# Effectiveness of Antidepressants: Comparative Remission Rates

Michael E. Thase, M.D.

Historically, clinical researchers have gauged the short-term effectiveness of antidepressants by response rates, which have been defined as a "significant" reduction of symptoms or a global impression of at least moderate benefit. However, increased focus over the past decade has led many researchers to suggest that remission, i.e., a virtual elimination of depressive symptoms and restoration of psychosocial functioning, should be the primary goal of the initial phase of therapy. This article examines the relative efficacy of various antidepressant therapies. There is some evidence that medications affecting multiple neurochemical systems, such as the tricyclics amitriptyline and clomipramine (in studies of hospitalized patients) and the more selective "dual reuptake inhibitor" venlafaxine, may result in higher rates of remission relative to other agents. Given the better tolerability of newer antidepressants relative to tricyclics, both logic and an increasing amount of data support a greater role for multiaction antidepressants. *(J Clin Psychiatry 2003;64[suppl 2]:3–7)*

Researchers rely on quantitative evaluation tools such as the Hamilton Rating Scale for Depression (HAM-D) to assess the efficacy of treatments for depression, chart the course of illness, and identify important points of change in illness activity, such as response, remission, and recovery. However, pragmatic obstacles have impeded the use of such measures in day-to-day clinical practice and, as a result, a gap has emerged between research practices and clinical realities. Understanding the deleterious influence of subsyndromal symptomatology on the longer-term outcome associated with depressive disorders has led an increasing number of researchers to regard a reduction in symptom severity as an insufficient indicator of successful treatment.

In order to optimize the prognosis of patients with depressive disorders, remission, i.e., a virtual elimination of symptoms and a return to premorbid functionality, has been recommended as the target of the initial phase of treatment. Establishing a more stringent standard of successful treatment may entail some practical problems; however, guidelines[1] now recommend that specific physician- or patient-rated evaluation tools and cutoff points be used in clinical practice to monitor treatment outcomes.

*From the University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, Pittsburgh, Pa.*

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*Corresponding author and reprints: Michael E. Thase, M.D., University of Pittsburgh Medical Center, Western Psychiatric Institute and Clinic, Department of Psychiatry, 3811 O'Hara St., Pittsburgh, PA 15213 (e-mail: thaseme@msx.upmc.edu).*

Many treatment options are available to help depressed patients achieve these higher standards. Some patients respond readily to conventional antidepressant monotherapy and rapidly achieve remission. For those who respond but who do not remit, increasing the dosage above the usual maximum or extending the duration of treatment may be worthwhile. The safety of newer antidepressants also permits physicians to combine these medications rather liberally. In addition, newer medications such as venlafaxine and mirtazapine, which affect multiple neurochemical systems, may reduce the need for combining antidepressants. Psychotherapy, alone or in combination with antidepressants, is another a potential option. In severe or treatment-resistant cases, electroconvulsive therapy (ECT) may be necessary. Due to the large number of viable treatment options, the chances of ultimately finding the right therapy for a particular patient with difficult-to-treat depressive disorder may never have been better.

## DEFINITIONS OF REMISSION AND RESPONSE

Until the early 1990s, treatment researchers had inconsistently applied and intermixed outcome definitions such as *response*, *remission*, and *recovery*. Despite wide use, the terms lacked the stable, univocal meaning necessary for comparing results across studies. In 1989, a task force was assembled to examine the consistency with which terms describing points of change in the course of depression were being used by researchers and the degree to which inconsistency might impede research. A review[2] of articles on depression published in 9 prominent journals during 1987 and 1988 showed no consensus among researchers of depression on the definition of remission or

Table 1. Clinical Correlates of Subsyndromal Depressive Symptoms

| Study | Risks Associated With Subsyndromal Symptoms |
|---|---|
| Paykel et al[9] | Increased risk of relapse |
| Van Londen et al[10] | Increased risk of relapse |
| Thase et al[11] | Increased risk of relapse |

on operational criteria for identifying it. Without clear consensus, it was difficult to establish the relative efficacy of various treatments.[3]

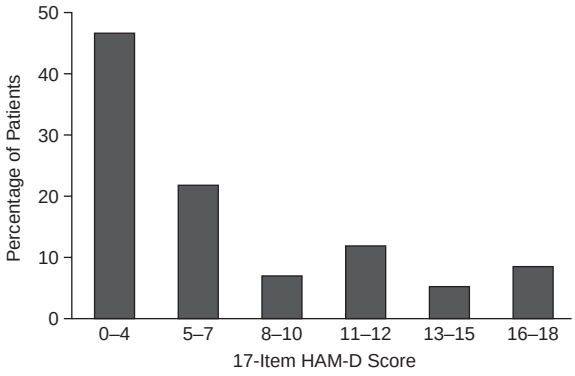
A convention emerged among researchers to regard a 50% reduction in depressive symptoms as measured, for example, by the HAM-D or Montgomery-Asberg Depression Rating Scale (MADRS) as an indicator of efficacy.[3] Physicians' ratings of therapeutic benefit, patients' self-reported improvement ratings, and appraisals by independent evaluators have sufficient agreement to justify the reliability of such a standard to test the efficacy of antidepressants relative to placebo.

However, a 50% reduction of a score on a depression rating scale usually does not reflect a true clinical remission. Even residual depressive symptoms have significant consequences. In a study of 9900 adults who had never been diagnosed with major depressive disorder, Horwath et al.[4] found that more than 50% of cases of first-onset major depression that occurred during a 1-year follow-up had been preceded by minor depressive symptoms. In a 1997 study, Judd et al.[5] found that subsyndromal depressive symptoms were associated with significant increases in health care costs, receipt of welfare and disability benefits, and suicidal ideation and attempts. In fact, Maier et al.[6] found that patients with subsyndromal depressive symptoms were as impaired as those with diagnosable depressive disorders (Table 1).

One proposed solution to the problem of identifying a higher grade of response was to require that the level of depressive symptoms fall below a low threshold value on a relevant rating scale such as the HAM-D. Frank et al.[3] recommended a score of ≤ 7 on the 17-item HAM-D. Ballenger[7] subsequently suggested a score of 1 (i.e., very much improved) on the Clinical Global Impressions (CGI) scale or a 70% reduction on a standard rating scale. Although the particular definitions are arbitrary, very few healthy, highly functional people have more than 1 or 2 minor depressive symptoms.

Research is clarifying the negative effect of residual symptoms on prognosis. For example, in a study of 215 outpatients with major depressive disorder being treated with fluoxetine, Nierenberg et al.[8] found that 10% of "remitters" actually met formal criteria for either minor or subsyndromal depression. Paykel and colleagues[9] found that 32% of those treated for major depression when remission was defined using Research Diagnostic Criteria had significant residual symptoms and 75% of those who had an early relapse also had residual symptoms (Figure 1). These results were echoed by a Dutch study[10] that found that patients with residual symptoms after treatment for major depressive disorder tended to relapse quickly, after an average of 4 months, compared with 12 months among those without residual symptoms. Thase et al.[11] examined the risk of incomplete remission in patients treated with cognitive therapy. They found that the risk of relapse among incompletely remitted patients was 5 times greater than among fully remitted patients during the first year after termination of therapy. Research of this kind has led an increasing number of experts to recommend that the goal of acute phase therapy is complete elimination of symptoms and a return to premorbid functioning.[12]

Figure 1. Percentages of Patients With Various Scores on 17-Item HAM-D at Time of Remission According to Research Diagnostic Criteria for Remission[a]




[a]Adapted with permission from Paykel et al.[9]
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

This definition of remission is, however, qualitatively different from the definition used in other areas of medicine. Whereas an oncologist may apply a pathologically based definition of remission (i.e., an absence of cancerous cells), clinicians treating depressed people must rely on reports of signs and symptoms. The assumption that depressed patients' mood disorders have been cured even after a sustained successful treatment period is unwarranted. Antidepressants appear to suppress the pathophysiologic correlates of depression, not truly cure the disorder. The clinical implication is that premature interruption of treatment may cause pathophysiologic mechanisms to rebound, thus hastening relapse. Increasingly long periods of continuation and maintenance pharmacotherapy are thus recommended to lessen vulnerability and to help ensure that remission will lead to sustained recovery.

## TREATMENT EFFICACY AND REMISSION

If the initial goal of the treatment of depression is remission, then determining if some therapies are more likely to

result in remission is important. Gathering data on the relative strengths of therapeutic modalities ultimately provides physicians with empirically justified treatment strategies for attaining remission.

### Tricyclic Antidepressants (TCAs)

The TCAs were the standard of antidepressant efficacy for 30 years; however, the adverse effects of TCAs have rendered them virtually obsolete as first-line choices. Montgomery et al.[13] conducted a meta-analysis of 42 studies of TCAs versus selective serotonin reuptake inhibitors (SSRIs) measuring discontinuation rates due to adverse side effects and a lack of efficacy. They found that 27.0% of patients discontinued TCAs due to adverse side effects compared with 19.0% ($p < .01$) of patients receiving SSRIs. The difference may be even greater in some higher risk populations. For example, in a 12-week study of 116 depressed elderly psychiatric patients treated with nortriptyline or paroxetine, Mulsant and colleagues[14] found that the rate of discontinuation due to side effects in the group treated with the TCA was double (33%) that of those treated with the SSRI (16%).

Despite poorer tolerability, some data indicate that TCAs are more efficacious treatments of severe depression. In meta-analyses of inpatient studies, TCAs have shown some advantage over both monoamine oxidase inhibitors (MAOIs)[15] and SSRIs.[16] This finding could reflect the effects of TCAs on noradrenergic neurotransmission, which may be more important for treatment of severe (i.e., "melancholic") depression. However, in Anderson's meta-analysis[16] only the tertiary amine TCAs were significantly more effective than the SSRIs. The so-called norepinephrine reuptake inhibitors (the TCAs desipramine, nortriptyline, and the tetracyclic maprotiline) were not. The tertiary amine TCAs are distinguished by greater affinity for the serotonin (5-HT) transporter. Clomipramine, amitriptyline, and possibly imipramine thus may be thought of as "dual reuptake inhibitors," at least at higher doses.

### MAOIs

MAOIs have been used as antidepressants for over 40 years. Although they have a strong record of efficacy, concerns about safety and tolerability have long precluded their use as first-line agents. Nevertheless, they still play an important role in hard-to-treat disorders. In a comprehensive meta-analysis of studies on the effectiveness of MAOIs through 1992, my colleagues and I[15] found that phenelzine and tranylcypromine were more effective than placebo but were significantly less effective than TCAs in studies of depressed inpatients. By contrast, in ambulatory studies, MAOIs were significantly more effective than TCAs. This latter finding is closely tied to MAOIs' utility for treating depressions characterized by reverse neurovegetative features.[17]

### SSRIs

In the 1990s, SSRIs rapidly became the first-line treatment of depression. In a study of prescription rates in the United Kingdom from 1993 to 1995, Donoghue et al.[18] found an overall increase of 133.8% in the prescription rates of SSRIs and only a 12.4% increase in prescriptions of TCAs. The popularity of SSRIs is largely the result of their better tolerability and safety, not the result of greater efficacy.

In a meta-analysis of 102 studies that included over 10,000 patients, Anderson[19] compared the efficacy and discontinuation rates of SSRIs with those of TCAs. Anderson found that the classes of medications were comparably effective except in studies of patients hospitalized for depression; in that case, TCAs were more effective. In a subsequent analysis by Barbui and Hotopf,[20] this advantage was largely delimited to the so-called dual reuptake inhibiting TCAs amitriptyline and clomipramine.

As noted previously, SSRIs were found to have a significantly lower rate of treatment discontinuation than TCAs.[19] In cases in which a single SSRI was compared with a single TCA, results showed that the relative risk of discontinuation was significantly lower with paroxetine. Fluoxetine, sertraline, and citalopram were all associated with a comparably lower relative risk of discontinuation when compared to individual TCAs, but these results did not achieve significance. Overall discontinuation rates were strongly influenced by the rate at which patients stopped treatment due to intolerable side effects, which researchers found to be less severe in SSRIs.[19]

### Multiaction Agents

Medications such as venlafaxine and mirtazapine operate by directly affecting serotonin and norepinephrine systems. However, antidepressants such as these are better tolerated than TCAs.

In a meta-analysis of original data, my colleagues and I[21] compared the remission rates in patients treated with venlafaxine with those of patients treated with SSRIs. The data were taken from 8 randomized, double-blind studies, including more than 2000 patients with major depressive disorder. We found that 45% of venlafaxine-treated patients remitted, compared with 35% of those given an SSRI and 25% of those given placebo. These results did not depend on inclusion of any one particular study nor the definition of remission used. In a related paper, Entsuah et al.[22] reported that this advantage was apparent for both men and women across all ages.

In a quantitative meta-analysis of 32 studies comparing venlafaxine with other antidepressants, Smith et al.[23] found that venlafaxine was superior to SSRIs. Although not focused on remission, this report does add further evidence for the relative advantage of a "dual" reuptake inhibitor.

Some research has documented the potential advantages of a second multiaction agent, mirtazapine, compared with

SSRIs. Unlike venlafaxine, mirtazapine affects 5-HT and norepinephrine systems through a blockade of a number of pre- and postsynaptic receptors ($\alpha_2$, 5-$HT_{2A}$, 5-$HT_{2C}$, 5-$HT_3$, and histamine[1]), Quitkin et al.[24] pooled data from 3 double-blind studies comparing mirtazapine with SSRIs and found that, although the number of responders at the end of the studies did not differ between the mirtazapine and SSRI groups, the onset of effect was more rapid in those patients treated with mirtazapine than those treated with SSRIs. I[25] confirmed this finding in a pooled analysis of a larger data set.

A single inpatient study[26] has compared the efficacy of venlafaxine and mirtazapine. Across 8 weeks of treatment, venlafaxine and mirtazapine therapies were not significantly different, although final remission rates were approximately 30% and 40%, respectively. Although the study did not have adequate statistical power to reliably detect modest differences between the treatments, symptom improvement appeared to be more rapid in the mirtazapine group. Mirtazapine therapy also resulted in significantly more improvement of sleep disturbance and lower attrition due to side effects.

Other multiaction antidepressants include milnacipran and duloxetine (which are not yet available in the United States) and, possibly, nefazodone and bupropion. One would expect that, as relatively well-tolerated dual reuptake inhibitors, milnacipran and duloxetine would share with venlafaxine an efficacy advantage over the SSRIs. Although some data suggest that may be the case,[27,28] too few studies have been completed to settle the question. By contrast, neither nefazodone nor bupropion have shown superior efficacy in head-to-head trials versus SSRIs. This may be because the proposed "dual" effects of these medications have not been established in vivo. Specifically, although the potency of nefazodone for 5-$HT_2$ antagonism is well-documented, it is not clear if relatively weak, short-lived binding to 5-HT and norepinephrine transporters is clinically significant. Similarly, the clinical significance of blockade of norepinephrine and dopamine transporters has still not been established for bupropion therapy.

Although research on medications that affect norepinephrine and 5-HT neurotransmission gives evidence to support their relative advantage in the acute phase of treatment, little is known about their efficacy over the long-term. Salient questions include evaluating if such greater efficacy is maintained during continuation phase therapy and if multiaction medications provide better protection against relapse. Research is currently being done on the long-term efficacy of venlafaxine as compared with fluoxetine.

### ECT

ECT continues to be the standard of treatment efficacy for severe or refractory depressive syndromes. In one of the most recent studies, researchers[29] administered bilateral ECT at levels 50% above the titrated seizure threshold to nonpsychotic (N = 176) and psychotic (N = 77) depressed patients. Remission was defined as a score ≤ 10 on the 24-item HAM-D and at least a 60% reduction in baseline depressive symptoms. The overall remission rate among those completing the study was 87%. Patients with psychotic depression remitted in 95% of cases and patients with nonpsychotic depression remitted in 83% of cases. Although ECT may effect remission at a relatively high rate, patients are at high risk of relapse after ECT is discontinued unless continuation phase pharmacotherapy is provided.[30]

### Psychotherapy

There are far fewer controlled clinical trials of psychotherapy than pharmacotherapy largely because of the lack of corporate research and development programs. Designing controlled experiments for testing the efficacy of psychotherapy also is challenging because of the lack of a "placebo therapy" condition.

Nevertheless, substantial evidence supporting the efficacy of psychotherapy does exist. Psychotherapies have been found to produce response rates comparable to those found with antidepressant medications in randomized clinical trials.[31,32] In a more selective review of 6 controlled studies, Casacalenda et al.[33] found that remission rates following 10 weeks of depression-focused psychotherapy were comparable to those resulting from therapy with TCAs or MAOIs (46.3% and 46.4%, respectively). Although no single form of depression-focused psychotherapy has proven itself superior to others, cognitive-behavioral and interpersonal therapies have received the greatest empirical support. There is evidence that psychotherapy is effective in combination with antidepressants. Adding cognitive therapy or interpersonal therapy to pharmacotherapy has been found to increase the likelihood of remission for patients with chronic,[34] severe recurrent,[35] resistant,[36,37] or partially treatment-responsive depressive syndromes.[38,39] In a longitudinal study of depressed elders, Reynolds et al.[40] observed the best prophylaxis against recurrent episodes among the subset of patients who received maintenance therapy with both nortriptyline and interpersonal therapy.

## CONCLUSION

A 50% reduction in depressive symptoms may be a reliable indicator of treatment response in clinical trials, but it is an inadequate goal for the initial phase of therapy. Remission, i.e., the virtual elimination of depressive symptoms and restoration of psychosocial capabilities, is fast becoming the criterion by which antidepressants are measured. However, thinking that remission conveys cure is misguided. Instead, treatment should be thought of as the long-term management of a potentially recurrent disorder.

Although a host of options to treat depression are currently available to physicians, the efficacy of pharmacologic therapies is most thoroughly documented. Compounds that have multiple mechanisms of action yet better tolerability and safety profiles than the TCAs may be the most promising. Given the long-term nature of treatments for depression, more research is needed to establish the long-term effects of many of the promising pharmacotherapies.

*Drug names:* amitriptyline (Elavil, Endep, and others), bupropion (Wellbutrin and others), citalopram (Celexa), clomipramine (Anafranil and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), maprotiline (Ludiomil and others), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Aventyl, Pamelor, and others), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), tranylcypromine (Parnate), venlafaxine (Effexor).

*Disclosure of off-label usage:* The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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