Long-Term Management of Major Depressive Disorder: Are Differences Among Antidepressant Treatments Meaningful?

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Recurrent depression poses a problem for up to 80% of patients with major depressive disorder (MDD) during their lifetime. Therefore, the optimal treatment goal established by the American Psychiatric Association and the Agency for Health Care Policy and Research is remission and virtual elimination of symptoms. Patients who have a high risk of recurrence often require maintenance therapy and long-term treatment. As a result, identification of antidepressants that are effective in maintaining remission in patients over the long-term and have acceptable tolerability profiles is important. The efficacy of antidepressants in conferring full remission and long-term recovery is an important priority for clinicians. Both selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have been examined for use in long-term treatment of MDD. Recently, 2 long-term (6 to 12 months), double-blind, placebo-controlled studies have shown that venlafaxine is effective in preventing relapse and recurrence. While long-term, head-to-head studies comparing SNRIs with SSRIs are rare, a recent open-label study compared venlafaxine to 4 SSRIs (fluoxetine, paroxetine, sertraline, or citalopram) in outpatients with MDD. The results show that the SNRI venlafaxine is comparable to the SSRIs in terms of remission rates, and venlafaxine may bring patients to remission earlier than SSRIs. Long-term treatment at maximally tolerated doses is also associated with similar incidence of common adverse events between venlafaxine and placebo and tolerability comparable to SSRIs. Thus, there is increasing evidence that venlafaxine and SSRIs are effective and well tolerated in long-term therapy. While it is unclear from the data if continued treatment with SNRIs confers advantages over SSRIs due to an early onset of remission, further studies will provide valuable insights into the efficacy of SNRIs and SSRIs in maintenance therapy.

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GOAL OF TREATMENT IS REMISSION

Major depressive disorder (MDD) is a chronic disorder that may include relapses for up to 50% of patients 4 to 6 months following treatment of a depressive episode.[1] It has also been reported that there is a relapse rate of approximately 30% within 1 year in MDD patients seen in primary care settings.[2] Other evidence[3] showed that 58% of patients treated for MDD who remained well for 5 or more years had a recurrence. Further, recurrent depression poses a problem for up to 80% of MDD patients during their lifetimes.[1,4] Finally, results of another study[5] demonstrated that patients whose first depressive episode was followed by residual subthreshold depressive symptoms had significantly worse future courses, suggesting that ongoing treatment is necessary. Based on these and other findings, the optimal treatment goal established by the American Psychiatric Association[6] and the Agency for Health Care Policy and Research[7] is to achieve and sustain remission, i.e., virtual elimination of symptoms.

Phases of Treatment

In order to accomplish this, treatment of MDD is divided into the 3 commonly known phases of acute, continuation, and maintenance therapy.[8] The acute phase may last 4 to 16 weeks after the initial depressive episode, and the goal of treatment during this phase is to elicit a treatment response, more specifically, to achieve remission of symptoms.[7,8] The next phase, the continuation phase, may last 4 to 9 months following response to initial treatment, and the goal of treatment during this phase is to maintain the response to acute-phase treatment by preventing a relapse (the return of depressive symptoms during remission but prior to recovery) or recurrence (a new episode of

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Table 1. Professional Organizations' Guidelines for Duration of Treatment for Major Depressive Disorder After Acute Treatment Response[a]

Organization	Recommended Duration of Continuation Treatment[b] After Medical Management of the Acute Episode (mo)	No. of Episodes That Would Indicate Longer Maintenance Treatment Is Appropriate
UK Defeat Depression Consensus Statement	4–6	> 2
US Agency for Health Care Policy and Research	4–9	> 3
British Association for Psychopharmacology	6	> 3 in past 5 years (or > 6 in total)
American Psychiatric Association	4–5	Not specified: "multiple"

[a]Data from Geddes et al.[10]
[b]At same dose.

Figure 1. Kindling of Recurrent Depressive Episodes[a]

[a]Adapted with permission from Kendler et al.[13]
[b]Odds ratio for depression given at least 1 stressful life event.

MDD following a response).[7–9] A number of professional organizations have published guidelines for continuation treatment (Table 1). The last phase is the maintenance phase, which may last from 1 year to a lifetime, and the goal of this phase is to prevent a recurrence.[7]

Predictors of Recurrence

Patients who have a high risk of recurrence often require maintenance therapy and long-term treatment. According to the American Psychiatric Association Practice Guidelines,[6] the factors to be considered in identifying patients who need maintenance treatment are (1) risk of recurrence, (2) severity of episodes, and (3) patient preferences.

The risk of recurrence is correlated with multiple prior episodes of MDD[6]; however, the number of depressive episodes that would indicate that a patient needs maintenance therapy ranges from greater than 2 to up to 6, based on different professional organizations (Table 1).[10] In addition, the presence of comorbid conditions (e.g., a nonaffective psychiatric diagnosis or a chronic general medical disorder),[6] persistent dysthymia between episodes,[6] and the presence of residual symptoms after partial remission[11] are predictors of recurrence.

Few patient characteristics have been shown to be predictive of a recurrent course of illness. Paykel et al.[11] found that only a greater severity of initial depressive illness was associated with the occurrence of residual symptoms (which were shown to be a predictor of recurrence); other factors including length of prior illness, dysthymia, and lower prior drug dose were not useful predictors. In addition, Mueller et al.[3] found few baseline or clinical characteristics (female sex, longer episode of illness before seeking treatment, greater number of prior episodes, and never marrying) that were predictive of a future recurrence of an affective disorder. Likewise, Simon et al.[12] found that long-term prognosis was not strongly correlated with baseline characteristics such as prior history of recurrent depression or medical or anxiety comorbidity. Instead, long-term prognosis was strongly correlated with remission status at 3 months.[12] Often, patients' recurrent depressive episodes are increasingly frequent and have declining association with stressful life events. This sensitization, or "kindling," is marked by depressive episodes that are increasingly autonomous (Figure 1).[13]

There is a lack of consensus regarding the optimal duration of maintenance therapy. Some authors recommend that maintenance therapy for patients with 3 or more major depressive episodes or 2 episodes plus a major risk factor should last 4 to 5 years (i.e., the approximate length of 2 major depressive episodes).[9] Regardless of the lack of definitive identification of factors that distinguish patients who will experience recurrences from those who will not, the importance of treatment guidelines and long-term treatment is inarguable.

Physiologic Evidence for the Importance of Early Remission

Despite the existence of many antidepressants that effectively treat MDD, only 42% of patients receive adequate treatment.[14] This may contribute to an unfortunate situation in which treatment delays allow neurophysiologic and neurochemical damage to progressively worsen, and the absence of treatment delays the reversal of these physiologic correlates. Patients with MDD have been found to have reduced hippocampal volume[15–20] that is reversed by antidepressant treatment.[21] Also the production of new neurons during antidepressant treatment in animal studies shows the loss of valuable recovery processes due to delays in treatment.[22] Using magnetic resonance imaging, investigators found that lithium-treated bipolar patients had significantly increased total gray matter volume compared with untreated bipolar patients.[23]

Taken together, these studies suggest that long-term treatment may provide a healthy nonstressful neurochemical environment in which central nervous system dysfunction occurring during MDD can be reversed. As a result, identification of antidepressants that are effective in achieving and maintaining remission over the long-term and have acceptable tolerability profiles is important.

EARLY REMISSION DETERMINES LONG-TERM EFFICACY

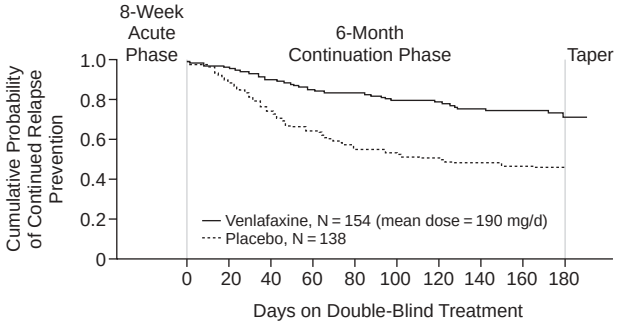
The efficacy of antidepressants in conferring full remission and long-term recovery is an important priority for clinicians. Many clinical trials assess the efficacy of antidepressants during the acute phase, with short-term studies lasting 8 to 12 weeks. Due to the high prevalence of relapse or recurrence during the continuation and maintenance phases, it is also important to understand the efficacy of these medications in the months and years following the acute-phase treatment response. Most antidepressants have data demonstrating that they are more efficacious than placebo in preventing depressive episodes with long-term treatment.

Long-Term Treatment Results

The results of a large randomized study[4] of 3-year maintenance treatment showed that imipramine (200 mg) is effective in preventing recurrence. A subsequent examination[24] of many of these patients over the next 2 years (5 years total) compared patients who received maintenance therapy with imipramine at the dose used to treat their acute episode (average dose, 200 mg) to patients with medication discontinuation. The investigators' survival analysis showed a significant prophylactic effect for imipramine in preventing recurrence beyond 3 years. Mirtazapine and amitriptyline have also been found to be effective in relapse prevention for up to 2 years of maintenance therapy, although amitriptyline showed some signs of reduced efficacy after 20 weeks.[25] The selective serotonin reuptake inhibitor (SSRI) escitalopram has also been found to be more effective than placebo in preventing relapse during 36 weeks of double-blind treatment that followed 16 weeks of acute-phase treatment.[26] A recent systematic review[10] of 31 randomized trials on over 4400 patients demonstrated that continued therapy with all classes of antidepressants significantly reduced the risk of relapse ($p < .00001$) for up to 36 months, with the bulk of the trials lasting 12 months. Specifically, maintenance therapy with antidepressants reduced the odds of relapse by 70% compared with treatment discontinuation ($p < .00001$). Patients in the treatment group had an average relapse rate of 18% compared with patients in the placebo group who had an average relapse rate of 41%.[10]

In addition to tricyclic antidepressants (TCAs), both SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) have been examined for use in long-term treatment of MDD. Recently, 2 long-term (6 to 12 months), double-blind, placebo-controlled studies have shown that venlafaxine is effective in preventing relapse[27] and recurrence.[28] In a study by Simon et al.,[27] MDD patients responding to 8 weeks of open-label treatment with venlafaxine extended release (ER), 75 to 225 mg/day, were randomly assigned to receive double-blind venlafaxine (N = 154) or placebo (N = 138) for up to 6 months additionally. The primary efficacy outcome was the number of patients that had a relapse of depression, based on a Clinical Global Impressions-Severity of Illness scale (CGI-S) score ≥ 4. Time to relapse was analyzed by survival analysis using the log-rank test. At 3 months, the relapse rate was 19% for venlafaxine-treated patients compared with 44% in the placebo group. This pattern continued and reached significance at 6 months with a relapse rate of 28% for patients in the venlafaxine group and 52% for patients in the placebo group (χ^2 test, $p < .001$).[27] The cumulative probability of relapse prevention was also significantly better in the venlafaxine-treated patients than placebo-treated patients (Figure 2).

Figure 2. Cumulative Probability of Relapse Prevention With Venlafaxine Long-Term Treatment[a]



[a]Reprinted with permission from Simon et al.[27] Log rank score: $p < .001$.

In another large, long-term study[28] that was double-blind, randomized, and placebo-controlled, patients with MDD were treated with venlafaxine immediate release, 100 to 200 mg/day, or placebo for up to 6 months. Patients who responded to venlafaxine and were relapse-free during a 6-month open-label period were randomly assigned to a double-blind group of venlafaxine (N = 109) or placebo (N = 116) for up to 12 additional months.[28] The primary efficacy outcome was the same as in the Simon et al. study.[27] After 12 months of double-blind treatment, the cumulative recurrence rate was 22% for venlafaxine-treated patients, which was significantly lower than the rate for placebo-treated patients (55%; χ^2 test, $p < .001$).[28]

The investigational SNRI duloxetine has also been tested in 2 long-term studies: (1) a large scale, open-label, 1-year study[29] and (2) a large, long-term, randomized,

double-blind, and placebo-controlled trial.[30] In the 26-week continuation-phase treatment study,[30] duloxetine-treated patients (60 mg/day) fared significantly better than placebo-treated patients on the primary outcome measure of time to relapse. Also, significantly fewer patients given duloxetine relapsed than did patients in the placebo group.[30]

Few Comparative Head-to-Head Studies

While long-term head-to-head studies comparing SNRIs to SSRIs are rare, a few publications are available to provide insight on the comparative efficacy of several classes of antidepressants. First, in a large systematic review of 31 randomized trials with 4410 patients, Geddes et al.[10] examined mainly TCAs (15 randomized trials) and SSRIs (10 randomized trials), while another 4 included monoamine oxidase inhibitors (MAOIs), 2 included noradrenergic reuptake inhibitors, and 1 included an "other" class (one trial had included both a TCA and an MAOI). The majority of the 31 analyzed trials examined 12 months of follow-up treatment following acute-phase treatment. In this meta-analysis, the investigators did not detect any significant difference in efficacy between antidepressant classes.[10]

Kelsey and Entsuah[31,32] conducted a pooled analysis of 8 double-blind, randomized, active-comparator–controlled trials with parallel groups in which patients were treated with venlafaxine (75–375 mg/day) or SSRIs (fluoxetine, paroxetine, or fluvoxamine). The analyses examined remission rates in depressed patients with a shorter (≤ 52 weeks) or longer (> 52 weeks) duration of illness. Venlafaxine-treated patients had significantly higher remission rates than SSRI- and placebo-treated patients for depression durations ≤ 52 weeks and > 52 weeks. Remission rates were also examined for depression duration divided into 4 quartiles: ≤ 8 weeks, > 8 to ≤ 24 weeks, > 24 to ≤ 72 weeks, and > 72 weeks. Remission rates were significantly greater for venlafaxine than SSRIs beginning at week 2 in patients who had been diagnosed with MDD within the last 52 weeks and beginning at week 6 in patients who had been diagnosed more than 52 weeks prior to the study. Also of note, venlafaxine may be better than SSRIs in treating depression of long duration (i.e., severe depression), based on the significantly higher remission rates for venlafaxine compared with SSRIs in patients who had been diagnosed with MDD more than 72 weeks prior to the study.

In one recent randomized, controlled, rater-blinded trial,[33] outpatients with MDD were randomly assigned to receive open-label treatment with venlafaxine ER (75–225 mg/day) or one of 4 SSRIs (fluoxetine, paroxetine, sertraline, or citalopram) for 180 days. The sustained remission rates were significantly higher for venlafaxine than SSRIs at 90 days ($p = .041$) and nearly significant at 135 days ($p = .051$). Also, Kaplan-Meier time to remission was significantly better for venlafaxine than SSRIs ($p = .006$). These results suggest that the SNRI venlafaxine is at least as effective as SSRIs and may bring patients to remission earlier than SSRIs. However, long-term, head-to-head studies are needed to determine if there are long-term advantages to SNRIs over SSRIs. While it is unclear from the available evidence if the short-term differences seen between SNRIs and SSRIs disappear later in treatment, it may be that the early onset of remission with SNRIs has long-lasting benefits in terms of patient prognosis and preventing relapses.[31]

In order to draw definitive conclusions on the comparative efficacy of different classes of antidepressants, and SNRIs versus SSRIs specifically, several qualifications would need to be met. First of all, more long-term head-to-head randomized controlled trials are needed. Second, standardized trial designs and statistical methods are needed.[34] For example, long-term studies that lack an active comparator or placebo group are of limited use when attempting to evaluate relative efficacy. Similarly, studies can be limited by the lack of a prospective design to evaluate relapse or recurrence prevention, the lack of a precise definition of relapse, or failure to randomize patients following acute-phase treatment to determine group assignment for the continuation phase.[34] As a consequence of insufficient group sizes, many studies lack the statistical power to conduct important statistical analyses.[35] Further, without larger sample sizes on the order of 300 patients per arm, negative results may be due to equal efficacy between groups or a false-negative due to type II error.[36]

Another problem that arises, especially in long-term studies, is a high dropout rate. In shorter clinical trials, approximately 15% to 30% of patients will withdraw before completing the study.[7,10,36,37] In long-term studies, the dropout rates for placebo groups may be 45% to 60%, while active-treatment groups may have dropout rates of approximately 21% to 35%.[28,38] In order to compare results from different clinical trials, these dropouts and missing data points need to be handled with similar statistical methods, or if different methods are used, their differences need to be well understood by clinicians. For example, the last-observation-carried-forward (LOCF) method assumes that there is no further improvement in outcome beyond the last observation point. Another method is the likelihood-based mixed-model repeated measures (MMRM) approach.[29,38] This model uses information from previous data points to estimate data for missing points.[38] What is most important for clinicians to understand is that mean changes from baseline to endpoint and remission rates are numerically greater with the MMRM method than the LOCF method.[38]

Long-Term Tolerability

Discontinuation for lack of efficacy is often higher in the placebo group than the treatment group in long-term studies of antidepressants in patients with MDD, which demonstrates the low incidence of side effects adversely

affecting patients' compliance. Discontinuations due to adverse events have been similar for placebo (7%) and venlafaxine (5%) in long-term studies.[28] Venlafaxine has not been associated with any increased risk for an individual adverse event.[33] Treatment with maximally tolerated venlafaxine doses is also associated with an incidence of common adverse events similar to that of placebo and tolerability comparable to SSRIs.[33,39] The side effects most noteworthy during long-term venlafaxine administration are weight gain and sexual dysfunction, with 6% of men reporting sexual dysfunction in 1 study.[28]

SUMMARY

Both SSRIs and SNRIs have been shown to be effective and similarly well-tolerated in long-term treatment of MDD. While it is unclear from the data if continued treatment with SNRIs confers advantages over SSRIs, due to an early onset of remission, further studies will provide valuable insights into the efficacy of SNRIs and SSRIs in maintenance therapy.

Drug names: amitriptyline (Elavil and others), citalopram (Celexa), duloxetine (Cymbalta), escitalopram (Lexapro), fluoxetine (Prozac and others), imipramine (Tofranil and others), lithium (Eskalith, Lithobid, and others), mirtazapine (Remeron and others), paroxetine (Paxil and others), sertraline (Zoloft), venlafaxine (Effexor).

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