SNRIs in the Management of Acute Major Depressive Disorder

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Remission of a patient’s index major depressive episode is essential in preventing a recurrent or chronic depressive course. Once remission is established, the subsequent goal is to maintain remission and prevent a relapse of the episode with a minimum of 4 to 9 months of continuation treatment. Common belief suggests that all antidepressants have equivalent efficacy when measured by remission, but this may be a misconception based on limitations in current clinical trial methods. Furthermore, major depressive disorder (MDD) is a complex illness with a variety of co-occurring somatic and often painful symptoms. In addition, increasing evidence suggests that, in some depressed patients, serotonin-norepinephrine reuptake inhibitors (SNRIs) may provide benefits of treating a broader range of target symptoms than single-acting agents, such as selective serotonin reuptake inhibitors (SSRIs). Given the available evidence and the importance of remission, the pendulum has swung to consider using agents with dual reuptake inhibition (e.g., SNRIs) as standard and initial treatment for depression.

Major depressive disorder (MDD) has an estimated lifetime prevalence of about 18% and has been ranked by the World Health Organization as the fourth greatest contributor to global illness burden. According to recent estimates, the economic burden of depression exceeds $83 billion due largely to lost productivity resulting from missed workdays and decreased performance while at work. In fact, disability from depression exceeds that of most chronic general medical conditions, including hypertension, diabetes, arthritis, and lung disease. In addition, depression is associated with poorer medical outcomes for patients with concomitant medical illnesses (e.g., diabetes, cardiovascular disease).

Many patients with MDD experience multiple depressive episodes throughout their lives, and the probability of recurrence increases with each subsequent depressive episode. Moreover, depressive episodes can become increasingly frequent and occur irrespective of any life stressors, different than earlier episodes. There is a growing literature that suggests, similar to other chronic medical illnesses, achieving and sustaining remission of a patient’s first depressive episode decreases the likelihood of a recurrent or chronic depressive course. Similar to other chronic illness, remission of the index episode of depression is critical to optimal long-term outcomes. Unfortunately, even among patients who respond to treatment, approximately 45% fail to achieve remission. Patients who achieve response without remission continue to experience subsyndromal depression or symptoms of depression, and data suggest unfavorable long-term outcomes relative to patients who achieve an initial full remission.

Specifically, failure to achieve full remission has been associated with more chronic depressive episodes, shorter durations between episodes, a greater risk of suicide, and ongoing psychosocial impairment. Therefore, remission is considered the standard of treatment. Treatment of the index episode should focus on tailoring the treatment to the individual patient, with the goal of full remission, whether this is accomplished using monotherapy antidepressants, combination pharmacotherapies, or antidepressants combined with psychotherapy.

Historically, it was commonly believed that all antidepressants have equal efficacy. However, recent data suggest that there may certainly be differences in the relative efficacy of antidepressants, especially when using the standard outcome of “remission,” rather than “response.” Conflicting results from various studies may be partially the result of differences in outcomes assessment tools (e.g., Hamilton Rating Scale for Depression [HAM-D] vs. Montgomery-Asberg Depression Rating Scale [MADRS]).
response vs. remission) or unintended biases in the patient samples, which tend to be relatively small and consist of similar participants from a subset of depressed patients. This is confounded by the fact that many contemporary randomized controlled clinical trials report negative results, show substantial placebo effects, or find a relatively small difference between drug and placebo outcomes.\(^ {15-17}\) Therefore, very few individual studies on antidepressants have the statistical power to distinguish between the effectiveness of 2 different antidepressants.\(^ {18}\) When pooled analyses are employed to investigate the differences in efficacy between antidepressants, overall differences can more readily be identified due to the power conferred by examining a large number of patients from a variety of subpopulations.

Despite the common perception that all antidepressants have relatively comparable efficacy, evidence has suggested that there may be meaningful differences between antidepressant classes. Antidepressants that inhibit reuptake of more than one neurotransmitter may have an efficacy advantage compared with single-acting agents in specific subpopulations of MDD patients. Specifically, results of traditional meta-analyses, pooled analyses, and some individual studies have suggested a greater benefit with dual-acting agents, such as the tricyclic antidepressants (TCAs) amitriptyline and clomipramine compared with single-acting agents, including the selective serotonin reuptake inhibitors (SSRIs).\(^ {19,20}\)

**REVIEW OF EFFICACY**

**Efficacy Advantages With Dual Reuptake Inhibition in Severe Depression**

Differences in efficacy between dual- and single-acting agents have been most apparent in populations of patients with more severe depression, such as depressed inpatients. For example, findings from a recent study demonstrate that a combination of an SSRI with a noradrenergic TCA was more efficacious than either agent alone. Specifically, the SSRI fluoxetine and the noradrenergic TCA desipramine were investigated in a randomized, double-blind study.\(^ {21}\) Inpatients with MDD (N = 38) were assessed for depression with the HAM-D or MADRS and treated for 6 weeks. The combination of fluoxetine and desipramine was associated with significantly higher rates of remission than treatment with either drug alone (53.8% vs. 7% and 0%, respectively) (\(\chi^2 = 13.49, p = .001\)). These results suggest that simultaneous increases in serotonergic and noradrenergic synaptic concentrations may have synergistic effects that create an enhanced neuronal environment that is beneficial for the remission of MDD.

Evidence suggests that dual-acting TCAs may provide greater efficacy than SSRIs in depressed inpatients. The Danish University Antidepressant Group conducted randomized controlled trials comparing the efficacy of the dual-acting TCA clomipramine with the SSRIs citalopram\(^ {19}\) or paroxetine.\(^ {20}\) The results demonstrated that the dual-acting agent was more effective than the single-acting agents in producing remission in depressed inpatients. Similarly, in a series of meta-analyses of double-blind studies, the dual-acting TCAs clomipramine and amitriptyline, but not the predominantly noradrenergic TCAs (imipramine, desipramine, and maprotiline), were more effective than SSRIs in the treatment of depressed inpatients.\(^ {22-24}\)

Similar results are seen in comparisons of serotonin-norepinephrine reuptake inhibitors (SNRIs) and SSRIs. For example, venlafaxine was compared with fluoxetine for efficacy in patients hospitalized with MDD and melancholia in 2 double-blind, randomized controlled trials.\(^ {25,26}\) In these clinical trials, venlafaxine was significantly more effective in producing remission than fluoxetine (\(p \leq .05\)). In another study of patients who failed treatment with 2 prior antidepressants, venlafaxine was associated with significantly greater remission rates compared with paroxetine (42.3% vs. 20.0%; \(p = .01\)), suggesting that SNRIs may also be more effective in some treatment-resistant patients.\(^ {27}\)

**Greater Overall Efficacy With Dual Reuptake Inhibition**

Comparisons of SNRIs and SSRIs in populations of depressed outpatients typically included in clinical trials have suggested generally modest, but statistically significant differences in antidepressant efficacy.

*Venlafaxine versus SSRIs in acute treatment of MDD.* Thase et al.\(^ {28}\) reported the results of a meta-analysis of 8 double-blind studies (4 of which included a placebo treatment arm) in which venlafaxine was compared with an SSRI (fluoxetine, paroxetine, or fluvoxamine) for acute (up to 8 weeks) treatment of MDD. Analyses were conducted on individual patient data. Of the 2045 patients from the intent-to-treat sample, 851 were treated with venlafaxine (75–375 mg/day), 748 were treated with an SSRI (fluoxetine [20–80 mg/day], N = 554; paroxetine [20–40 mg/day], N = 160; fluvoxamine [100–200 mg/day], N = 34), and 446 were given a placebo.\(^ {29}\) Remission was operationally defined as a score of 7 or less on the HAM-D.\(^ {17}\) Remission rates were significantly higher in patients treated with venlafaxine (45%) compared with those given SSRIs (35%) or placebo (25%) (\(p < .001\) for both pairwise comparisons) (Figure 1). Further, the odds ratio (OR) for remission was 1.50 (95% confidence interval [CI] = 1.3 to 1.9) in favor of venlafaxine compared with SSRIs. The results suggest that venlafaxine is associated with a higher probability of achieving remission than SSRIs and placebo in some patients.\(^ {28}\) Remission rates from a similar analysis of data from 33 studies were consistent with the findings of Thase et al.\(^ {28}\): 41.2% for venlafaxine/venlafaxine ER and 34.6% for the studied
Figure 1. Remission (HAM-D$_{17}$ score ≤ 7) in MDD Patients Following Short-Term Treatment With Venlafaxine, SSRIs, or Placebo

SSRIs (p < .0001). A more comprehensive analysis of remission rates is nearing completion.

Similar findings were reported from a meta-analysis of 32 randomized, double-blind trials that compared the efficacy and tolerability of venlafaxine with SSRIs (fluoxetine, fluvoxamine, paroxetine, sertraline) and other antidepressants (various TCAs, trazodone, and mirtazapine). Remission rate was a secondary outcome, measured by pooling data from 18 of the 32 original studies. Dose ranges of venlafaxine and the active comparators were not reported. The overall OR for achieving remission with venlafaxine versus all other antidepressants was 1.36 (95% CI = 1.14 to 1.61). The overall OR for achieving remission with venlafaxine compared with the SSRIs, based on data from 16 of the 32 studies, was 1.43 (95% CI = 1.21 to 1.71). 30

**Duloxetine in acute treatment of MDD.** Supporting the notion of the advantages provided with dual reuptake antidepressants, the second selective SNRI in the U.S. market, duloxetine, demonstrates superior efficacy compared with placebo in treating acute MDD. In 2 randomized, double-blind, placebo-controlled studies, duloxetine was given to patients with MDD. 31,32 In both studies, patients were treated with duloxetine, 60 mg once daily (N = 251), or placebo (N = 261) for 9 weeks. “Response” was defined as ≥ 50% reduction in baseline HAM-D scores. Response rates (last observation carried forward [LOCF]) were significantly higher among duloxetine-treated patients (45% and 50%) compared with placebo-treated patients (23% and 35%; p < .05 for duloxetine vs. placebo in both studies). 31,32 Rates of “remission” (LOCF) (defined as HAM-D ≤ 7) were significantly greater with duloxetine treatment than with placebo in one study (31% vs. 15%, respectively; p = .003), 31 but not the other (32% vs. 24%, respectively; p = .212). 32

A review was conducted of 6 studies of depressed outpatients treated with duloxetine 40 mg/day to 120 mg/day (N = 755), an active comparator (2 studies with fluoxetine 20 mg/day, N = 70; 2 studies with paroxetine 20 mg/day, N = 175), or placebo (N = 585) for 8 to 9 weeks. 33 In 4 of the 6 studies described (including the two 9-week placebo-controlled studies mentioned earlier), patients given duloxetine had significantly lower mean total HAM-D$_{17}$ scores than those given placebo (p ≤ .05). In 3 of the 6 studies, duloxetine treatment (at doses of 60 mg q.d., 60 mg b.i.d., or 40 mg b.i.d.) was associated with a significantly greater probability of remission compared with placebo. The probability of remission with duloxetine (60 mg b.i.d., 57%) was significantly greater than that with paroxetine (20 mg q.d., 25%) in one 8-week study (p = .002). 33

In a pooled analysis of 6 randomized, double-blind, placebo-controlled trials with active SSRI comparators, remission rates (HAM-D ≤ 7) were analyzed for all 3 treatment groups. 34 The duloxetine doses evaluated for efficacy ranged from 80 mg/day to 120 mg/day (N = 711). Other treatments consisted of fluoxetine 20 mg/day (N = 70), paroxetine 20 mg/day (N = 359), or placebo (N = 516). Remission rates for all patients were significantly greater for duloxetine and SSRIs when compared with placebo (p < .05). The remission rates for duloxetine-treated patients were not significantly different from those for SSRI-treated patients, among the entire study population, which included patients with baseline HAM-D ≥ 15. However, when the subgroup of more severely depressed patients (i.e., patients with a baseline HAM-D ≥ 19) was examined, duloxetine treatment was associated with significantly greater remission rates than SSRI treatment (p = .013) (Figure 2). 34

Overall, the results of these meta-analyses and clinical trials suggest that the dual reuptake inhibition of venlafaxine and duloxetine may confer a therapeutic advantage over SSRIs when utilizing the expected outcome of remission for the acute treatment of MDD. Large-scale head-to-head comparisons of SNRIs and SSRIs or additional meta-analysis of pooled original patient data from future randomized controlled trials would provide additional opportunities to test this hypothesis. Further examination of clinical trial data may also be useful in identifying various factors underlying the modest differences in efficacy observed in general populations of depressed patients.

**Potential Factors Involved in Efficacy for SNRIs**

*More rapid onset of remission.* Measuring the onset of an “early” initial response to antidepressant treatment is associated with multiple methodological challenges in
There is some evidence that rapid titration of venlafaxine during the first week of therapy may lead to a faster response in some patients. In one study, the sustained response rates for venlafaxine were significantly better than placebo and approached significance versus fluoxetine at days 7 and 14.

**Broad array of symptoms treated by SNRIs.** Evidence suggests that dual reuptake inhibitors, by virtue of stimulating both serotonergic and noradrenergic neurotransmission, may be effective in treating a wider array of the emotional and physical symptoms of depression than single-acting agents in some patients.

Somatic and painful symptoms. It is widely recognized that the diagnostic criteria for MDD require the presence of either depressed mood or loss of interest or pleasure for at least 2 weeks in addition to 3 additional co-occurring symptoms such as significant weight change, sleep disturbance, observable psychomotor agitation, fatigue, feeling worthless, inappropriate guilt, diminished concentration, or recurrent suicidal ideation. However, physical symptoms are also common in MDD patients and can include headache, dizziness, gastrointestinal problems (nausea, vomiting, and diarrhea), sexual dysfunction, nonspecific pain, and specific pains in the head, back, joints, limbs, abdomen, or chest. In fact, data from the World Health Organization international study of psychological disorders in general health care indicated that more than two thirds of depressed patients reported physical symptoms as their primary presenting complaint. Moreover, the number of physical symptoms has been shown to be highly predictive of the presence of an underlying or coexisting psychiatric disorder. Additionally, the degree of painful physical symptoms was associated with greater functional disability, and the presence of physical symptoms is correlated with poor treatment outcomes, including the presence of residual physical symptoms in patients who fail to achieve remission.

Some TCAs, particularly those that inhibit reuptake of both serotonin and norepinephrine, such as amitriptyline, are efficacious in treating chronic pain not related to depression (e.g., diabetic peripheral neuropathic pain, migraine, or postherpetic neuralgia). Newer dual-acting antidepressants have also been evaluated for their effects on pain. Early data suggest the efficacy of SNRIs and mirtazapine in managing various chronic pain states (e.g., diabetic peripheral neuropathy, fibromyalgia, headache).

Similarly, treatment with SNRIs has been shown to effectively treat physical symptoms associated with depression. Original patient data from 31 randomized, double-blind, comparator-controlled studies (9 of which were also placebo-controlled) were pooled and analyzed to compare relative rates of remission of physical symptoms such as backaches, headaches, muscle aches, loss of energy, and fatigue (defined as HAM-D somatic–general item = 0) following treatment with venlafaxine, an SSRI (fluoxetine, paroxetine, sertraline, citalopram, or fluvoxamine), or placebo. Significantly more patients achieved remission of physical symptoms of depression with venlafaxine treatment than with SSRIs or placebo starting at week 2 and continuing through week 8 (p ≤ .01) (Figure 3). In addition, treatment with venlafaxine was significantly more effective than treatment with the studied SSRIs in reduction of the anxiety/somatization symptoms associ-
ated with depression (HAM-D, items: anxiety–psychic, anxiety–somatic, somatic symptoms–gastrointestinal, somatic symptoms–general, hypochondriasis, and insight). The efficacy of duloxetine in alleviating painful physical symptoms in patients with MDD was evaluated as a secondary outcome in 3 randomized controlled trials, including 1 paroxetine-controlled study using a visual analog scale and the Somatic Symptom Inventory. Duloxetine treatment was associated with a significantly greater reduction in overall pain severity relative to placebo treatment in all 3 studies.

**Other symptoms.** Additional analyses were performed on the data from the 31 double-blind studies comparing venlafaxine, SSRIs (fluoxetine, paroxetine, sertraline, citalopram, and fluvoxamine), and placebo. The results suggested that treatment with venlafaxine was effective in ameliorating a wide range of emotional, physical, and functional symptoms of depression. In one analysis, rates of complete symptom remission (HAM-D item score = 0) at 8 weeks were significantly greater among venlafaxine-treated patients than patients treated with the studied SSRIs for depressed mood, feelings of guilt, suicidal ideation, work/activities, retardation, agitation, anxiety–psychic, anxiety–somatic, somatic–general, and genital symptoms. A separate analysis that compared relative rates of complete symptom remission among patients with varying degrees of symptom severity at baseline found that, after 8 weeks of treatment, there were significantly greater rates of complete remission associated with venlafaxine treatment than with the studied SSRIs on a variety of individual symptoms, including insomnia, depressed mood, hypochondriasis, feelings of guilt, suicidal ideation, work/activity, anxiety–psychic, and agitation.

Several clinical trials of duloxetine in depressed patients included evaluations of improvement in symptoms of anxiety as secondary outcome measures. Anxiety data from 4 short-term studies (2 placebo-controlled, 1 placebo- and paroxetine-controlled, and 1 placebo- and fluoxetine-controlled) were analyzed and included the HAM-D anxiety/somatization factor score, HAM-D item 10 (anxiety–psychic), and HAM-A (in 2 studies). Across the 4 studies, duloxetine at doses ≥ 60 mg/day (60 mg q.d., 40 mg b.i.d., or 60 mg b.i.d.) was associated with significant improvement compared with placebo on 8 of 10 outcomes and was associated with significantly greater improvement compared with fluoxetine or paroxetine on 3 of 6 outcomes.

Overall, the results of these studies suggest that SNRIs effectively treat a broad array of symptoms. In some patients, SNRIs appear to provide a statistically significantly greater superiority in acute depression than SSRIs in treating a number of specific symptoms, including somatic and painful physical conditions. In addition, although increased noradrenergic activity might be expected to produce or exacerbate symptoms of anxiety associated with depression, this evidence suggests that the SNRIs seem to confer a pattern in reducing these symptoms.

**Dosing Considerations**

Conclusions of differential efficacy based on comparisons in the pooled analyses discussed above are somewhat limited, due to differences in dosing between SNRIs and SSRIs. The doses of venlafaxine and SSRIs used in the studies pooled for the Nemeroff et al. analysis were generally comparable (mean doses overall = venlafaxine, 139 mg/day and SSRIs, approximately 30 mg/day fluoxetine equivalent). However, the studies in the duloxetine pooled analysis utilized a wide range of duloxetine doses (40–60 mg b.i.d.), while fluoxetine and paroxetine were limited to the minimum effective doses (20 mg q.d.). More accurate assessments of relative efficacy could be made if comparable dosing is used for comparison. This is particularly relevant in light of the fact that evidence suggests that some antidepressants are associated with a positive dose-response effect.

While a significant dose-response effect generally has not been observed with the SSRIs, there is some evidence to suggest a dose response with SNRIs. For example, some clinical trials have shown evidence of greater efficacy with higher doses in some depressed patients treated with venlafaxine. Therefore, it would be useful to maximize the dose of venlafaxine before declaring treatment failure. Currently, the U.S. Food and Drug Administration–approved labeling for duloxetine states that there is no increase in efficacy with doses greater than the maximum approved 60 mg/day; however, several clinical trials have used doses as high as 120 mg/day.

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**Figure 3. Resolution of Physical Symptoms With Venlafaxine and SSRIs**

![Graph showing resolution of physical symptoms with venlafaxine and SSRIs.](image)

*Data from Entsuah et al. 41

SSRIs include fluoxetine (N = 1641), paroxetine (N = 692), sertraline (N = 652), citalopram (N = 198), or fluvoxamine (N = 34).

*Somatic–general items include backache, headache, muscle aches, loss of energy, and fatigue.

†p ≤ .001 vs. placebo; †p < .01 vs. SSRI; ‡p ≤ .001 vs. placebo.
Further studies are needed to define a possible dose-response effect with duloxetine.

**TOLERABILITY OF SNRIs**

Tolerability is an important consideration when choosing between treatment with a TCA, an SSRI, or an SNRI for patients with MDD. Although the TCAs and MAOIs have long been known to be efficacious, issues related to their tolerability and safety render them more appropriate for second-line treatment. For outpatients, controlled trials demonstrate that SSRIs are tolerated better than TCAs, including discontinuation rates due to adverse events (in both acute and long-term treatment).

Newer dual-acting agents, such as SNRIs, generally possess comparable tolerability to SSRIs. The results of the pooled analyses indicated that the discontinuation rates due to adverse events associated with venlafaxine (9%) and SSRI treatment (7%) were comparable (p = .185), and the rates of individual side effects were low for both treatments.

Two percent of placebo-treated patients discontinued due to adverse events (p = .001 for venlafaxine vs. placebo and SSRIs vs. placebo). In addition, a recent open-label long-term study of venlafaxine extended release (ER) and SSRIs (fluoxetine, paroxetine, sertraline, or citalopram) in depressed primary care patients reported that venlafaxine ER was not associated with an increased risk for any individual adverse event compared with SSRIs. In studies with active SSRI comparators, duloxetine was found to have tolerability comparable to the studied SSRIs (fluoxetine and paroxetine). The rates of discontinuation due to adverse events were not significantly different for duloxetine compared with either SSRI individually, and the incidence of most individual adverse events was comparable between groups.

In general, both venlafaxine ER and duloxetine are similarly well tolerated. Both are associated with nausea, which generally tends to be dose related, occur early (i.e., in the first week or 2), and diminish after a few weeks of treatment.

While the cardiovascular profile of duloxetine and venlafaxine is safer than that of the TCAs, both agents have been associated with treatment-related increases in blood pressure, and periodic monitoring of blood pressure during treatment is recommended.

**CONCLUSIONS**

Achieving and sustaining remission of a patient’s index episode of major depression provide the best clinical intervention to protect against the development of a recurrent, chronic depressive course and potentially a more malignant illness. The clinical consequences of not achieving remission are well established. Achieving and maintaining remission requires an understanding of options available in antidepressants.

Despite the common misperception that all antidepressants are equally comparable, evidence from individual studies and meta-analyses has suggested that there may be clinical advantages for treatments with a broader pharmacologic profile. A growing body of evidence suggests that inhibiting reuptake of both serotonin and norepinephrine, as can be achieved with dual-acting agents, such as the SNRIs or with combinations of noradrenergic and serotonergic antidepressants, may have therapeutic advantages compared with inhibiting reuptake of a single neurotransmitter. Further, the dual mechanism of action of SNRIs may account for the higher rates of remission in a growing number of controlled trials associated with these agents compared with SSRIs. It is unlikely that the observed advantages extend universally to all depressed patients. Rather, there appear to be possible factors that account for the overall differences in remission rates, including advantages for SNRIs in treating more severe depression, a shorter time to remission with SNRIs, and greater efficacy of SNRIs in treating specific symptoms, such as physical or somatic symptoms.

Selection of an antidepressant treatment should reflect multiple factors. Ideally, treatment should be selected to maximize the likelihood of remission with initial therapy. By taking into account the drug’s mechanism of action, the patient’s constellation of somatic symptoms, and the weight of the supporting evidence from clinical trials demonstrating the drug’s effectiveness in treating the patient’s MDD symptoms, treatment can be optimized. Because SNRIs are efficacious overall, and seem to predict greater effect than SSRIs in treating somatic symptoms, these antidepressants can be considered as a first-line treatment for MDD.

It may be useful to compare treatment of a patient’s index episode of major depression to the treatment of a serious infection; that is, in both cases, broad-spectrum treatment is a useful approach to fully eradicate the illness from the start. Failure to reach remission could result in a more difficult-to-treat illness later. This construct is particularly applicable to depression for which, in the case of SNRIs and SSRIs, there are relatively few differences in tolerability that would render the broader spectrum agents less desirable.

**Drug names:** amitriptyline (Elavil and others), citalopram (Celexa), clomipramine (Anafranil and others), desipramine (Norpramin and others), duloxetine (Cymbalta), fluoxetine (Prozac and others), imipramine (Tofranil and others), mirtazapine (Remeron and others), paroxetine (Paxil and others), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).

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