

Characterizing the Ideal Antidepressant Therapy to Achieve Remission

Ian Nicol Ferrier, M.D.

© A paradigm shift in the management of depression has transpired in recent years with the modification of treatment goals toward remission, an outcome that transcends response. Pharmacotherapy, psychotherapy, electroconvulsive therapy, and combination therapies are treatment modalities available to the clinician for facilitating remission in depressed patients. For patients with moderate-to-severe depression, pharmacotherapy, either alone or in combination with other therapeutic approaches, is the treatment of choice. Antidepressants have heterogeneous effects on neurotransmitter systems that are manifested in different levels of selectivity and potency, influencing the drugs' safety profile through their potential for inducing drug-drug interactions. In terms of the pharmacokinetic-pharmacodynamic characteristics of antidepressants, a positive dose-response relationship has been shown to enhance the achievement of full remission because it allows the clinician to maximize drug dosage to optimize efficacy. Evidence from several studies indicates that treatment strategies that involve combined serotonergic and noradrenergic mechanisms result in pharmacologic synergism that leads to an enhanced antidepressant effect. This article identifies key characteristics of antidepressants that have been associated with greater efficacy. (*J Clin Psychiatry* 2001;62[suppl 26]:10–15)

Current guidelines for the treatment of major depression in the clinical practice setting aim for the achievement of remission, i.e., the state of well-being characterized by a reduction in and ultimate removal of all signs and symptoms of depression, a restoration of pre-morbid psychosocial and occupational functioning, and a reduction in the risk of relapse and recurrence.^{1,2} Operationally, remission is generally defined as a Hamilton Rating Scale for Depression (HAM-D) score ≤ 7 ,² although some studies define remission as a HAM-D score < 10 .^{3–5} Earlier clinical trials have evaluated treatment efficacy according to a less stringent criterion of response—a $\geq 50\%$ reduction in symptoms relative to baseline. However, the apparent attainment of a treatment response may only, in fact, be indicative of a partial treatment response, because, quite commonly (especially in treatment-resistant depression), residual symptoms and functional impairment may still persist (see Bakish⁶). The trend in psychiatry of shift-

ing the treatment goal from the attainment of response to the achievement of remission raises treatment expectations and applies more stringent criteria toward the evaluation of therapeutic options, including pharmacotherapy, psychotherapy, and electroconvulsive therapy.

For patients with moderate-to-severe depression, drug therapy, either alone or in combination with other approaches, is the treatment of choice.¹ Drug therapy is often preferred over psychotherapy in this setting because it has a faster onset of effect and therefore provides faster symptom relief. For the same reason, drug therapy is sometimes preferred for patients with mild depression, even though its use is less widely accepted for that patient population. The following sections will focus on antidepressant therapy and, particularly, on identifying those characteristics of an antidepressant that are associated with greater efficacy. Since there is considerable interest in evaluating the newer selective antidepressants in comparison with the older mainstays of therapy, the tricyclic antidepressants (TCAs), particular focus is given to those agents.

From the Department of Psychiatry, School of Neuroscience and Psychiatry, University of Newcastle upon Tyne, Newcastle upon Tyne, United Kingdom.

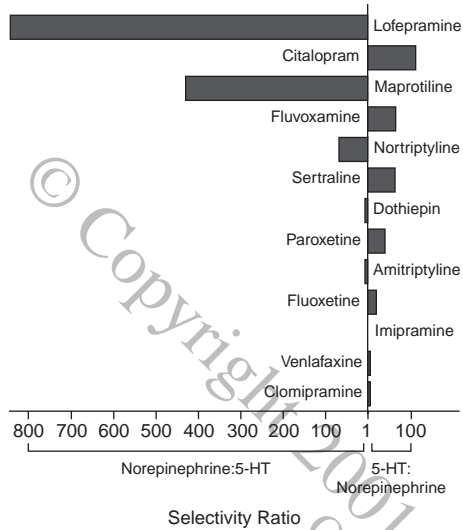
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Reprint requests to: Ian Nicol Ferrier, M.D., University Department of Psychiatry, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP, UK (e-mail: i.n.ferrier@ncl.ac.uk).

CHARACTERIZING ANTIDEPRESSANTS

Derangements in the neurotransmission of catecholamines, particularly norepinephrine and serotonin, are postulated to be key mechanisms in the pathophysiology of depression.^{7,8} Most antidepressants directly affect 1 or both of these neurotransmitter systems and, to a lesser extent, dopamine neurotransmission by blocking their reuptake, hence increasing their presynaptic levels.⁹

Figure 1. Selectivity of Antidepressants for Reuptake Inhibition of Norepinephrine Over Serotonin (5-HT; norepinephrine:5-HT) and 5-HT Over Norepinephrine (5-HT:norepinephrine)^a



^aAdapted from Richelson,⁹ Noble and Benfield,¹⁰ and Bolden-Watson and Richelson.¹¹ Selectivity is expressed as the ratio of inhibition constant (K_i) for norepinephrine and 5-HT.

Antidepressants, even those within the same class, have heterogeneous effects on neurotransmitter systems that are manifested in different levels of selectivity and potency. Selectivity is derived from the ratio of the kinetic parameter inhibition constant (K_i) for 2 neurotransmitters, i.e., K_i for reuptake blockage of norepinephrine over that of serotonin; potency is defined as the inverse of the K_i . Antidepressants have varying levels of selectivity for neurotransmitters. An antidepressant is equally selective for 2 neurotransmitters when the ratio approaches 1 (Figure 1).⁹⁻¹¹ In general, antidepressants that have a 20-fold or greater selectivity ratio for serotonin over norepinephrine (e.g., the selective serotonin reuptake inhibitors [SSRIs]) are not likely to inhibit norepinephrine reuptake at therapeutic dosages.⁸ Conversely, the TCAs lofepramine, maprotiline, and nortriptyline are substantially more selective for norepinephrine than they are for serotonin. Other TCAs such as imipramine, clomipramine, and amitriptyline have a dual mechanism of action, with roughly equivalent selectivity for norepinephrine and serotonin (selectivity ratio lower than 6).^{7,8} The newer antidepressant venlafaxine (a serotonin-norepinephrine reuptake inhibitor [SNRI]) also exhibits a selectivity ratio consistent with a dual mechanism of action.^{8,11} Data from healthy volunteers confirmed preclinical findings, showing the sequential engagement of the serotonin and norepinephrine systems throughout the clinically relevant dosage range of venlafaxine.¹²

The potency of an antidepressant is a crucial pharmacological property that determines efficacy and tolerability.

Potent reuptake inhibitors tend to block the reuptake of a particular neurotransmitter at relatively lower dosages than agents with a similar mechanism of action but with lower potency.⁸ The TCAs desipramine and protriptyline, for instance, are substantially more potent at blocking norepinephrine reuptake than other TCAs, whereas the SSRI paroxetine is substantially more potent at blocking serotonin reuptake than sertraline and fluoxetine.^{9,11} Hence, both the selectivity and potency of antidepressants may potentially influence treatment efficacy as it relates to the achievement of remission and improvement of treatment outcomes.

The synaptic effects of antidepressants help to define their side effect profiles. Most of the side effects of these agents are related to the blockade of reuptake of norepinephrine, serotonin, and dopamine or the blockade of histaminergic, cholinergic, and α_1 -adrenergic receptors on postsynaptic neurons.^{8,9} TCAs, for example, present side effects related to their norepinephrine activity (tremors, tachycardia, erectile dysfunction, and effects on blood pressure) and to their particularly high affinities for postsynaptic receptors.⁸ The blockade of the histamine H_1 receptor is associated with sedation, drowsiness, and weight gain; the blockade of muscarinic receptors is commonly associated with constipation and dry mouth. Orthostatic hypotension and palpitations have been attributed to the affinity of TCAs for α_1 -adrenergic receptors.¹³ Overall, newer antidepressants have a much lower affinity for histaminergic, muscarinic, and α_1 -adrenergic postsynaptic receptors than do the TCAs.⁸ SSRIs produce fewer anticholinergic and cardiovascular adverse effects than the TCAs and are not associated with weight gain.¹⁴ Venlafaxine has minimal affinity for postsynaptic receptors and demonstrates an improved adverse effects profile compared with TCAs.^{15,16}

Another important characteristic of antidepressants that impacts their safety profile is their potential for inducing drug-drug interactions. Pharmacokinetic interactions can result from inhibition of the cytochrome P450 isoenzyme system, which is involved in the metabolism of many drugs.⁹ Inhibition of this enzyme system can lead to an increase in plasma levels of certain drugs used concomitantly with antidepressants. Among the newer antidepressants, the SSRIs, and paroxetine and fluoxetine in particular,¹⁷ are associated with significant inhibition of the cytochrome P450 2D6 enzyme.⁹ The dual SNRI venlafaxine has minimal or no effects on the cytochrome P450 system.⁷

In terms of the pharmacokinetic-pharmacodynamic characteristics of antidepressants, a positive dose-response relationship also plays a role in increasing the likelihood of inducing full remission since it enables the clinician to maximize drug dosage in order to reach optimal efficacy and a better treatment outcome. SSRIs are characterized by relatively flat dose-response relationships,¹⁴ which may limit their utility in patients who may need potent antidepressant effects. TCAs have a positive dose-response rela-

tionship¹⁸; however, titrating to maximally effective dosages is often problematic because of their safety and tolerability profiles. In comparison, venlafaxine demonstrates a positive dose-response relationship,¹⁹ which has been attributed to increased reuptake inhibition of norepinephrine that parallels increases in dose.

DOES A DUAL MECHANISM OF ACTION PROVIDE SUPERIOR ANTIDEPRESSANT EFFICACY?

A number of studies and meta-analyses have examined whether antidepressants with a dual mechanism of action (i.e., influencing both serotonin and norepinephrine) have a therapeutic advantage over agents that predominantly influence the activity of a single neurotransmitter system.²⁰⁻²³ When the study endpoint is remission, a more stringent and clinically meaningful endpoint than response, differences in efficacy among antidepressants with single versus dual action are evident.

Nelson²² reviewed 15 double-blind, randomized studies on nonpsychotic major depression that evaluated TCAs exhibiting primarily noradrenergic effects (lofepramine, maprotiline, desipramine, and nortriptyline) and SSRIs (fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, and zimeldine). All but 5 of these studies were conducted in outpatients. No significant differences in treatment response between the noradrenergic and serotonergic agents were found in any individual study. The pooled data also showed no significant differences in overall response rates between the SSRIs and the noradrenergic TCAs. Furthermore, in 3 of the 4 studies evaluating patients with severe depression, the efficacy of treatment with SSRIs and noradrenergic TCAs was comparable. A follow-up analysis of 16 studies evaluating a combined population of more than 2000 patients, which included 7 of the studies previously reviewed by Nelson,²² showed similar results.²⁴

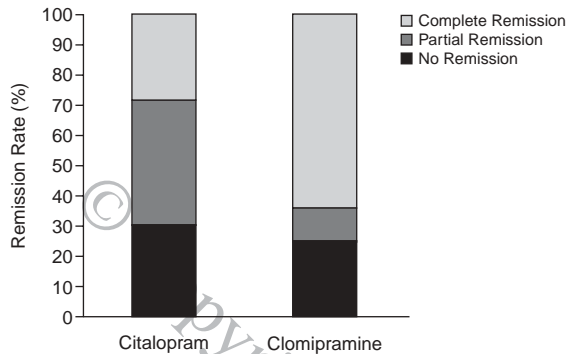
Conversely, early evidence from a small study comparing monotherapy with the noradrenergic TCA desipramine and combination therapy with fluoxetine and desipramine suggested that treatment that engages both noradrenergic and serotonergic systems may enhance remission rates.²⁵ In this study, 14 inpatients with severe depression who did not exhibit a response after 1 week of hospitalization without antidepressant therapy were treated for 4 weeks with desipramine (with rapid dose adjustment using 24-hour plasma desipramine levels) and fluoxetine. A retrospective comparison of this severely ill group with a less severely ill group of 52 patients hospitalized on the same unit who had received 4 weeks of desipramine monotherapy revealed an early robust efficacy for the desipramine-fluoxetine group compared with the monotherapy group in mean HAM-D scores ($p = .007$, week 1), which were maintained throughout the study ($p = .0001$, week 4). Remission was significantly more prevalent in the combina-

tion group, with 71% of patients remitting by week 4 compared with only 6% of those who received desipramine alone ($p = .0002$). Likewise, in another prospective double-blind, placebo-controlled randomized trial of 38 inpatients treated with fluoxetine or desipramine as monotherapy or in combination, a greater proportion of patients receiving combination treatment remitted compared with those receiving either agent alone.³

These studies suggest that the combination of noradrenergic and serotonergic mechanisms of action results in a synergistically enhanced antidepressant effect. This hypothesis has been examined in a number of meta-analyses with the power to detect differences between treatments that do not emerge in individual trials.²⁶ A meta-analysis performed by Anderson and Tomenson²⁷ consisted of data from 55 double-blind studies comparing treatment with SSRIs (fluoxetine, fluvoxamine, paroxetine, sertraline, or citalopram) and TCAs in 4630 patients. The studies were categorized according to patient status (inpatients vs. outpatients), severity of depression (high vs. low baseline scores), and TCA selectivity (serotonergic vs. noradrenergic TCAs).²⁷ Results of this meta-analysis showed no significant difference in response rates between patients treated with SSRIs and those treated with TCAs. Important differences began to emerge, however, when the various subgroups were analyzed. In inpatients and in those with more severe illness, equivalence between SSRIs and TCAs was ambivalent; paroxetine, in particular, was significantly less effective when compared with serotonergic TCAs. Clomipramine and amitriptyline, mixed noradrenergic-serotonergic TCAs, also showed a pharmacotherapeutic edge over SSRIs.

Data from a more recent and updated meta-analysis²³ of a total of 102 randomized controlled trials that evaluated 10,706 patients revealed a similarly significant ($p = .012$) advantage of TCAs over SSRIs in inpatients. Amitriptyline was found to be significantly more effective than the SSRI comparators in this population. Similar findings were obtained when the meta-analysis was restricted to a hospitalized and severely ill patient population.²⁸ The conclusion from these meta-analyses, that TCAs with a dual mechanism of action are significantly more efficacious than SSRIs, echoes the findings of 2 multicenter, randomized, double-blind studies comparing the efficacy of clomipramine with that of paroxetine²⁰ or citalopram.²¹ In the study²¹ comparing citalopram with clomipramine, 30% of patients receiving citalopram and 60% of those receiving clomipramine achieved complete remission after 5 weeks of therapy ($p < .005$). Interestingly, the citalopram group showed higher rates (42%) of partial remission (HAM-D total score of 8-15) than did the clomipramine group (15%; Figure 2).²¹ Similarly, in the study²⁰ comparing paroxetine and clomipramine treatments, the remission rates at the end of the trial (week 6) were 19% and 46%, respectively.

Figure 2. Percentage of Patients With Complete, Partial, and No Remission at Week 5 in a Study Comparing Treatment With Citalopram (N = 50) Versus Clomipramine (N = 52)^a



^aAdapted with permission from the Danish University Antidepressant Group.²¹ $p < .005$, clomipramine vs. citalopram for rates of complete remission.

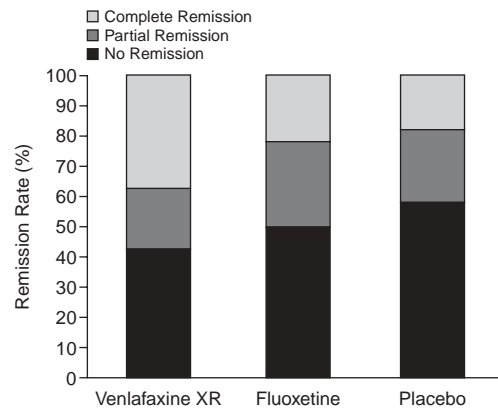
EVIDENCE FOR REMISSION WITH VENLAFAXINE XR TREATMENT

Like some TCAs,²⁹ venlafaxine inhibits both norepinephrine and serotonin reuptake.³⁰ However, unlike TCAs, venlafaxine has no appreciable affinity for histaminergic, α_1 -adrenergic, or muscarinic receptors,³⁰ a characteristic that confers a superior side effect profile over TCAs.

A number of studies have compared the efficacy of venlafaxine and SSRIs in patients with differing clinical status (inpatients, outpatients, melancholic patients, and treatment-resistant patients).^{4,5,31,32} Consistent with conclusions from meta-analyses comparing dual-action TCAs and SSRIs,^{23,27} the results of these studies suggest that venlafaxine produces a significantly more robust effect than do SSRIs. Clerc and colleagues³² reported that venlafaxine was significantly ($p < .05$) more effective than fluoxetine in the treatment of inpatients with major depression and melancholia at the end of a 6-week study. Treatment tolerability was similar for both agents.³² Similarly, in an 8-week study⁴ of treatment-resistant inpatients and outpatients randomly assigned to treatment with either venlafaxine or paroxetine, response rates were significantly better with venlafaxine than with paroxetine (52% vs. 33%, $p = .044$). More importantly, from a clinical perspective, remission rates were significantly higher with venlafaxine than with paroxetine (42% vs. 20%, $p = .01$).⁴

Data from 2 larger studies conducted in outpatients with relatively milder depression support the aforementioned findings.^{5,31} An 8-week, placebo-controlled study³¹ compared the efficacy of treatment with venlafaxine extended-release (XR) formulation and fluoxetine in 301 outpatients (intent-to-treat analysis, N = 295) with major

Figure 3. Percentage of Patients With Complete, Partial, and No Remission at the Final Week 8 Assessment in a Study Comparing Treatment With Venlafaxine Extended Release (XR; N = 103), Fluoxetine (N = 95), or Placebo (N = 97)^a

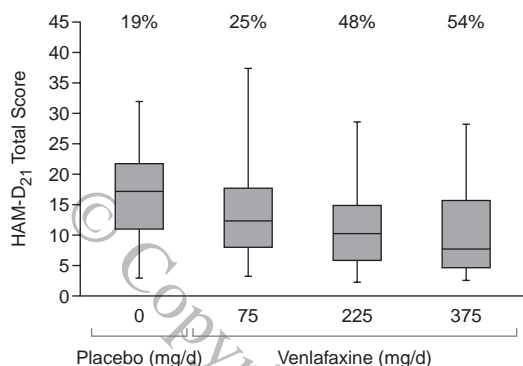


^aAdapted with permission from Rudolph and Feiger.³¹ $p < .05$, venlafaxine XR vs. fluoxetine and placebo for rates of complete remission.

depression. Active drugs were titrated every 2 weeks to maximally tolerated doses to improve treatment response. A significantly ($p < .05$) greater proportion of patients treated with venlafaxine XR achieved full remission compared with those treated with either fluoxetine or placebo (Figure 3).³¹ Remission rates for venlafaxine XR, fluoxetine, and placebo were 37%, 22%, and 18%, respectively, with venlafaxine XR-treated patients also showing lower rates of partial remission than patients receiving the active comparator or placebo.³¹ Likewise, robust differences between venlafaxine and sertraline were seen in the treatment outcome of 147 outpatients with major depression.⁵ Sixty-eight percent of patients treated with venlafaxine achieved remission by the end of the study compared with 45% of patients treated with sertraline ($p = .008$).

Antidepressants with a dose-response effect have a therapeutic advantage over those agents without this pharmacologic property, as long as safety and tolerability of treatment are not compromised at higher drug doses. A number of dose titration studies have shown a substantially more robust effect on remission rates with venlafaxine in comparison with paroxetine,⁴ fluoxetine,^{33,34} or sertraline.⁵ In 2 dose-response studies,^{35,36} higher doses of venlafaxine enhanced antidepressant effects. In a multicenter, double-blind, placebo-controlled study³⁶ of 358 outpatients, the median HAM-D₂₁ total scores decreased progressively as the total daily dose of venlafaxine increased from 75 mg/day to 375 mg/day, while the percentage of patients achieving remission increased proportionally (Figure 4). Likewise, a positive dose-response relationship was demonstrated in another 6-week study³⁵ evaluating the efficacy and safety of 3 different doses of venlafaxine in outpatients with major depression.

Figure 4. Dose-Response Effect of Venlafaxine in 21-Item Hamilton Rating Scale for Depression (HAM-D₂₁) Total Scores and Remission Rates (HAM-D₂₁ total score ≤ 8)^a



^aAdapted with permission from Rudolph et al.³⁶ The dose-response relationship was significant ($p \leq .01$, Jonckheere-Terpstra test for ordered alternatives). Vertical lines represent the full range of scores, boxes represent the middle 50% of scores, horizontal lines in boxes represent median group scores, and numbers above the vertical lines indicate percentage of patients who achieved remission in each group.

The overall clinical profile of venlafaxine XR as well as emerging data suggest that the robust antidepressant effects of this drug may exceed the attainment of full acute remission, potentially facilitating a sustained recovery that will improve the long-term prognosis of patients with major depression.

CONCLUSIONS

The high prevalence of major depression and the risk of chronicity and persisting subsyndromal states that contribute to high levels of disability and impairment underscore the importance of treating a depressed patient to full remission. There is a pressing need for antidepressant medications that can effectively and safely resolve the signs and symptoms of this disorder and restore premorbid levels of functioning among patients with major depression. Antidepressant efficacy appears to be enhanced by a dual mechanism of action involving serotonin and norepinephrine neurotransmitter systems as well as a dose-response relationship profile. The use of TCAs as first-line antidepressant treatment may no longer be justifiable due to issues relating to safety and tolerability. SSRIs have significantly lower affinity for the neuroreceptors that are associated with the side effects of TCAs, but, on the other hand, SSRIs are not as effective as the dual-action TCAs in some circumstances. Dual-action venlafaxine is significantly better than the SSRIs in achieving remission and has a benign side effect profile even at higher therapeutic doses that are, in turn, associated with good outcome. These characteristics suggest that the efficacy and safety profile of venlafaxine may offer important therapeutic advantages over other existing agents, including SSRIs and TCAs.

Drug names: amitriptyline (Elavil and others), citalopram (Celexa), desipramine (Norpramin and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), paroxetine (Paxil), protriptyline (Vivactil), sertraline (Zoloft), venlafaxine (Effexor).

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