Serotonin Norepinephrine Reuptake Inhibitors: Spectrum of Efficacy in Major Depressive Disorder

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ABSTRACT

Randomized, double-blind, placebo-controlled trials remain the gold standard by which the efficacy of a particular pharmacologic intervention for the treatment of a medical disorder or condition is proven or ruled out. This is particularly true for major depressive disorder (MDD) and anxiety disorders, where the magnitude and variability (from one trial to another) of the placebo response remains considerable despite efforts to minimize its effects in antidepressant efficacy trials. This article will summarize evidence establishing the efficacy of four serotonin norepinephrine reuptake inhibitors—venlafaxine, desvenlafaxine succinate, duloxetine, and milnacipran—for the treatment of MDD.

INTRODUCTION

Randomized, double-blind, placebo-controlled trials remain the gold standard by which the efficacy of a particular pharmacologic intervention in treating a medical disorder or condition is established or ruled out.1-3 This is particularly true in the case of major depressive disorder (MDD) and anxiety disorders, where the magnitude and variability (from one trial to another) of the placebo response remains considerable despite efforts to minimize its effects in antidepressant efficacy trials.1-3 The first article in this supplement focused on providing an historical overview on a specific class of antidepressant drugs, the serotonin norepinephrine reuptake inhibitors (SNRIs); the second article reviewed the neurobiology of SNRIs. This article summarizes evidence establishing the efficacy of four SNRIs used for MDD treatment: venlafaxine, desvenlafaxine succinate, duloxetine, and milnacipran.

VENLAFAXINE

Venlafaxine was the first SNRI approved by the Food and Drug Administration for the treatment of MDD in adults. Specifically, an immediate-release (IR) form of venlafaxine was approved by the FDA for the treatment of MDD in 1993, while an extended-release (ER) formulation was approved by the FDA for the treatment of MDD in 1997.
Major Depressive Disorder in Adults

At least 16 randomized, double-blind, placebo-controlled trials focusing on the use of venlafaxine or venlafaxine ER for the treatment of adults with MDD have been published or presented at major scientific meetings. Four of these trials also compare venlafaxine or venlafaxine ER with a selective serotonin reuptake inhibitor (SSRI), and one trial compares the drug with trazodone, and one trial compares venlafaxine with a tricyclic antidepressant. In the largest placebo-controlled trial, Rudolph and colleagues randomly assigned, under double-blind conditions, 460 patients with MDD to receive treatment with either venlafaxine, fluoxetine, or placebo for a total of 6 weeks. Significantly greater Clinical Global Impressions (CGI), Montgomery Åsberg Depression Rating Scale (MADRS), and 17-item Hamilton Rating Scale for Depression (HAM-D17) sustained response rates were achieved with venlafaxine-treated patients compared with placebo-treated patients (CGI, 30% versus 16%, P=0.007; MADRS, 21% versus 12%, P=0.037; HAM-D17, 22% versus 12%, P=0.035) at 14 days. In addition, a recent meta-analysis pooling all SSRI- and placebo-controlled trials of venlafaxine for MDD showed significantly greater remission rates for venlafaxine treatment overall compared with placebo after 8 weeks of treatment (difference in remission rates between venlafaxine and placebo=13%; 95% CI 9% to 16%; N=9 trials). This difference was not related to whether the studies examined venlafaxine IR or ER. A major limitation of this meta-analysis is that it pooled a broad range of trials characterized by considerable design variability; included trials were either open-label or double-blind, enrolled both inpatient and outpatient populations, ranged in duration from 4 to 24 weeks, and used venlafaxine doses ranging between 37.5–399 mg/day. Nevertheless, the robustness of the findings is supported by the fact that end point efficacy measures indicated little between-trial heterogeneity. Moreover, the results were not altered by inclusion or exclusion of any single trial, or by inclusion of trials not funded by the drug's manufacturer. In summary, these studies support continued treatment with venlafaxine among venlafaxine responders and remitters in order to minimize the risk of MDD relapse or recurrence.

Anxiety Symptoms Associated with MDD

Controlled clinical trials indicate that venlafaxine effectively reduces symptoms of anxiety associated with MDD. In an analysis of pooled data from six double-blind, placebo-controlled trials of venlafaxine in adults with symptoms of anxiety associated with MDD (eg, a score of ≥2 on the Hamilton Rating Scale for Anxiety/psychic item, n=1,398), venlafaxine IR (75–375 mg/day) led to significantly greater reductions in both somatic and psychic symptoms of anxiety than placebo. In two randomized, placebo-controlled trials, venlafaxine ER (75–225 mg/day) exhibited an advantage over placebo for relief of psychic anxiety, emerging at week 1 (study 2) or week 4 (study 1) among subjects with moderate anxiety at baseline (HAM-D anxiety/psychic score ≥3). Among patients with severe anxiety at baseline (HAM-D anxiety/psychic ≥4) in study 1, an advantage with venlafaxine ER was observed beginning at week 6. In a separate multicenter, randomized, double-blind, placebo- and active-controlled trial, the anxiolytic properties of once-daily venlafaxine ER (75–225 mg/day) were examined. At study weeks 8, 12, and end point, compared to patients given placebo, patients given venlafaxine ER exhibited significantly greater reductions from baseline on mean Hamilton Rating Scale for Anxiety (HAMA) scores. Moreover, at week 12, more patients using venlafaxine ER were HAMA responders (eg, ≥50% reduction from baseline HAMA; 68%) than were those given placebo (35%; P<0.001). Venlafaxine ER is also approved by the FDA for the treatment of generalized anxiety disorder (GAD), panic disorder, and social anxiety disorder, conditions that are often comorbid with MDD.
Pain Symptoms Associated with MDD

Evidence on the effectiveness of venlafaxine for symptoms of pain associated with MDD is limited to a single report based on a 1-year, open-label trial, which described significant improvements in such symptoms with venlafaxine. Placebo-controlled investigations are needed in order to formulate reliable conclusions regarding the benefit of venlafaxine for ameliorating pain associated with MDD.

MDD in Special Populations

Sex differences

Thase and colleagues32 pooled data from eight short-term, randomized, controlled trials and showed that at study end point, men and women treated with venlafaxine exhibited remission of MDD symptoms at statistically similar rates (P>.05). However, as illustrated in Figure 1, it appears that the advantage of venlafaxine compared with placebo was more pronounced among postmenopausal women who were not taking hormone replacement therapy (HRT; remission rates 50% versus 16% for venlafaxine and placebo, respectively) than premenopausal women (remission rates 44% versus 26% for venlafaxine and placebo, respectively). Remission rates among men given venlafaxine were similar regardless of age group (Figure 1). Such findings, while preliminary, suggest that antidepressant efficacy of venlafaxine may be particularly effective (versus placebo) for the treatment of postmenopausal women with MDD.

![Figure 1](image_url)

**Figure 1**

**Rate of MDD Remission (HAM-D<17 ≤7) With Venlafaxine, by Patient Age, Sex, and HRT Use**

Elderly patients, children, and adolescents

Only a single placebo-controlled trial has focused on the use of venlafaxine for the treatment of elderly patients with MDD. Schatzberg and Roose33 randomly assigned 300 elderly (≥65 years of age, mean age±SD=71±5) patients with MDD to receive treatment under double-blind conditions with either venlafaxine (75–225 mg/day), fluoxetine (20–60 mg/day), or placebo, for a total of 8 weeks. No difference in antidepressant efficacy was reported among patients who received venlafaxine or placebo. Similarly, the results of two randomized, double-blind, placebo-controlled trials focusing on the use of venlafaxine for children and adolescents with MDD (7–17 years of age) did not reveal a difference in antidepressant efficacy among patients who received venlafaxine or placebo.33 Recently, a large randomized trial in adolescents (12–18 years of age) with MDD who failed to respond to an initial SSRI trial demonstrated that switching to venlafaxine (150–225 mg/day) or a second SSRI (paroxetine, citalopram, fluoxetine, 20–40 mg/day) was similarly effective, marked by statistically comparable rates of response (48.2% versus 47.0%, respectively) after 12 weeks of treatment. Nevertheless, the trial did not utilize placebo control, thus caution must be exercised when interpreting such findings.

DESVENLAFAXINE SUCCINATE

Major Depressive Disorder in Adults

Desvenlafaxine succinate (desvenlafaxine) is the major active metabolite of venlafaxine. Desvenlafaxine was FDA-approved for the treatment of MDD in adults in 2008. Also, desvenlafaxine is the newest SNRI to be approved for the treatment of MDD in adults. At least nine randomized, double-blind, placebo-controlled trials of desvenlafaxine for the treatment of MDD in adults have been completed to date (protocol #223, 304, 306, 308, 309, 317, 320, 332, and 333), some of which have been published (protocol #304, 36 306, 37 308, 38 320, 39 332, 40 333, 41 309, 42 and 317)),35

In the context of these trials, a total of 1,805 patients were treated with desvenlafaxine and 1,108 with placebo.35 Five studies involved a fixed-dose design (200 mg versus 400 mg desvenlafaxine [protocol 223 and 308]; 100 mg versus 200 mg versus 400 mg [protocol 306]; 50 mg versus 100 mg [protocol 332 and 333]), while four were of flexible-dose design (100–200 mg/day [protocol 304]; 200–400 mg/day [protocols 309, 317, and 320]). All studies lasted 8 weeks.

Currently, clinical investigations of desvenlafaxine have focused on identifying effective and well-tolerated doses for treatment of MDD in adults, ranging from 50–400 mg/day.

Table 1 summarizes the primary antidepressant outcomes for each of the trials reported to date. Four of the trials found superior antidepressant effects of desvenlafaxine (versus placebo)
with ≥1 of the doses studied. Recently, analysis of pooled data from all nine available placebo-controlled trials, which affords greater statistical power, found that all doses of desvenlafaxine examined (range: 50–400 mg/day) were associated with significant antidepressant effects (versus placebo) of similar magnitude; doses >50 mg/day were not found to confer any additional antidepressant therapeutic benefit. As illustrated in Figure 2, response rates based on the HAM-D₁₇ with desvenlafaxine doses of 50–400 mg/day ranged between 51% and 60%. Pooled remission rates for each desvenlafaxine dose and placebo from these nine trials are also presented in Figure 2. In a separate integrated analysis of data from the two trials that included a venlafaxine ER treatment arm, changes from baseline HAM-D₁₇ scores at week 8 were of similar magnitude with desvenlafaxine (200–400 mg/day: -14.21) and both doses of venlafaxine ER (75–150 mg/day: -14.26; 150–225 mg/day: -14.51). In this analysis, improvements among all active treatment groups were statistically significantly greater than with placebo (11.87; all P≤0.001). The recommended starting dose of desvenlafaxine is 50 mg/day for the treatment of MDD in adults.

Finally, as has been shown with all other approved medications for the treatment of MDD, there is also evidence to support the efficacy of desvenlafaxine for the prevention of relapse and/or recurrence in MDD. Specifically, Rickels and colleagues randomly assigned 375 patients with MDD who had experienced sufficient symptom improvement following treatment with desvenlafaxine (≤12 weeks, 200–400 mg daily flexible dose) to either continue on desvenlafaxine or switch to placebo (double-blind) and continue treatment with placebo for an additional 6 months. Twenty-four percent of patients who

### Table 1
**SUMMARY OF PRIMARY OUTCOMES IN PLACEBO-CONTROLLED TRIALS OF DESVENLAFAXINE³⁶-⁴²**

<table>
<thead>
<tr>
<th>Protocol #</th>
<th>Study</th>
<th>Design</th>
<th>Primary Outcome Measure</th>
<th>Treatment Groups (mg/day)</th>
<th>Final Observation</th>
<th>P Value (vs. placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>223</td>
<td>Unpublished</td>
<td>Phase 2</td>
<td>HAM-D₁₇, change from baseline total score</td>
<td>Placebo</td>
<td>-8.5</td>
<td>0.586</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fixed dose</td>
<td></td>
<td>200 mg/day</td>
<td>-9.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>400 mg/day</td>
<td>-9.3</td>
<td></td>
</tr>
<tr>
<td>304</td>
<td>Liebowitz et al, 2007</td>
<td>Phase 3</td>
<td>Final HAM-D₁₇ total score</td>
<td>Placebo</td>
<td>15.1</td>
<td>NS†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flexible</td>
<td></td>
<td>100–200 mg/day</td>
<td>14.1</td>
<td></td>
</tr>
<tr>
<td>306</td>
<td>DeMartinis et al, 2007</td>
<td>Phase 3</td>
<td>HAM-D₁₇, change from baseline total score</td>
<td>Placebo</td>
<td>-7.65</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fixed dose</td>
<td></td>
<td>100 mg/day</td>
<td>-10.60</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>200 mg/day</td>
<td>-9.63</td>
<td>0.076</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>400 mg/day</td>
<td>-10.74</td>
<td>0.002</td>
</tr>
<tr>
<td>308</td>
<td>Septien-Velez et al,</td>
<td>Phase 3</td>
<td>HAM-D₁₇, change from baseline total score</td>
<td>Placebo</td>
<td>-9.3</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>2007³⁸</td>
<td>Fixed dose</td>
<td></td>
<td>200 mg/day</td>
<td>-12.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>400 mg/day</td>
<td>-12.1</td>
<td></td>
</tr>
<tr>
<td>320</td>
<td>Feiger et al, 2009³⁹</td>
<td>Phase 3</td>
<td>HAM-D₁₇, change from baseline total score</td>
<td>Placebo</td>
<td>-7.48</td>
<td>0.078</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flexible</td>
<td></td>
<td>200–400 mg/day</td>
<td>-9.08</td>
<td></td>
</tr>
<tr>
<td>332</td>
<td>Liebowitz et al, 2008</td>
<td>Phase 3</td>
<td>HAM-D₁₇, change from baseline total score</td>
<td>Placebo</td>
<td>-9.5</td>
<td>0.018</td>
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<tr>
<td></td>
<td></td>
<td>Fixed dose</td>
<td></td>
<td>50 mg/day</td>
<td>-11.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100 mg/day</td>
<td>-11.0</td>
<td>0.065</td>
</tr>
<tr>
<td>333</td>
<td>Boyer et al, 2008⁴¹</td>
<td>Phase 3</td>
<td>HAM-D₁₇, change from baseline total score</td>
<td>Placebo</td>
<td>-10.7</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fixed dose</td>
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<td>50 mg/day</td>
<td>-13.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100 mg/day</td>
<td>-13.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>309</td>
<td>Lieberman et al, 2008</td>
<td>Phase 3</td>
<td>HAM-D₁₇, change from baseline total score</td>
<td>Placebo</td>
<td>-12.5</td>
<td>0.381</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flexible</td>
<td></td>
<td>200–400 mg/day</td>
<td>-13.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>75–150 mg/day</td>
<td>-13.8</td>
<td>0.171</td>
</tr>
<tr>
<td>317</td>
<td>Lieberman et al, 2008</td>
<td>Phase 3</td>
<td>HAM-D₁₇, change from baseline total score</td>
<td>Placebo</td>
<td>-9.78</td>
<td>0.488</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flexible</td>
<td></td>
<td>200–400 mg/day</td>
<td>-10.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>150–225 mg/day</td>
<td>-12.6</td>
<td>0.005</td>
</tr>
</tbody>
</table>

All P values shown based on comparisons of active drug vs. placebo, using analysis of covariance.
* All doses are desvenlafaxine unless otherwise noted.
† No P value given.
‡ Dose is venlafaxine extended release.
= versus; HAM-D₁₇=17-item Hamilton Rating Scale for Depression; NS=not significant versus placebo.

continued on desvenlafaxine experienced an MDD relapse over the course of 6 months versus 42% of patients who continued on placebo (P<0.05). Taken together, these studies support the use of desvenlafaxine for the treatment of MDD as well as for the prevention of relapse and/or recurrence of MDD.

Anxiety Symptoms Associated with MDD

The impact of desvenlafaxine on anxiety symptoms associated with MDD has not yet been described extensively in the literature. In one report based on analysis of data pooled from seven randomized, placebo-controlled trials in adult outpatients with MDD, desvenlafaxine (100–400 mg/day), given for ≤8 weeks, was associated with reductions in scores on the HAM-D anxiety/psychic item (item #10) that were statistically greater than those with placebo (P<0.001). Similar improvements with desvenlafaxine were also found based on adjusted mean scores for the Covi Anxiety Scale. In another integrated analysis of data from five fixed-dose, randomized, placebo-controlled trials, desvenlafaxinex 50 mg/day led to significant final on-therapy reductions from baseline HAM-D anxiety subscale (items 10-13, 15, and 17) and Covi Anxiety Scale scores; greater anxiolytic efficacy was not observed with higher doses.

Pain Symptoms Associated with MDD

In four published trials of desvenlafaxine for MDD in adults, pain symptoms associated with MDD were assessed based on Visual Analog Scale–Pain Intensity (VAS-PI) ratings. In all of these trials, significant advantages of desvenlafaxine over placebo were described for pain relief in study participants. For example, in the report from DeMartinis and colleagues, decreases from baseline VAS-PI ratings of overall pain intensity with desvenlafaxine 100 mg/day (–13.9) were significantly greater than decreases with placebo (–5.9; P=0.002); highly significant decreases in VAS-PI ratings for arm, leg, and joint pain were also found with the 100 mg/day (–14.3 versus placebo, P<0.001) and 400 mg/day doses (–11.4 versus placebo, P=0.019). Interestingly, in the trial by Liebowitz and colleagues where no significant antidepressant effects with desvenlafaxine 100–200 mg/day were detected based on the HAM-D, pain symptoms were highly improved, evidenced by differences from placebo on VAS-PI ratings of overall pain intensity, back pain, and arm, leg, and joint pain (all P<0.01). Similarly, in an analysis of pooled data from six existing trials, Brisard and colleagues found desvenlafaxine to be superior to placebo in the treatment of painful symptoms associated with MDD (overall pain, back pain, chest pain, limb and joint pain).

MDD in Special Populations

Treatment of MDD with desvenlafaxine appears to be equally effective in both men and women and in patients ≤65 and ≥65 years of age. Based on data pooled from five fixed-dose trials, desvenlafaxine was comparably effective (versus placebo) among men and women. There was no evidence of greater efficacy among either women or men given desvenlafaxine doses >50 mg/day. Similarly, in a broader analysis of data

* * *

FIGURE 2

HAM-D17 Response and Remission Rates with Desvenlafaxine (50–400 mg/day) at Final, On-Treatment Evaluation, Based on Pooled Data from Nine Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Desvenlafaxine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 mg/day</td>
<td>47</td>
<td>44</td>
</tr>
<tr>
<td>100 mg/day</td>
<td>56</td>
<td>38</td>
</tr>
<tr>
<td>200 mg/day</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>400 mg/day</td>
<td>51</td>
<td>51</td>
</tr>
</tbody>
</table>

* P<0.01 vs placebo, based on analysis of covariance model, with baseline HAM-D total score as the covariate, Fisher exact test.

† P<0.001 vs placebo, Fisher exact test.

HAM-D17: 17-item Hamilton Rating Scale for Depression.
pooled from nine randomized, placebo-controlled trials, no interaction between treatment and gender was detected. Men (n=709) and women (n=1,096) given desvenlafaxine exhibited comparable final on-therapy HAM-D17 total scores significantly lower than scores among patients given placebo (P<.001). Furthermore, patients <65 (n=1,727) and ≥65 years of age (n=78) given desvenlafaxine exhibited comparable final on-therapy HAM-D17 total scores, which were significantly lower than with placebo (P<.001). Although data based on elderly patients in these trials is limited, desvenlafaxine appears to be effective in this patient population. No placebo-controlled data are yet described in the literature concerning the antidepressant efficacy of desvenlafaxine in adolescent patients.

**DULOXETINE**

In 2004, duloxetine was the second SNRI to be FDA-approved for the treatment of MDD in adults. Major Depressive Disorder in Adults

Ten randomized, double-blind, placebo-controlled trials focusing on the use of duloxetine for the treatment of MDD have been published to date. Five of these studies also included an SSRI as an active comparator. Of the 10 trials, nine demonstrated a greater resolution of MDD symptoms among patients treated with duloxetine than placebo. A pooled analysis of studies comparing duloxetine with placebo confirmed the efficacy of duloxetine for the treatment of MDD. As shown in Figure 3, study end point remission rates for duloxetine (40.3%) were significantly higher than with placebo (28.4%; P<.0001). The advantage of duloxetine over placebo was found to be even greater among patients with severe MDD (remission rate of 35.9% for duloxetine and 17.7% for placebo; P<.0001) than the difference in remission rates reported for the overall population (Figure 3).

In line with findings for other antidepressant agents indicated for the treatment of MDD, there is also evidence to support the efficacy of duloxetine for the prevention of relapse in MDD. Specifically, Perahia and colleagues randomly assigned 278 patients with MDD who had experienced sufficient symptom improvement following treatment with duloxetine (≥12 weeks) to either continue on duloxetine or switch to placebo (double-blind) and continue treatment for an additional 26 weeks. Fewer patients who continued on duloxetine 60 mg/day (17.4%) experienced an MDD relapse over the course of 26 weeks versus patients who continued on placebo (28.5%; P<.05).

**Anxiety Symptoms Associated with MDD**

Symptoms of anxiety associated with MDD have been shown to decrease during the treatment with duloxetine. In an overview of four separate, randomized, placebo-controlled trials of duloxetine in adult outpatients with MDD, Dunner and colleagues described the effects of duloxetine therapy on item #10 of the HAM-D17 (ie, anxiety/psychic item), the HAM-D17 anxiety/somatization subfactor (items 10–13, 15, and 17), as well as the HAM-A (assessed in two of the four studies). In two of the studies, beginning at week 2 and continuing throughout the studies, duloxetine 60 and 80 mg/day were associated with significant improvements from baseline on the HAM-D17 somatization subfactor and HAM-D17 item #10 (all P<.01) compared with placebo; mean end point decrease from baseline HAM-A total score (–6.6) was significantly greater with duloxetine 80 mg/day than with placebo (–4.3; P<.05). In the other studies, duloxetine 20-, 40-, and 120-mg/day were associated with less consistent improvements in anxiety, with significant advantages over placebo found on >1 of the anxiety measures at some, but not all, time points. Similar benefits of duloxetine 60, 90, or 120 mg/day for anxiety associated with MDD have been described in a more recent 12-week, open-label trial. Duloxetine is also approved for the treatment of GAD.

**Pain Symptoms Associated with MDD**

Several trials have demonstrated a greater resolution of some measures of painful symptoms of MDD among patients who received treatment with duloxetine over placebo. The table below shows the remission rates for duloxetine and placebo in MDD remission studies.

**FIGURE 3**

MDD REMISSION WITH DULOXETINE (40–120 MG/DAY), BASED ON ANALYSIS OF DATA POOLED FROM SIX RCTS.

<table>
<thead>
<tr>
<th>Remission Rate (%)</th>
<th>Overall</th>
<th>Severe MDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>28.4%</td>
<td>17.7%</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>40.3%</td>
<td>35.9%</td>
</tr>
</tbody>
</table>

Remission: HAM-D17 total score <7 at week 8 or study end point. Severe MDD: Baseline HAM-D17 total score ≥19.

* P<.001 versus placebo, based on Chi-square test.


Papakostas GI. *Primary Psychiatry.* Vol 16, No 5. 2009.
finding that duloxetine is effective in resolving painful symptoms in MDD patients was recently confirmed in a meta-analysis. Krebs and colleagues pooled data from eight placebo-controlled trials that examined the impact of duloxetine therapy (40–120 mg/day) on pain symptoms associated with MDD or dysthymia. Results of the analysis showed that duloxetine was superior to placebo for pain relief in depressed patients, based on VAS-PI outcomes. Duloxetine is the only SNRI currently approved for the treatment of diabetic peripheral neuropathic pain.

**MDD in Special Populations**

**Sex differences**

In an analysis of data pooled from seven randomized, placebo-controlled trials involving a total of 1,622 patients (men, n=560; women, n=1,062) Kornstein and colleagues reported no significant gender-treatment interaction.

**Elderly patients**

Only one placebo-controlled trial has examined the use of duloxetine for the treatment of elderly patients with MDD. Raskin and colleagues randomly assigned 311 elderly (≥65 years of age, mean age±SD=73±5.7) patients with MDD to receive treatment (under double-blind conditions) with either duloxetine (60 mg/day) or placebo for a total of 8 weeks. A greater resolution of MDD symptoms was reported among duloxetine- than placebo-treated patients. In addition, there was a greater resolution of cognitive and painful MDD symptoms among duloxetine- than placebo-treated patients. No placebo-controlled trials of duloxetine for adolescents with MDD have yet been reported.

**MILNACIPRAN**

**Major Depressive Disorder in Adults**

Milnacipran is available for the treatment of MDD in several countries in the European Union, Asia, and Latin America. It was recently FDA-approved for treatment of fibromyalgia; it is not approved for the treatment of any mood or anxiety disorder. Three randomized, double-blind, placebo-controlled trials focusing on milnacipran for MDD treatment in adults have been published to date. The first study compared milnacipran 25, 50, and 100 mg twice a day (fixed dose) with placebo for a total of 8 weeks (n=527 outpatients). A greater resolution of MDD symptoms was reported among patients treated with 50 or 100 mg twice a day milnacipran than placebo (using the MADRS). The second trial compared milnacipran 50 mg twice a day (fixed dose) with placebo for a total of 6 weeks (n=117 inpatients). A greater resolution of MDD symptoms was reported among patients treated with milnacipran 50 mg twice a day than placebo (using the HAM-D17). The third trial compared milnacipran 50 mg twice a day (fixed dose) with placebo for a total of 5 weeks (n=58 inpatients). A greater resolution of MDD symptoms was reported among patients treated with 50 mg milnacipran twice a day than placebo (using the MADRS). As illustrated in Figure 4, pooling trial data demonstrated milnacipran 50 mg twice daily to be superior to placebo in the treatment of MDD, using both the HAM-D17 and MADRS.

As with all other antidepressants approved by the FDA or EMEA for the treatment of MDD, there is also evidence to support the efficacy of milnacipran for the prevention of relapse and/or recurrence in MDD. Specifically, Rouillon and colleagues randomly assigned 214 patients with MDD who had experienced sufficient symptom improvement following treatment with milnacipran 50 mg twice a day and had sustained such improvement for a total of 4 months to either continue on milnacipran or switch to placebo (double blind) and continue treatment with placebo for an additional 12 months. Sixteen percent of patients who continued on milnacipran experienced an MDD relapse over the course of 12 months versus 23% of patients who continued on placebo (P<.05).

**Associated Symptoms and Special Populations**

Placebo-controlled trials of milnacipran for the treatment of anxiety or painful symptoms associated with MDD are absent. Similarly, to the best of current knowledge, the efficacy of milnacipran for MDD in adolescent or elderly patient populations or in male or female subgroups has not been examined in the context of placebo-controlled trials.

**FIGURE 4**

**EFFICACY OF MILNACIPRAN IN MDD (POOLED DATA ANALYSIS FROM THREE RCTS, N=377, PER PROTOCOL POPULATION)**

<table>
<thead>
<tr>
<th>Change from Baseline Score</th>
<th>MADRS</th>
<th>HAM-D17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-12.2</td>
<td>-10.2</td>
</tr>
<tr>
<td>Milnacipran 50 mg BID</td>
<td>-18.1</td>
<td>-14.3</td>
</tr>
</tbody>
</table>

*P<.01 vs placebo.

MDD=major depressive disorder; RCTs=randomized controlled trials; MADRS=Montgomery Åsberg Depression Rating Scale; HAM-D17=17-item Hamilton Rating Scale for Depression.

DISCUSSION

Evidence derived from randomized, double-blind, placebo-controlled trials establishes the efficacy of all four SNRIs—venlafaxine, desvenlafaxine, duloxetine, and milnacipran—for the acute-phase treatment of adults with MDD. Preliminary “leads” suggest potentially greater efficacy (compared with placebo) and therefore a potential “treatment niche” for some SNRIs in the treatment of specific symptoms or specific subpopulations associated with MDD, including anxiety, treatment of postmenopausal women (venlafaxine), painful MDD symptoms (desvenlafaxine and duloxetine), and in severe MDD (duloxetine). However, such leads have yet to be prospectively confirmed (ie, with the use of clinical trials specifically designed to answer a particular clinical question) and, therefore, at the present time remain merely suggestive. In addition, evidence derived from long-term, randomized, double-blind, placebo-substitution trials establishes the efficacy of long-term treatment with all four SNRIs in preventing a relapse of MDD among patients who experienced a significant improvement in symptoms following the acute phase of pharmacotherapy. However, it should be noted that there is considerable variability in the length of maintenance therapy trials with all four SNRIs; as with other antidepressants, future research needs to focus on defining optimal duration of maintenance treatment. Placebo-controlled trials of the SNRI antidepressants in special populations (ie, elderly patients, adolescents, patients with comorbid conditions) are very limited in scope and number. In elderly patients with MDD, results have been mixed; one trial of venlafaxine did not demonstrate superiority compared with placebo62 while a trial of duloxetine did demonstrate superiority compared with placebo.63 Similarly, in adolescent patients with MDD, placebo-controlled trials failed to detect a therapeutic effect of venlafaxine although one report (nonplacebo controlled) suggested it may be as effective as an SSRI in nonresponsive adolescent patients64; no trials of other SNRIs in depressed adolescents have yet been described. Moreover, no trials of any SNRI have yet been described for patients with specific comorbid medical disorders, such as diabetes, postmyocardial infarction, poststroke, or cancer. It seems warranted to conclude that although the existing evidence indicates potential usefulness of the SNRIs in certain special populations, it has not been firmly established. Finally, placebo-controlled trials focusing on the use of these agents in mood disorders other than MDD (dysthymic disorder, MDD episodes in patients with bipolar disorder, psychotic MDD) have not been published to date. Future studies are necessary to expand the spectrum of efficacy of the SNRIs in MDD.

CONCLUSION

The efficacy of all four SNRIs (venlafaxine, desvenlafaxine, duloxetine, and milnacipran) in the treatment and prevention of MDD relapse among adults has been well established with the use of randomized, double-blind, placebo-controlled trials. In addition, there is preliminary evidence, at least for some SNRIs, to suggest that they may be particularly effective (versus placebo) in the treatment of specific symptoms such as anxiety and pain associated with MDD or for specific MDD subpopulations (severe MDD, postmenopausal women not on HRT). Future studies are required to confirm these preliminary leads as well as to expand the spectrum of efficacy of the SNRIs in MDD. PP

REFERENCES


42. Rickels K, Montgomery SK, Tourin KA, Gaedt JD, Pitsilos V, Padmanabhan SK. A multicenter, randomized, double-blind, placebo-controlled, parallel group study of desvenlafaxine succinate for prevention of depressive relapse in adult outpatients with major depressive disorder. Poster presented at: Annual Meeting of the American Psychiatric Association; May 3–8, 2008; Washington, DC.


60. Rickels K, Montgomery SK, Tourin KA, Gaedt JD, Pitsilos V, Padmanabhan SK. A multicenter, randomized, double-blind, placebo-controlled, parallel group study of desvenlafaxine succinate for prevention of depressive relapse in adult outpatients with major depressive disorder. Poster presented at: Annual Meeting of the American Psychiatric Association; May 19–24, 2007; San Diego, CA.
