Treatment of Major Depression: Is Improvement Enough?

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The goals of antidepressant treatment are to induce remission and prevent relapse or recurrence. While response is the standard criterion applied to comparisons of antidepressant drugs indicating an improvement from baseline, the more stringent criterion of remission is more relevant to clinical practice because it indicates that the patient is asymptomatic (i.e., "well"). Patients may enter into a remission or partial remission, which is characterized by the presence of residual symptoms and an increased risk of relapse, impairment, and suicide. Studies with many antidepressants demonstrate response rates of 50% to 60% but remission rates of only 20% to 30%. Venlafaxine is an antidepressant that is characterized as a serotonin-norepinephrine reuptake inhibitor (SNRI). Using the criterion of remission, placebo-controlled and comparative trials demonstrate a higher remission rate with venlafaxine than with other antidepressants, thus improving the proportion of patients who are "well." Selection of optimal antidepressant therapy should consider drugs that have the greatest potential to induce remission. *(J Clin Psychiatry 1999;60[suppl 6]:10–14)*

Drug development in psychiatry has evolved from a process dependent on chance discovery to one based on targeting specific mechanisms of action believed to be important in the pathophysiology underlying psychiatric syndromes. Antidepressant pharmacotherapy is the first area to have substantially benefited from this evolution. The primary goals of antidepressant treatment are the reduction and elimination of all signs and symptoms of the depressive syndrome, the restoration of occupational and psychosocial function to that of the asymptomatic state, and a reduction of the likelihood of relapse and recurrence.[1] Despite the positive response to antidepressant therapy by some patients, the data from clinical trials indicate that as many as 40% to 50% of depressed patients do not respond to monodrug therapy.[1] An even lower rate is reported when the more stringent definition of remission is used. In addition, questions have arisen about the efficacy of selective serotonin reuptake inhibitors (SSRIs), especially in hospitalized patients with severe, melancholic depression.[2–5] Important issues for consideration are the optimal outcome measure to assess response and the effectiveness of antidepressant therapy in attaining this response.

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Presented at the satellite symposium "Goal of Antidepressant Therapy: Response or Remission and Recovery?" which was held at the 21st Collegium Internationale Neuropsychopharmacologicum Congress, July 14, 1998, in Glasgow, Scotland, and supported by an unrestricted educational grant from Wyeth-Ayerst Laboratories.

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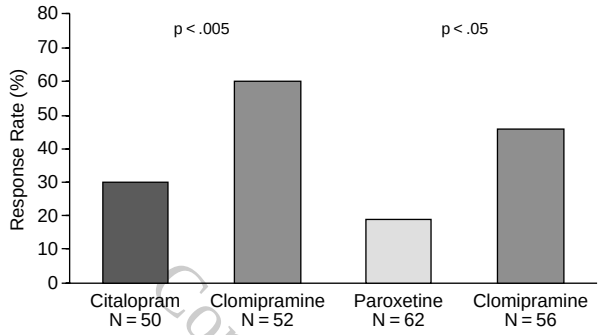
WHAT IS THE OPTIMAL OUTCOME FROM ANTIDEPRESSANT TREATMENT?

An important issue in the pharmacotherapy of major depression is the criterion that defines the outcome of antidepressant therapy. Response, usually a 50% or greater reduction from baseline in the Hamilton Rating Scale for Depression (HAM-D) or Montgomery-Asberg Depression Rating Scale (MADRS) score, is the standard criterion applied in clinical trials of antidepressant drugs. However, response may not be a relevant endpoint for major depression in clinical practice since a responder may still display residual symptomatology. For example, a patient with severe depression and a baseline HAM-D score of 30 may be classified as a responder with a HAM-D score of 15 but still have significant symptoms. Further, because HAM-D scores tend to decline at a similar rate regardless of the severity of depression, severely depressed patients may require a longer course of therapy to achieve a response.[6]

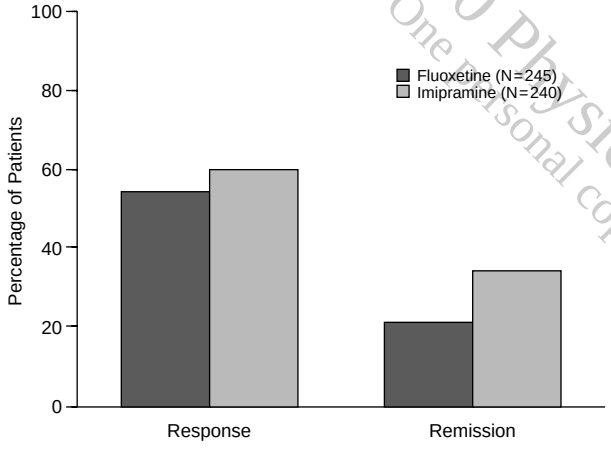
Partial remission, in which patients experience residual symptoms of depression, has been reported in up to 30% to 40% of patients,[7,8] and may be associated with a higher relapse rate,[9–11] functional impairment,[12] and, by inference, a higher suicide rate. Patients experiencing partial remission are characterized by a greater initial severity of depression, more psychological symptoms, female gender, the emergence of passive/dependent/avoidant traits, and deteriorating self-esteem.[8] When faced with a partial remission, the approach is to ensure optimal dose and duration of the current drug therapy. Alternative strategies are to switch to a different drug, use augmentation or drug combination strategies, or introduce other treatment strategies, such as psychotherapy or electroconvulsive therapy.

Figure 1. Remission or "Complete Response" (HAM-D-17 total score ≤ 7) in Inpatients With Major Depression[a]



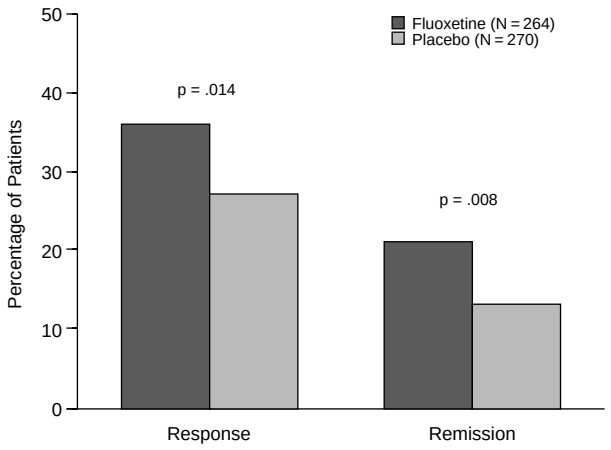
[a]Data from references 2 and 3. Abbreviation: HAM-D-17 = 17-item Hamilton Rating Scale for Depression.

Figure 2. Response (≥ 50% decrease HAM-D-21 total score) and Remission (HAM-D-21 total score ≤ 7) in Inpatients With Major Depression[a]



[a]Data from reference 14. Abbreviation: HAM-D-21 = 21-item Hamilton Rating Scale for Depression.

Figure 3. Response (≥ 50% decrease in HAM-D score) and Remission (HAM-D-21 total score ≤ 7) in Geriatric Patients With Major Depression[a]



[a]Data from reference 15. p Value is for difference between fluoxetine and placebo.

The more stringent criterion of remission, which may be defined by a HAM-D score of less than 8 or a Clinical Global Impressions (CGI) improvement score of 1, may be more relevant to clinical practice because it indicates that the patient is well and without residual symptoms of depression.[13] Increasingly, clinical trials should be conducted with remission as the primary outcome criterion for comparing efficacy.

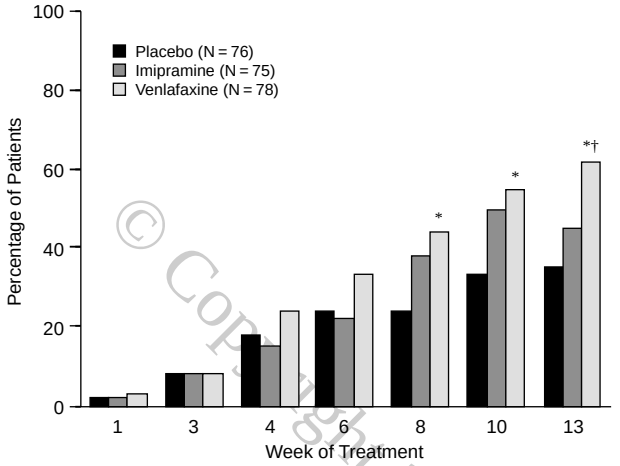
REMISSION RATES WITH ANTIDEPRESSANTS

Published literature on antidepressant treatment of major depression was surveyed to identify studies that reported remission rates so as to highlight differences among treatments, particularly with SSRIs and tricyclic antidepressants (TCAs). In most cases, remission was defined as a 17- or 21-item HAM-D score of 10 or less or a CGI improvement score of 1 (very much improved).

The SSRIs paroxetine and citalopram were compared with clomipramine in hospitalized patients with severe depression.[2,3] Overall, the results from the Danish University Antidepressant Group (DUAG) trials indicated that a significantly greater proportion of patients achieved remission with clomipramine than with paroxetine or citalopram (Figure 1).[2,3] Both studies enrolled inpatients with endogenous and nonendogenous major depression and defined outcome as a final 17-item HAM-D total score ≤ 7. Among patients randomly assigned to 5 weeks of clomipramine or citalopram, 28% taking citalopram and 60% taking clomipramine achieved remission ($p < .005$).[2] In the second study, 19% of patients taking paroxetine and 46% taking clomipramine achieved remission ($p < .05$).[3]

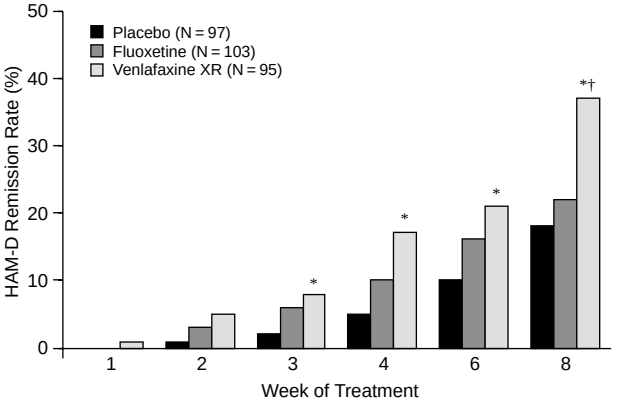
Two controlled studies reported remission rates with fluoxetine. In a 6-week multicenter trial, severely depressed inpatients with a mean baseline 21-item HAM-D score > 28 were randomly assigned to fluoxetine or imipramine.[14] Using an outcome criterion of a final HAM-D-21 score ≤ 7, 21.2% of patients taking fluoxetine and 34.3% taking imipramine achieved remission (Figure 2). In a multicenter, placebo-controlled trial, ambulatory patients aged 60 years and older with major depression were randomly allocated to placebo or fluoxetine 20 mg/day for 6 weeks.[15] Remission (final HAM-D-21 score ≤ 7 after ≥ 4 weeks of therapy) was reported in 21% of patients with fluoxetine and 13% with placebo ($p < .05$) (Figure 3). These results are consistent with other placebo- or active-controlled clinical trials, which show a remission rate of approximately 20% to 30% with SSRIs during short-term therapy.[16–19]

Figure 4. Proportion of Patients With a CGI Improvement Score of 1 (very much improved) During 13 Weeks of Treatment[a]



[a]Adapted from reference 22, with permission.
Abbreviation: CGI = Clinical Global Impressions scale.
*p < .05 vs. placebo.
†p < .05 vs. imipramine.

Figure 5. HAM-D Remission Rates for Patients Treated With Placebo, Fluoxetine, or Venlafaxine XR[a]



[a]Adapted from reference 24, with permission. Remission defined as HAM-D-21 total scores less than 8.
*p ≤ .05 vs. placebo.
†p < .05 vs. fluoxetine.

REMISSION WITH VENLAFAXINE

Results from controlled clinical trials comparing venlafaxine with SSRIs and TCAs consistently demonstrate a significant benefit for venlafaxine using various criteria for remission.[20–24]

A 13-week, placebo-controlled trial compared venlafaxine and imipramine (75 to 150 mg/day) in patients with depression treated in the general practice setting.[22] Overall, venlafaxine was significantly superior to placebo and comparable to imipramine. When patients with a CGI improvement score of 1 (very much improved) were considered, venlafaxine produced a significantly ($p < .05$) greater improvement than either imipramine or placebo at week 13 (Figure 4).

A number of controlled studies have reported remission rates with venlafaxine and SSRIs during short-term therapy. A comparative, randomized, multicenter trial of venlafaxine, 200 to 300 mg/day, and paroxetine, 30 to 40 mg/day, was conducted in inpatients and outpatients with major depression.[23] Using a remission criterion of a final HAM-D-17 score < 10, significantly ($p = .02$) more patients receiving venlafaxine than paroxetine achieved remission. A multicenter, parallel study randomly allocated outpatients with major depression to venlafaxine or fluoxetine. In this study, the dose of medication could be increased to venlafaxine, 150 mg/day, or fluoxetine, 40 mg/day, after 3 weeks.[21] Among the subgroup of patients who increased their dose, significantly ($p < .05$) more patients taking venlafaxine (58%) than fluoxetine (35%) achieved a CGI improvement score of 1 (very much improved) at the final evaluation.

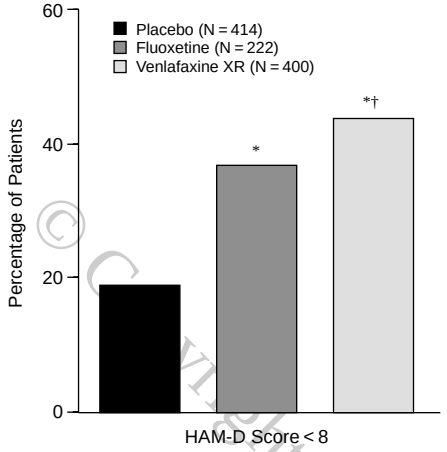
The robust efficacy with higher doses of venlafaxine has also been observed in a comparative trial with sertraline.[20] This 8-week comparative, multicenter trial randomly assigned hospitalized patients and outpatients with major depression to either venlafaxine or sertraline. Significantly ($p < .05$) more patients taking venlafaxine than taking sertraline achieved remission (HAM-D-21 score < 10) at both the 8-week and the final evaluation. Among patients who increased their dose after 2 weeks, the remission rate was 62% with venlafaxine and 30% with sertraline ($p < .05$).

Venlafaxine extended release (XR) and fluoxetine were compared in a multicenter, randomized, placebo-controlled study.[24] In this study, outpatients with major depression were randomly assigned to 8 weeks of treatment with either venlafaxine XR (75 to 225 mg/day), fluoxetine (20 to 60 mg/day), or placebo. Response rates (≥ 50% reduction in the HAM-D-21 score) were comparable; however, significantly ($p < .05$) more patients taking venlafaxine XR (37%) achieved full remission (HAM-D-21 total score < 8) at the end of treatment than patients receiving either fluoxetine (22%) or placebo (18%) (Figure 5).[24] The proportion of patients who attained full remission with venlafaxine XR was approximately twice that of fluoxetine or placebo. A pooled analysis of data from 4 studies found a significantly higher remission rate (final HAM-D score < 8) with venlafaxine XR (45%) compared with placebo (18%) or fluoxetine (37%) (Figure 6).[24–27]

VENLAFAXINE: HYPOTHESIS FOR MORE ROBUST EFFICACY

Clearly, there are questions about the efficacy of SSRIs in hospitalized patients with major depression.[2–5]

Figure 6. Pooled Analysis of Remission Rate (final HAM-D score < 8) for Venlafaxine XR and Fluoxetine From Placebo-Controlled Trials[a]



[a]Data from references 24–27.
*p ≤ .001 vs. placebo.
†p < .05 for venlafaxine XR vs. fluoxetine.

Major depression may be related to disturbances of both the norepinephrine and serotonin systems within the brain that affect functional neurobehavioral systems.[28] It has been hypothesized that differences in efficacy between SSRIs and antidepressants with combined serotonin-norepinephrine activity may be due to the single mechanism of action of SSRIs.[29] Some authors have suggested that antidepressants with a combined mechanism of action may produce a more robust response in a broader range of patients.[29] Thus, it may be that the enhanced efficacy of venlafaxine results from the engagement of 2 or more mechanisms of action over a clinically relevant dosing range that are capable of mediating an antidepressant response.[30] This combination of 2 mechanisms of action and a positive dose-response may explain the robust efficacy of venlafaxine, especially at higher doses, compared to other antidepressants. Indeed, the results of comparative and placebo-controlled trials conducted in diverse patient populations and settings indicate that when using the stringent criterion of remission, venlafaxine consistently demonstrates superiority over other antidepressants.

The dose-response effects of venlafaxine were clearly demonstrated in a placebo-controlled trial in outpatients with major depression.[31] Patients received either placebo or venlafaxine at doses of 75, 150 to 225, or 300 to 375 mg/day. A dose-related decrease in HAM-D scores was noted over time. More importantly, as the dose of venlafaxine increased, median HAM-D scores decreased, while the proportion of patients with a HAM-D score of 8 or less increased from 25% to 54%. On the basis of these findings, this study established a positive relationship between increasing venlafaxine dose and remission over the dosage range of 75 to 300 mg/day.

CONCLUSION

An unmet need in depression is for drugs that get the patient to full recovery or well. Common definitions of clinical response can be misleading since patients may still have residual symptomatology after treatment of major depression. Partial remission is a common outcome of major depression and is associated with a high rate of relapse and the potential for the development of treatment resistance or chronic depression. A more relevant outcome in clinical practice is remission, because it indicates the absence of symptoms; in effect, the patient is "well."

While response rates of 50% to 60% are common with all antidepressants, much lower remission rates of 20% to 30% are typical with SSRIs. A growing body of clinical data with venlafaxine demonstrates a consistently higher remission rate of 35% to 45% or greater, particularly with higher doses, in comparative studies with TCAs or SSRIs, thus improving the proportion of depressed patients who get "well." Selection of optimal antidepressant therapy should consider drugs with the greatest potential to induce remission and hence complete patient recovery.

Drug names: citalopram (Celexa), clomipramine (Anafranil), fluoxetine (Prozac), imipramine (Tofranil and others), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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