Treating Depression to Remission

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Over the last several years, the recommended end point in the treatment of depression has become remission. Patients who achieve remission not only enjoy the benefits of decreased disability and improved functioning in work, family, and social situations, they also have a lower risk of disease progression and relapse. Despite the benefits associated with remission, many patients are left with residual symptoms that prevent them from achieving these benefits. Potential obstacles to reaching remission include diagnostic issues, inadequate treatment, lack of adherence to the treatment regimen, satisfaction with partial improvement, and failure to recognize residual symptoms. Strategies for treating to remission include ensuring appropriate diagnosis, setting treatment goals, selecting antidepressants that are more likely to result in remission, providing patient education and adequate treatment, assessing for residual symptoms, and heeding partial response or lack of response by switching or augmenting treatment. *(J Clin Psychiatry 2003;64[suppl 15]:7–12)*

For many years, remission was not a feasible goal for patients with depression. Until the late 1980s, use of the only available antidepressants—the tricyclic antidepressants (TCAs) and the monoamine oxidase inhibitors (MAOIs)—was limited because of side effects and safety issues. It was often challenging to maximize efficacy of these medications while limiting safety and tolerability issues. For many patients, it was not possible to undergo treatment with these medications at adequate doses for a length of time sufficient to reach and sustain remission. Physicians and patients accepted partial relief of symptoms as a reasonable outcome. Clinical trials were conducted using an end point of either effect size or response, which was usually defined as a 50% or greater reduction in score on the Hamilton Rating Scale for Depression (HAM-D) or on the Montgomery-Åsberg Depression Rating Scale. Research had begun to show, however, that inadequate response (failure to achieve remission) not only prohibits the immediate benefits of remission, but increases the risk of relapse and recurrence.

The introduction in the 1980s of the selective serotonin reuptake inhibitors (SSRIs) provided greater safety and tolerability relative to their efficacy, and more patients were able to tolerate adequate treatment trials. Because of this, many patients were able to achieve remission using these medications. Further refinement of antidepressants has resulted in medications that increase both norepinephrine and serotonin levels, yet provide safety and tolerability comparable to those of the SSRIs. In the last few years, newer and more tolerable dual-action antidepressants, such as venlafaxine and mirtazapine, have become available, making remission an achievable goal for an increasing number of patients.

Remission has become the recommended end point in the treatment of depression. Current guidelines from the U.S. Agency for Healthcare Research and Quality (formerly the U.S. Agency for Health Care Policy and Research), the American Psychiatric Association, the British Association for Psychopharmacology, the Canadian Psychiatric Association, and the Canadian Network for Mood and Anxiety Treatments state that the treatment goal should include remission of symptoms and a return to premorbid social and occupational function.[1–4]

DEFINING REMISSION

In clinical research, remission is measured using dimensional rating scales that assess the severity of depression and determine improvement with treatment. Although researchers have defined remission in a variety of ways, a widely accepted definition is a score of 7 or less on the 17-item HAM-D (HAM-D-17); minimal or no symptoms of depression; loss of the diagnosis, i.e., the patient no longer meets the criteria for major depressive disorder listed in the *Diagnostic and Statistical Manual of Mental Disorders*; and the return of normal psychosocial and occupational function.

In clinical practice, time-consuming rating scales are rarely used, but researchers' concept of remission can be extrapolated to the clinical setting. This requires the clini-

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cian, at the beginning of treatment, to thoroughly probe and carefully document all depressive symptoms, both psychological and somatic, including the patient's deficits in psychosocial function. In clinical practice, the goal of treatment, which is remission, consists of the complete resolution of depressive symptoms, along with the restoration of the patient's ability to engage in work, family life, hobbies, and social and community activities. A patient who has responded to treatment, i.e., who shows improvement in symptoms and psychosocial function but who has not reached remission, would be defined in the researcher's terms as someone who has had a 50% or greater reduction in HAM-D-17 score compared with that at the beginning of treatment. Approximately 50% of patients fall into this category: they respond to treatment but do not reach remission. They have residual symptoms and remain at high risk for relapse. The challenge for clinicians is to treat these patients aggressively until they reach remission.

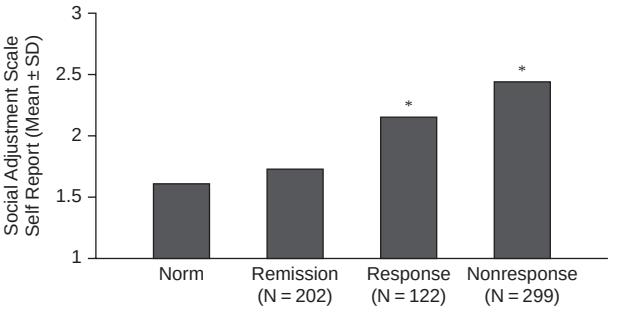
CONSEQUENCES OF RESIDUAL SYMPTOMS

Less than half of depressed patients achieve remission.[5,6] Patients whose residual symptoms linger are at risk for poor long-term outcomes. Among the consequences of a failure to achieve remission are ongoing morbidity and mortality, impaired psychosocial function, and an increased tendency to relapse. Ensuring an optimal response from the beginning is critical.

Studies that measure changes in psychosocial and occupational functioning have supported the importance of remission. In one study,[7] chronically depressed patients were assessed before and after 12 weeks of treatment. Those who were in remission had levels of psychosocial function at the end point that equaled or approached those of community samples. Patients who had not responded to treatment continued to show serious impairment in psychosocial function, while patients who had responded to treatment but who were not in remission showed an intermediate level of impairment (Figure 1).

In other studies comparing patients who have achieved remission with those who have residual symptoms, it has been shown that patients in remission are far less likely to relapse. In a study of patients who were treated with cognitive behavioral therapy, those who reached remission were more likely to remain symptom free and to avoid relapse than were those who responded to treatment but did not reach remission.[8] Another study evaluated the effect of residual symptoms on the risk of relapse in patients with major depression.[9] Patients were followed for 12 to 15 months after reaching remission, or until 15 months had elapsed without reaching remission. The presence of residual symptoms (defined as a HAM-D score of 8 or more) at 15 months was an important predictor of subsequent early relapse. More patients with HAM-D scores

Figure 1. Social Adjustment Normalizes With Remission[a]



[a]Data from Miller et al.[7]
*p < .05 compared with the remission group.

of 8 or more relapsed (76%) compared with patients who had HAM-D scores of 7 or less (25%). In a third study, 237 patients were followed naturalistically for at least 10 years after treatment.[10] Of the patients who relapsed, those with residual symptoms relapsed more than 3 times faster than those who were asymptomatic following treatment.

Depressed patients face an increased risk of morbidity and mortality from general medical conditions. Specifically, depression worsens outcomes for patients after myocardial infarction and increases the risk of mortality following a cardiac event.[11,12] Depression is also associated with worse outcomes in nursing home residents,[13] stroke patients,[14] and patients with cancer or acquired immunodeficiency syndrome.[15]

Medical care costs may decrease in patients who achieve remission. Depressed patients use health care services 3 times more often than do nondepressed patients.[16] Patients with depression, on average, have overall medical costs that are approximately twice as high as those of the average person without depression.[17] Patients recovering from depression incurred 49% lower overall medical costs in the year following their treatment compared with patients whose depression persisted.[18]

Treating to remission is also important in slowing the progression of depression. Patients with residual symptoms after treatment of a first episode of major depressive disorder have a significantly more severe and chronic course of illness than do patients who are treated to remission. In addition to relapsing sooner, they typically have more recurrences, shorter intervals of wellness, and fewer symptom-free weeks during follow-up.[19] Achieving remission early and sustaining remission should result in the optimal goal of recovery.

Failure to achieve remission may possibly contribute to the long-term development of treatment resistance. According to this hypothesis, repeated exposure to antidepressants without full remission may result in a patient's inability to respond to treatment. Although this idea is

Table 1. Potential Obstacles to Attaining Remission in Clinical Practice

Undertreatment, in the form of underdosing or inadequate duration of treatment.
Lack of patient adherence to the treatment regimen due to frustration, lack of motivation, or dissatisfaction with side effects.
Failure on the part of the patient to recognize and report residual symptoms, or failure on the part of the clinician to recognize and treat residual symptoms and psychosocial impairments.
Patient and clinician satisfaction with a partial improvement in symptoms.

untested, if correct, it would increase the advantages of treating depression aggressively from the outset.

STRATEGIES FOR ACHIEVING AND SUSTAINING REMISSION

Clinicians can utilize many strategies in treating patients to remission. The first and simplest is ensuring adequate treatment. Studies have repeatedly shown that the majority of patients in clinical practice receive inadequate doses of medication[20–22] (Table 1). Rapid titration to the maximum tolerated dose best enables a patient to achieve remission. An adequate length of the antidepressant trial is also critical. Most studies have found that between 4 and 8 weeks of medication at the recommended dose is useful in predicting the likelihood of eventual response,[23,24] and current guidelines reflect these findings.[1,2] If, after 4 to 6 weeks, the patient has responded to treatment, the medication should be continued at that dosage. If the patient has not responded to treatment, the medication should be continued for 2 to 4 additional weeks, but at the maximum tolerated dose.[25] At that point, if the patient has had no response, the antidepressant should be switched. Once a medication is effective and the patient has reached remission, treatment should be continued at the same dosage for an additional 6 months.[2] Maintenance treatment beyond 6 months, at the same dosage, is appropriate for patients who are likely to relapse.[26]

Successful treatment also depends on patient adherence to the treatment regimen. Depressed patients, who typically feel hopeless and lack motivation, often discontinue treatment. In one study, even when patient adherence was monitored through monthly telephone interviews, 53% of patients discontinued treatment within 6 months.[27]

Patient education has been shown to improve patient adherence to treatment. In addition to specific information about when and how often to take medication, it is necessary to stress the importance of continuing to take medication and of consulting a physician before discontinuing. Patients are less likely to quit in frustration if they know in advance that finding an effective and tolerable medication may be a process of trial and error. They are more likely to adhere to the treatment plan and to return for follow-up care if they are aware of how long it will be before the effects of the medication are noticeable. The possibility of side effects should also be discussed.[28] Because a patient may be reluctant to discuss sexual side effects, the clinician should introduce a discussion about this possibility. It is also important to instruct the patient that full symptomatic improvement is the goal of treatment.

During treatment, the patient's response should be monitored carefully. The earliest signs of response are reductions in the symptoms of depression, which are variable from one patient to another. It is common to see improvements first in sleep, appetite, and cognitive function, then in mood and in the ability to experience pleasure. Improvements in psychosocial function usually come later. In practice, it often takes careful inquiry to determine whether or not a patient has reached remission. Even the patient may be a poor judge, particularly if a patient has had chronic depression and has not been well for some time. A patient may not even remember how it feels to be well and may find any reduction in symptoms a welcome relief. A patient may report feeling much better long before reaching remission. In addition, patients generally look better before they feel better. However, careful, open-ended questioning may reveal that remission is still remote. Patients can be encouraged to describe areas that still need improvement, how they felt before the depression developed, or how they would like to be feeling. This "wish list" or keeping track of target symptoms over time can be a useful indicator of the presence of residual symptoms and of remaining gaps in psychosocial function.

If a patient is not responding to treatment, it may be necessary to reconsider the diagnosis. Depressed patients with untreated comorbid anxiety disorders tend to be more severely depressed than patients with depression alone. They tend to respond more slowly to treatment and are more likely to have residual symptoms.[29,30] Similarly, patients with obsessive-compulsive disorder frequently develop depression,[31] yet they may be reluctant to report their symptoms, thereby remaining undiagnosed. Bipolar disorder may also be difficult to diagnose; patients with bipolar disorder often present during an episode of depression. In a survey of bipolar patients, 40% reported that initially they had been diagnosed with major depressive disorder.[32] Undetected substance abuse may impede treatment with antidepressants as well as increase the likelihood of patient noncompliance.[33] Additionally, certain general medical conditions or their treatments may cause or worsen symptoms of depression. These conditions include diabetes, coronary artery disease, human immunodeficiency virus infection, cancer, and chronic pain. Endocrine disorders, such as Cushing's disease, Addison's disease, or hypothyroidism, can cause depressive symptoms as well.[30,34]

If a patient has experienced intolerable side effects or has not responded after 4 weeks of treatment at typical

clinical doses, with an additional week or 2 of treatment at the maximally tolerated dose, it is appropriate to switch to a different antidepressant. Switching within the same class may be effective. For example, switching to another SSRI after the first SSRI has been ineffective or intolerable has been shown to be effective, with response rates of 42% to 71%.[35–38] Another strategy is to switch to an antidepressant in a different class.[39–42]

If a patient has experienced some improvement in symptoms, however, it could be quite discouraging to switch medications and lose this partial benefit. If a patient has experienced an improvement of 25% or more, another antidepressant could be added (a combination strategy), the medication can be augmented, or psychotherapy could be added. Specific forms of psychotherapy have been demonstrated to be an effective adjunct to pharmacotherapy. In a recent study, chronically depressed patients receiving the antidepressant nefazodone as well as psychotherapy were more likely to reach remission than were patients receiving either therapy alone.[43,44] In this study, the psychotherapy administered was specifically developed for treating patients who have chronic depression and it drew on a variety of behavioral, cognitive, and interpersonal techniques. Additional emerging data on specific psychotherapies for treating depression and on tailoring the therapy to individual patients will provide more support for clinical treatment decisions.[45]

Besides psychotherapy, another antidepressant or an augmenting compound may be added to the treatment regimen. The disadvantages of a combination strategy or augmentation, however, are that they are more complicated and expensive, and there is a greater potential for side effects. The best studied and most widely used augmentation compounds are lithium[46] and triiodothyronine,[47] but the use of many other compounds is supported by small, uncontrolled studies and anecdotal reports.[48] Combination therapy, the use of 2 antidepressants with different mechanisms of action, may also be appropriate. It is not clear, however, whether this approach is superior to switching to an antidepressant with a broader mechanism of action, such as clomipramine or venlafaxine.[25]

Given the importance of quickly achieving remission, the ability of a medication to bring about remission should be a major consideration in treatment selection, along with such issues as side effects, safety profile, and cost. Practice guidelines state that, for most patients, all antidepressants approved by the U.S. Food and Drug Administration are "generally considered equally effective."[2] Studies have found that the SSRIs are equally efficacious when they are compared within the class of SSRIs.[49,50] As a group, they also appear to be approximately equal in efficacy to TCAs.[44]

Other recent studies and meta-analyses of clinical trials, however, are beginning to draw distinctions between classes of antidepressants. Clinical trials have suggested that agents that affect both the noradrenergic and serotonergic systems may be more efficacious than SSRIs when looking at rates of remission. For example, trials comparing the dual-action TCA clomipramine with the SSRIs citalopram and paroxetine found superior efficacy for clomipramine,[51,52] and the greater efficacy of the dual-action antidepressant venlafaxine has been confirmed in 3 recent analyses. In one of these studies, data were pooled and analyzed on 2045 patients who participated in 8 clinical trials that each compared venlafaxine with an SSRI. With remission defined as a HAM-D score of 7 or less, remission rates at week 8 were 45% for venlafaxine, 35% for the SSRIs, and 25% for placebo. These differences were significant (venlafaxine vs. SSRIs, venlafaxine vs. placebo, SSRIs vs. placebo; $p < .001$ for each). Venlafaxine was shown to be more effective in achieving remission than the SSRIs, beginning at week 2 and continuing through the end of the study.[53]

These results were confirmed in a meta-analysis of 25 clinical trials that compared the efficacy of SSRIs with that of TCAs[44] and by a more recent meta-analysis of 32 clinical trials in which venlafaxine was compared with other antidepressants, including TCAs, SSRIs, trazodone, and mirtazapine. In this analysis, standardized effect sizes were estimated based on the efficacy data reported for each treatment group. These were used to calculate the pooled standardized difference in mean treatment effect, which was used as the primary measure of outcome. Venlafaxine was shown to be more efficacious than the SSRIs, and the effect was consistent across all the drugs.[54]

Mirtazapine also lacks some of the side effects associated with TCAs. The limited data available on mirtazapine suggest that it is comparable in efficacy to amitriptyline, clomipramine, and venlafaxine,[55] but further trials and meta-analyses are needed to confirm these conclusions.

The MAOIs are also effective antidepressants. Although the availability of antidepressants with milder side effects has relegated this class of antidepressants to use as second-line therapy, when safer medications fail, they are a reasonable alternative. Indeed, data suggest that MAOIs are particularly useful in treating patients with depression with atypical features.[56]

If poor response continues, the presence of undetected impediments to treatment should be considered, such as possible patient noncompliance or the presence of comorbid general medical conditions or psychiatric conditions (including alcohol or substance abuse). For patients who fail to respond to multiple trials of antidepressants, electroconvulsive therapy is a safe and effective alternative, with response rates of 50% to 60%.[57] The disadvantages of this treatment option, however, are possible memory loss[58] and a high rate of relapse.[59]

CONCLUSION

Multiple studies report that patients with depression are regularly undertreated and left with residual symptoms. Treating to remission not only provides immediate benefits to patients, but it can also prevent the progression of this chronic disorder with its more severe relapses of increasing frequency. Treating to remission may also prevent the development of treatment resistance. Now that newer medications put remission within reach for more patients, clinicians can select at the outset a treatment that is likely to achieve this outcome. Careful monitoring of each patient's response to treatment may reveal residual symptoms or lingering impairment in psychosocial function that should be considered signs of active illness. In that case, further treatment tailored to the individual is required until remission is achieved. Partial improvement is not an acceptable outcome for a patient with depression, just as it is not an acceptable outcome for a patient with any other treatable medical illness.

Drug names: amitriptyline (Elavil and others), citalopram (Celexa), clomipramine (Anafranil and others), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), trazodone (Desyrel and others), venlafaxine (Effexor).

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