacy variables included Clinical Global Impressions–Improvement and –Severity of Illness, Sheehan Disability Scale, duration of current episode, and early HAM-D17 improvements.
- Remission (≥65% decrease in baseline HAM-D score).

Methods

Data were pooled from 6 multicenter randomized, double-blind, placebo-controlled fixed-dose studies of desvenlafaxine 50 mg/d or placebo. Five of the 6 studies included sites in the United States, with additional sites in Japan (1 study) and Canada (1 study). One study was conducted at sites in Europe and South Africa.

Results

Table 1: Treatment Success Definition: Response (≥50% decrease in baseline HAM-D17) vs Placebo

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients (%)</th>
<th>Placebo 20.0</th>
<th>Placebo 21.4</th>
<th>Placebo 22.4</th>
<th>Placebo 23.4</th>
<th>Placebo 24.4</th>
<th>Placebo 25.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desvenlafaxine 50 mg/d</td>
<td>39.1</td>
<td>72.2%</td>
<td>72.0%</td>
<td>54.9%</td>
<td>84.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>42.3</td>
<td>75.7%</td>
<td>76.1%</td>
<td>51.1%</td>
<td>90.4%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Treatment Success Definition: Substantial Response (≥65% decrease in baseline HAM-D17) vs Placebo

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients (%)</th>
<th>Placebo 20.0</th>
<th>Placebo 21.4</th>
<th>Placebo 22.4</th>
<th>Placebo 23.4</th>
<th>Placebo 24.4</th>
<th>Placebo 25.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desvenlafaxine 50 mg/d</td>
<td>36.2</td>
<td>70.3%</td>
<td>70.6%</td>
<td>53.8%</td>
<td>83.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>45.1</td>
<td>74.8%</td>
<td>74.6%</td>
<td>73.7%</td>
<td>73.7%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Odds Ratio and P Value for Response (≥50% decrease in baseline HAM-D17) vs Placebo

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Odds Ratio</th>
<th>P Value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desvenlafaxine 50 mg/d</td>
<td>9.37</td>
<td>&lt;0.0001 (7.23, 12.15)</td>
</tr>
</tbody>
</table>

Figure 1: Data were presented at the Annual Meeting of the New Clinical Drug Evaluation Unit, 2009;70(3):344-353. A double-blind, randomized, placebo-controlled study assessing the efficacy and tolerability of desvenlafaxine 10 and 50 mg/d in adult outpatients with major depressive disorder (MDD) was reported by the investigators. The study included 1067 patients with MDD. The results showed that desvenlafaxine 50 mg/d was more effective than placebo in reducing symptoms of depression as measured by the Hamilton Depression Rating Scale (HAM-D17) at week 8. A logistic regression model was used to examine the predictive value on response (defined as ≥50% improvement in HAM-D17 score) and remission (defined as ≥65% improvement in HAM-D17 score) compared with placebo.

Discussion

The study results indicated that early improvement in HAM-D17 scores during treatment was a strong predictor of later treatment success. The odds of response were significantly higher in the desvenlafaxine group compared to placebo (OR=9.37 [95% CI: 7.23, 12.15], p<0.0001). Similarly, the odds of remission were also significantly higher in the desvenlafaxine group (OR=14.7 [9.39, 23.01], p<0.0001).

Conclusion

Desvenlafaxine 50 mg/d was found to be a more effective treatment for major depressive disorder compared to placebo. Early improvement in HAM-D17 scores during treatment was a strong predictor of response and remission.

References

1. ECDEU Assessment Manual for Psychopharmacology.
2. Investigators. A double-blind, randomized, placebo-controlled study assessing the efficacy and tolerability of desvenlafaxine 10 and 50 mg/d in adult outpatients with major depressive disorder (MDD). Presented at the Annual Meeting of the New Clinical Drug Evaluation Unit, 2009;70(3):344-353.
3. Investigators. A double-blind, randomized, placebo-controlled study assessing the efficacy and tolerability of desvenlafaxine 10 and 50 mg/d in adult outpatients with major depressive disorder (MDD). Presented at the Annual Meeting of the New Clinical Drug Evaluation Unit, 2009;70(3):344-353.
4. Investigators. A double-blind, randomized, placebo-controlled study assessing the efficacy and tolerability of desvenlafaxine 10 and 50 mg/d in adult outpatients with major depressive disorder (MDD). Presented at the Annual Meeting of the New Clinical Drug Evaluation Unit, 2009;70(3):344-353.
Abstract

**Background:** Early identification of likely responders to an antidepressant strategy may guide clinical treatment decisions, minimize the use of ineffective treatments, and ultimately improve adherence and treatment outcomes for patients with major depressive disorder (MDD). In this study, data on age, gender, baseline depressive and functional measures, duration of current episode, as well as improvements of depressive scores at earlier time points were examined to identify possible relevant predictors of treatment outcomes at 8 weeks among patients treated with desvenlafaxine 50 mg/d or placebo.

**Methods:** Data were pooled from double-blind, fixed-dose studies in adult patients with a diagnosis of MDD based on DSM-IV or DSM-IV-TR. Patients were randomly assigned to desvenlafaxine or placebo. Primary end point was change in the 17-item Hamilton Rating Scale for Depression (HAM-D17) scores from baseline to week 8 (or last observation carried forward [LOCF]). A logistic regression model was used to examine the predictive value on response (defined as ≥50% improvement in HAM-D17 scores) or remission of depression (defined as an achievement of HAM-D17 scores ≤7) of the following variables: age, gender, baseline HAM-D17 total scores, baseline Sheehan Disability Scale (SDS) total scores, duration of current episode, and early HAM-D17 improvements (weeks 2, 3, and 4).

**Results:** Desvenlafaxine led to significant improvement of depression (HAM-D17 scores from baseline to study end point, response and remission) compared with placebo (P<0.0001) and was statistically significant for both the youngest (≤40 years of age) and the oldest (≥55 years of age) subgroups. For the 41 to 54 years age group, desvenlafaxine also produced significant improvement for both response and improvement in HAM-D17 scores, but not for remission. An equal or greater than 20% improvement on HAM-D17 scores at week 3 strongly predicted response (OR=9.37 [7.23, 12.15]) and remission (OR=14.7 [9.39, 23.01]) of depression at week 8 (both P<0.0001). A positive predictive value (number of patients remitted at week 8 and with 20% improvement at week 3/those improved at week 3) indicated that 3/6% of patients that improved at week 3 also remitted at week 8. In addition, a negative predictive value (those who did not remit at week 8 nor improve at week 3/those who did not remit at week 8) showed that 96% of the patients who did not improve at week 3 also did not remit at week 8.

**Conclusions:** Clinical observations of patients’ early response to the starting/recommended dose of desvenlafaxine (50 mg/d) may have a clinical value in predicting further outcomes with this antidepressant agent and guide patient management.

Background

- Early identification of likely responders to an antidepressant strategy may guide clinical treatment decisions, minimize the use of ineffective treatments, and ultimately improve adherence and treatment outcomes for patients with MDD.
- The presence or absence of early symptomatic improvement during the first few weeks of treatment has been shown to predict later response or remission with some antidepressants.
- In this post hoc pooled analysis of placebo-controlled studies in patients with MDD treated with 50 mg/d of desvenlafaxine (administered as desvenlafaxine succinate), various baseline characteristics and improvement of depressive scores at early time points were examined to identify possible relevant predictors of treatment outcomes at 8 weeks among patients treated with desvenlafaxine 50 mg/d or placebo.

Methods

**Pooled Data Set**

- Data were pooled from 6 multicenter randomized, double-blind, placebo-controlled fixed-dose studies of desvenlafaxine 50 mg/d in MDD.
  - At the time this analysis was conducted, the study set represented all available short-term studies in MDD conducted by the sponsor company (Pfizer Inc) that included a fixed-dose desvenlafaxine 50-mg treatment arm (the recommended therapeutic dose for MDD) and weekly efficacy assessments in the first month of the study (ie, weeks 1, 2, 3, and 4). One additional study was excluded because it focused on a specific subgroup of perimenopausal and postmenopausal women.
  - Five of the 6 studies included sites in the United States, with additional sites in Japan (1 study) and Canada (1 study). One study was conducted at sites in Europe and South Africa.
- As shown in Table 1, the 6 studies included in the analysis were of similar design. In summary:
  - All studies enrolled adult outpatients with a diagnosis of MDD based on criteria from the DSM-IV or the DSM-IV-TR for at least 30 days. Exclusion criteria were designed to select a sample of medically stable patients with a principal diagnosis of MDD (excluding bipolar and psychotic depression).
  - Patients were randomly assigned to receive placebo or a fixed dose of desvenlafaxine 10, 25, 50, or 100 mg/d (or duloxetine 60 mg/d in 1 trial); each trial included a 50-mg/d treatment arm.
  - Most studies were 8 weeks in duration; 1 study continued for 12 weeks.
  - The primary efficacy end point for each individual study was change from baseline in the HAM-D17 total score, secondary efficacy variables included Clinical Global Impressions—Improvement and —Severity of Illness scales, Montgomery-Asberg Depression Rating Scale, SDS, and WHO 5-item Well-Being Index.
- Safety and tolerability were assessed throughout the studies.

Table 1. Studies Included in Pooled Analysis

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Study Objective</th>
<th>Study Design</th>
<th>Treatment Arms</th>
<th>Study N</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>332*</td>
<td>Efficacy, safety in MDD</td>
<td>Randomized, double-blind, placebo-controlled, fixed dose</td>
<td>Desvenlafaxine 50 mg/d or placebo</td>
<td>451</td>
<td>8 weeks</td>
</tr>
<tr>
<td>333*</td>
<td>Efficacy, safety in MDD</td>
<td>Randomized, double-blind, placebo-controlled, fixed dose</td>
<td>Desvenlafaxine 50 mg/d or placebo</td>
<td>485</td>
<td>8 weeks</td>
</tr>
<tr>
<td>335*</td>
<td>Efficacy, safety in MDD</td>
<td>Randomized, double-blind, placebo-controlled, fixed dose</td>
<td>Desvenlafaxine 50 mg/d or placebo</td>
<td>616</td>
<td>8 weeks</td>
</tr>
<tr>
<td>335P</td>
<td>Efficacy, safety in MDD</td>
<td>Randomized, double-blind, placebo-controlled, fixed dose</td>
<td>Desvenlafaxine 50 mg/d or placebo</td>
<td>699</td>
<td>8 weeks</td>
</tr>
<tr>
<td>336P</td>
<td>Efficacy, safety in MDD</td>
<td>Randomized, double-blind, placebo-controlled, fixed dose</td>
<td>Desvenlafaxine 50 mg/d or placebo</td>
<td>673</td>
<td>8 weeks</td>
</tr>
<tr>
<td>4415P</td>
<td>Efficacy, safety in MDD or functional outcomes in employed patients</td>
<td>Randomized, double-blind, placebo-controlled, fixed dose</td>
<td>Desvenlafaxine 50 mg/d or placebo</td>
<td>427</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

*Note: This number (451) is of the safety population (all randomized patients who took at least 1 dose of study medication).
Objectives
- The primary aim of this post hoc pooled analysis was to determine whether early improvement during treatment with desvenlafaxine or placebo predicts later treatment success at study end point (8 weeks)
- Secondary aims included evaluation of other baseline predictors

Statistical Analysis
- Analyses were performed on the intent-to-treat (ITT) population, defined as all subjects who were randomly assigned to treatment, who had a baseline primary efficacy evaluation, took at least 1 dose of double-blind study drug, and had at least 1 primary efficacy evaluation after the first dose of double-blind study drug
- Changes from baseline in HAM-D, were analyzed using analysis of covariance with study, baseline, and treatment (s) in the model
- Response and remission rates were analyzed using logistic regression with study, baseline, and treatment (s) in the model
- Logistic regression (for both treatments combined and by treatment) was performed to evaluate predictors of various levels of treatment success at end point, according to the following definitions:
  - Minimal acceptable improvement: ≥45% decrease from baseline HAM-D
  - Response: ≥50% decrease from baseline HAM-D
  - Substantial response: ≥65% decrease from baseline HAM-D
  - Remission: HAM-D, total score ≤7
- Early improvement in depression symptoms (week 2 or 3) was evaluated as a predictor of later treatment success
- Based on prior published analyses, an arbitrary threshold of 20% improvement was first evaluated as a predictor of end point response/remission (using week 3 data)
- Receiver operating characteristic (ROC) analysis was subsequently conducted to determine the thresholds of improvement (% change from baseline HAM-D) based on the optimal operating point (OOP) at the week 2 and week 3 time points that predicted treatment success at end point (as defined above) for the overall population and by treatment group
- Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) at each of these thresholds were computed
- Odds ratios were computed from the logistic regression results to assess the predictability of week 2 or 3 percent change in HAM-D on treatment success; adjustments for baseline variables were added to the model to assess whether week 2 and week 3 percent change in HAM-D, remained a strong predictor of treatment success with these adjustments
- In addition to early improvement, the following baseline characteristics were included in the model as potential predictors of treatment success: treatment, age category (18-40; 41-54; ≥55), gender, weight, duration of current episode, baseline HAM-D score, and baseline SDS score (total and work, social, and family domains)
- All end point efficacy analyses were performed at week 8 using the LOCF method to account for missing data

Results
- A total of 2274 patients who were randomly assigned to treatment, took at least 1 dose of study drug, and had a baseline and at least 1 on-treatment primary efficacy evaluation met the criteria for anxious depression and were included in the primary analysis (desvenlafaxine 50 mg, n=1207; placebo, n=1067)
- Baseline characteristics were consistent between pooled desvenlafaxine 50-mg and placebo groups (Table 2)

Table 2. Baseline Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Desvenlafaxine 50 mg (n=1207)</th>
<th>Placebo (n=1067)</th>
<th>Total (n=2274)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>47.1</td>
<td>47.8</td>
<td>47.5</td>
</tr>
<tr>
<td>Range</td>
<td>18-88</td>
<td>18-85</td>
<td>18-85</td>
</tr>
<tr>
<td>Sex, % (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>443 (36.7)</td>
<td>410 (38.4)</td>
<td>853 (37.8)</td>
</tr>
<tr>
<td>Female</td>
<td>764 (63.3)</td>
<td>697 (61.6)</td>
<td>1461 (62.2)</td>
</tr>
<tr>
<td>Race, % (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>863 (71.5)</td>
<td>740 (69.4)</td>
<td>1603 (71.5)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>174 (14.4)</td>
<td>149 (14.0)</td>
<td>323 (14.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>121 (9.9)</td>
<td>108 (10.1)</td>
<td>229 (10.1)</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>4 (0.3)</td>
<td>3 (0.3)</td>
<td>7 (0.3)</td>
</tr>
<tr>
<td>Other Hispanic or Other Pacific Islander</td>
<td>0</td>
<td>3 (0.3)</td>
<td>3 (0.3)</td>
</tr>
<tr>
<td>Other</td>
<td>36 (3.0)</td>
<td>39 (3.7)</td>
<td>75 (3.3)</td>
</tr>
<tr>
<td>Duration of current episode, % (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to &lt;6 months</td>
<td>575 (47.8)</td>
<td>428 (40.1)</td>
<td>995 (43.8)</td>
</tr>
<tr>
<td>6 to &lt;12 months</td>
<td>262 (21.7)</td>
<td>258 (24.0)</td>
<td>520 (22.9)</td>
</tr>
<tr>
<td>12 to &lt;24 months</td>
<td>197 (16.5)</td>
<td>187 (17.5)</td>
<td>384 (16.9)</td>
</tr>
<tr>
<td>24 to &lt;36 months</td>
<td>129 (10.8)</td>
<td>121 (11.3)</td>
<td>249 (11.0)</td>
</tr>
<tr>
<td>36 to 132 months</td>
<td>97 (8.1)</td>
<td>98 (9.2)</td>
<td>196 (8.6)</td>
</tr>
<tr>
<td>≥132 months</td>
<td>45 (3.7)</td>
<td>45 (4.2)</td>
<td>90 (3.9)</td>
</tr>
<tr>
<td>Baseline HAM-D, total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>23.55 (12.16)</td>
<td>23.23 (11.32)</td>
<td>23.17 (12.37)</td>
</tr>
<tr>
<td>Baseline CGI-I, % (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal, mild at 8</td>
<td>2 (0.1)</td>
<td>3 (0.3)</td>
<td>5 (0.2)</td>
</tr>
<tr>
<td>Mildly Ill</td>
<td>8 (0.7)</td>
<td>7 (0.7)</td>
<td>15 (0.7)</td>
</tr>
<tr>
<td>Moderately Ill</td>
<td>528 (43.7)</td>
<td>423 (40.0)</td>
<td>951 (41.8)</td>
</tr>
<tr>
<td>Markedly Ill</td>
<td>148 (12.3)</td>
<td>148 (13.9)</td>
<td>300 (13.1)</td>
</tr>
<tr>
<td>Severely Ill</td>
<td>23 (1.9)</td>
<td>18 (1.7)</td>
<td>41 (1.8)</td>
</tr>
</tbody>
</table>

At the final evaluation (week 8, LOCF), desvenlafaxine treatment was associated with significantly greater improvement of depression on the HAM-D, (primary efficacy evaluation in the individual studies) compared with placebo for the total population (P=0.0001), the 18-40 age group (P=0.0001), and the 41-54 age group (P=0.01); results were generally similar when the analysis was replicated including the one study excluded from this analysis (which enrolled only perimenopausal and postmenopausal women) with the exception that statistical significance also was demonstrated in the age group category of patients 55 and older
- Table 3 summarizes the response and remission outcomes at end point for the various age groups and the total population

Table 3. Response and Remission at End Point (Week 8, LOCF) by Age Groups*

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Treatment Groups (%)</th>
<th>HAM-D, Response</th>
<th>HAM-D, Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-40</td>
<td>Desvenlafaxine 50 mg (N=1207)</td>
<td>45.9</td>
<td>19.0</td>
</tr>
<tr>
<td></td>
<td>Placebo (N=1067)</td>
<td>36.0</td>
<td>15.1</td>
</tr>
<tr>
<td>41-54</td>
<td>Desvenlafaxine 50 mg (N=1207)</td>
<td>53.0</td>
<td>25.5</td>
</tr>
<tr>
<td></td>
<td>Placebo (N=1067)</td>
<td>43.5</td>
<td>14.3</td>
</tr>
<tr>
<td>≥55</td>
<td>Desvenlafaxine 50 mg (N=1207)</td>
<td>63.2</td>
<td>30.0</td>
</tr>
<tr>
<td></td>
<td>Placebo (N=1067)</td>
<td>53.5</td>
<td>22.1</td>
</tr>
</tbody>
</table>

*This study was sponsored by Pfizer Inc, Collegeville, PA.

In the initial predictor analysis, a threshold of ≥20% improvement on HAM-D₂₁ scores at week 3 strongly predicted response (OR=9.37 [7.23, 12.15]) and remission (OR=14.7 [8.39, 23.01]) of depression at week 8 (both P<0.0001).

- PPV (number of patients remitted at week 8 and with 20% improvement at week 3/those improved at week 3) indicated that 36% of patients that improved at week 3 also remitted at week 8. In addition, an NPV (those who did not remit at week 8 nor improve at week 3/those who did not remit at week 3) showed that 96% of the patients who did not improve at week 3 also did not remit at week 8.

Table 4 presents the thresholds that were derived from the ROC analysis and the corresponding sensitivity, specificity, PPV, and NPV for those thresholds.

- The OOP thresholds derived from ROC analysis were higher than the 20% threshold derived from previous literature. For the desvenlafaxine group, the week 2 OOP thresholds ranged from 0.4% improvement (for predicting minimally acceptable improvement at end point) to 30% improvement (for predicting remission at end point); the corresponding thresholds for week 3 improvement were higher, ranging from 32% to 41%

- The highest PPVs (75% at week 2; 79% at week 3) for week 8 treatment success were associated with the “minimally acceptable improvement” definition in desvenlafaxine patients, indicating that 75% to 79% of desvenlafaxine-treated patients with early improvement at week 2 to 3 achieved this level of treatment success (≥45% decrease in HAM-D₂₁) at end point.

- The highest NPVs (89% at week 2; 93% at week 3) for week 8 treatment success were found for remission at end point in the placebo group, indicating that 89% to 93% of placebo patients who did not meet the thresholds for early improvement at week 2 to 3 also did not achieve remission at end point.

Table 4. Operating Characteristics of Early Improvement in HAM-D₂₁ to Predict Later Treatment Success

<table>
<thead>
<tr>
<th>Week</th>
<th>Group</th>
<th>Early Improvement Threshold (% decrease in baseline HAM-D₂₁)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Desvenlafaxine 50 mg/d</td>
<td>30.8</td>
<td>70.7%</td>
<td>70.2%</td>
<td>75.1%</td>
<td>65.3%</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>20.0</td>
<td>68.3%</td>
<td>68.1%</td>
<td>61.1%</td>
<td>71.2%</td>
</tr>
<tr>
<td>3</td>
<td>Desvenlafaxine 50 mg/d</td>
<td>31.4</td>
<td>74.8%</td>
<td>75.1%</td>
<td>79.3%</td>
<td>70.8%</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>27.6</td>
<td>73.6%</td>
<td>73.7%</td>
<td>68.9%</td>
<td>77.0%</td>
</tr>
<tr>
<td>4</td>
<td>Desvenlafaxine 50 mg/d</td>
<td>29.6</td>
<td>74.8%</td>
<td>74.6%</td>
<td>74.6%</td>
<td>74.7%</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>25.6</td>
<td>74.8%</td>
<td>74.6%</td>
<td>74.6%</td>
<td>74.7%</td>
</tr>
</tbody>
</table>

As depicted in Figure 1 and Figure 2, the percentage of patients meeting the various definitions of treatment success at week 8 was high among those with early improvement at weeks 2 and 3 and at the OOP thresholds.

Logistic regression analyses for the 2 treatment groups combined found the following factors and/or baseline characteristics to be significant predictors for all 4 definitions of treatment success: treatment; baseline HAM-D₂₁ score; duration of current episode; and baseline SDS total, work, and family scores. Baseline SDS social score was a predictor for all definitions of treatment success except remission.

![Figure 1. Rates of Treatment Success at Week 8 According to Early Improvement With Desvenlafaxine 50 mg/d](image-url)
Odds ratios of the predictability of early improvement at week 2 or 3 for later treatment success computed from the univariate logistic regression high predictability across the definitions, multivariate analysis with adjustments for baseline predictor variables (Table 6) showed that early improvement remained a strong predictor of treatment success even with these adjustments.

Table 5. Multivariate Logistic Regression* Predicting Treatment Success at End Point Based on Early Improvement With Desvenlafaxine 50 mg/d or Placebo

<table>
<thead>
<tr>
<th>Treatment Success Definition</th>
<th>Group</th>
<th>Week 2 Early Improvement</th>
<th>Week 3 Early Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>P Value</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------------</td>
<td>--------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>45% improvement in HAM-D</td>
<td>Desvenlafaxine 50 mg</td>
<td>0.95 (0.94-0.96)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>0.96 (0.95-0.97)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>50% improvement in HAM-D</td>
<td>Desvenlafaxine 50 mg</td>
<td>0.95 (0.94-0.96)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>0.96 (0.95-0.97)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>55% improvement in HAM-D</td>
<td>Desvenlafaxine 50 mg</td>
<td>0.95 (0.94-0.96)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>0.96 (0.95-0.97)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Remission</td>
<td>Desvenlafaxine 50 mg</td>
<td>0.95 (0.94-0.96)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>0.96 (0.95-0.97)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*The logistic regression model included patient change in HAM-D at week 2 or 3, treatment, gender, baseline HAM-D, duration of current episode, age, marital status, and family.

Conclusions

In this population of patients, early symptomatic improvement at weeks 2 or 3 was highly predictive of later treatment success. These observations of patients’ early response to the starting/recommended dose of desvenlafaxine 50 mg/d may have clinical value in predicting further outcomes with this antidepressant agent and help guide patient management.

Disclosures

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Rana S. Fayyad, Cedric O’Gorman, and Christine J. Guico-Pabia are Pfizer employees.

References
