Achieving Remission and Managing Relapse in Depression

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Although antidepressants are effective, no more than one third of the depressed patients who begin treatment achieve full remission within 8 weeks of therapy. Remission, defined as virtually complete relief of symptoms and return to full functioning in all areas of life, should be thought of as the optimal goal for the initial phase of treatment of depression. This goal is recommended because residual symptoms (i.e., response without remission) are associated with a myriad of risks, including a higher rate of relapse. When compared with monotherapy, selective serotonin reuptake inhibitor (i.e., the current first-line standard of care) strategies may improve remission rates. These strategies include using maximally tolerated (i.e., higher than usual) doses of medication, switching to an antidepressant thought to have more than one mechanism of action, combining dissimilar medications (to presumably treat a broader range of symptoms), and using a combination of psychotherapy and medication. Ensuring that patients are indeed adherent with treatment is also worthwhile before assuming that a treatment has failed.
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The assessment of a depressed patient's response to a given antidepressant treatment involves both a categorical judgment, determining whether the patient is "better" or "still ill," and an assessment of functional status, i.e., determining if the patient has returned to premorbid healthy functioning. Where to draw the line between being ill and being well is rarely simple because many depressed people have been impaired for long periods of time and even normal well-being typically involves a few, generally intermittent, symptoms of depression. When in doubt it is best to assume that further improvement is possible: there is no such thing as responding too well to antidepressant therapy.

ASSESSMENT

To increase the chances of remission, it is also useful to have an accurate, ongoing assessment of the patient's symptomatic and functional status; however, problems exist with the current assessment tools. The use of structured assessments, such as described below, can help clarify the presence and symptom severity of depression, but few practitioners actually use these tools. Without proper context, a rating scale score also can be misleading.

For example, a 50% score reduction on the Hamilton Rating Scale for Depression[1] (HAM-D), a standard instrument in the study of depression, has historically been considered a satisfactory index for response. A severely depressed patient, though, could improve by 50% on the HAM-D and still be a long way from remission and returning to a normal range of function. A set cutoff involving an extremely low score, such as a HAM-D score ≤ 7, is more useful to define symptomatic remission. Again, however, the problem of clinicians not using standardized rating scales must be faced.

The terminology used to define certain stages of depression and recovery may also cause confusion. Prien et al.[2] reviewed data from research published in 9 different journals to determine how changes in the clinical course of depression are defined. Significant inconsistencies were found in the labeling and the definition of change points; for example, the term *recovery* was used inconsistently in 8 different studies.

Such inconsistency of assessment terminology led to a consensus conference supported by the MacArthur Foundation. In the resulting publication, Frank et al.[3] suggested operational definitions for the following outcomes: response, remission, relapse, recovery, and recurrence. With respect to the "positive" outcomes, response is a significant reduction of symptoms to a level below the threshold for major depressive disorder. Remission was defined as a relatively brief period during which an improvement of sufficient magnitude is observed such that the individual is

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virtually asymptomatic. On the Montgomery Asberg Depression Rating Scale (MADRS)[4] and the Beck Depression Inventory,[5] remission usually is reflected by a score of 10 or less; as described above, a score of 7 or less on the HAM-D works well. These thresholds typically separate patients who have reached remission from those who have improved but are still too symptomatic to be considered within a normal threshold. In practice, any working definition of remission should include the patient's ability to return to full functioning in all areas of life. The term *recovery* was proposed to describe a period of sustained remission. Although a written consensus is lacking, in the DSM-IV[6] at least 2 months of full remission is required before the term *recovery* is used.

The 2 negative outcomes are distinguished by temporal relation to the treated episode. Relapse is the return of symptoms, satisfying the full syndrome criteria after a patient has responded or remitted, but before recovery. A recurrence is a relapse that occurs after a clear-cut recovery. Conceptually, relapse is an exacerbation of the index or treated episode, whereas recurrence connotes an entirely new episode of depression.

STRATEGIES TO ACHIEVE REMISSION

Treatment follows 3 phases, which are tied to the outcomes described above. During the initial or acute stage of treatment, clinicians should aim for a response within 4 weeks and remission within 8 weeks. The probability of remission is better with medications that can be tolerated by most patients not just at minimum but, if necessary, at full therapeutic doses. Antidepressants that have a relatively broad spectrum of effects—for example, medications that are also beneficial for treatment of anxiety, insomnia, or attention-deficit/hyperactivity disorder—also may have a broader profile of symptomatic effects if tolerable.

One strategy for addressing incomplete remission is to add a second medication that is not an antidepressant to augment the actions of the first. Lithium, thyroid hormone, and buspirone are the most widely studied augmentation agents, although the former 2 agents are now seldom used. In the search for better options to help patients, clinical practice often outstrips the platform of evidence-based medicine. For example, in the 1990s, atypical antipsychotic medications were widely used to augment antidepressants even though the first positive placebo-controlled study did not make its way into the literature until 2001.[7] Several medications now in vogue as augmenters include pramipexole (a dopaminergic agonist) and modafinil (a medication used to treat daytime sleepiness). In one recent study,[8] 5 of 7 depressed patients improved during treatment with modafinil augmentation.

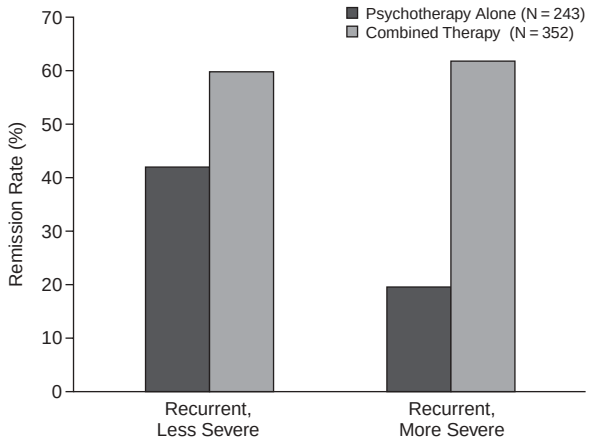
Psychostimulants also have a long history of being used to augment antidepressants. An open trial[9] of methylphenidate was used to augment selective serotonin reuptake inhibitor (SSRI) treatment in patients with DSM-III-R major depression. Five case studies were presented with patients receiving doses of methylphenidate ranging from 10 mg/day to 40 mg/day. All 5 patients reported rapid symptom reduction with the combination of methylphenidate and SSRI treatments.

There is likewise a strong interest in trying to broaden the spectrum of treatment efficacy by combining antidepressants with different mechanisms of actions. By far the most common combination is an SSRI and bupropion (a medication that is presumed to enhance noradrenergic and dopaminergic neurotransmission).[10] Mirtazapine also may be used to augment response to various selective reuptake inhibitors.[11] Despite the wide use of these and other combination strategies, however, it still has not been shown to be more helpful to combine with than to simply switch to the second medication.[12]

One still unresolved controversy is whether antidepressants that simultaneously and directly enhance serotonergic and noradrenergic neurotransmission are more effective than selective norepinephrine or serotonin reuptake inhibitors. One meta-analysis of pooled original data[13] compared the effects of venlafaxine (a dual reuptake inhibitor) with a grouping of 3 SSRIs (fluoxetine, paroxetine, and fluvoxamine) or placebo in patients for periods of up to 8 weeks. The analysis included data from a consecutive series of 8 double-blind, randomized clinical trials of patients with major depressive disorder. All patients had to score at least 20 on the 21-item HAM-D or 25 on the MADRS. Overall, the serotonin-norepinephrine reuptake inhibitor was significantly more effective than the SSRIs, which in turn were significantly more effective than placebo (remission rates were 45%, 35%, and 25%, respectively). Tolerability of venlafaxine and the SSRIs was generally comparable (attrition due to side effects: 9% for venlafaxine, 7% for fluoxetine), although in practice, more nausea early in the course of therapy and a number of relatively mild side effects attributable to noradrenergic effects (i.e., dry mouth, blurry vision, and constipation) are more common during venlafaxine therapy than with fluoxetine. In a second report,[14] patients were divided into age subgroups of ≤ 40, 41–54, 55–64, and ≥ 60 years. Patients within the ≤ 40 and the 41 to 54 year age groups receiving venlafaxine displayed significantly higher rates of remission (46% and 44%, respectively) than patients taking SSRIs (37% and 33%, respectively).

The results of a subsequent meta-analysis[15] of 19 randomized trials comparing venlafaxine and SSRIs yielded a similar conclusion: a modest yet reliable advantage favored the dual reuptake inhibitor. This trial is noteworthy because the same group of investigators had concluded just 2 years before that multiaction antidepressants were not more effective than SSRIs.[16] The difference is in the details: whereas the later study focused solely on venlafax-

Figure 1. Combined Treatment Versus Psychotherapy Alone for Severe, Recurrent Depression[a]



[a]Reprinted with permission from Thase et al.[17]

ine, the earlier one was heavily influenced by a large number of studies utilizing tricyclic antidepressants (TCAs). Although TCAs such as clomipramine and amitriptyline are indeed dual reuptake inhibitors, any possible efficacy advantage may have been "wiped out" by significantly poorer tolerability, particularly in studies of less severely depressed ambulatory populations.

The combination of psychotherapy and pharmacotherapy, either from the outset of therapy or in sequence, also may be recommended to increase the likelihood of a full remission. Using a data set pooled from 6 different ambulatory studies (N = 595), Thase et al.[17] found that the combination of antidepressants and interpersonal psychotherapy conveyed about a 12% advantage in remission rates when compared with psychotherapy alone. This relatively modest effect may not justify the higher cost of routinely using both forms of treatment. Among the patients with severe recurrent depression, however, there was a much larger benefit (Figure 1).[10,17] Keller et al.[18] likewise found a large advantage for the combination of a form of cognitive-behavioral therapy (CBT) and the antidepressant nefazodone when compared with the 2 monotherapies in a study of more than 600 patients with chronic forms of major depressive disorder.

Two studies have addressed the benefit of adding psychotherapy to incompletely effective antidepressant therapy. In a small study in Italy, Fava et al.[19] randomly assigned 40 incompletely remitted patients to either ongoing pharmacotherapy alone or in combination with ten, 40-minute sessions of CBT once every other week. Psychotherapy was particularly focused on treating residual depressive symptoms, including subsyndromal anxiety symptoms. Sequential psychotherapy produced a significant reduction in symptoms and, across 4 years of follow-up, the risk of relapse/recurrence was substantially lower with CBT than with clinical management (70% vs. 35%).[20] Paykel and colleagues[21] subsequently replicated this finding in a large, multicenter study of 158 incompletely remitted depressed outpatients.

RELAPSE AND RECURRENCE

It is important to remember that depression is a chronic condition with up to 80% of treated patients experiencing subsequent episodes.[22] However, patients who have been treated successfully and achieved full remission do not face such a high risk if their ongoing treatment is properly managed. By convention, subsequent episodes are called relapses if they occur proximal to the treatment episode (i.e., within 6–9 months of treatment response) or recurrences if they occur after a sustained period of complete remission. This classification, while arbitrary, represents the conceptual distinction between the reemergence of the index (i.e., treated) depressive episode and the onset of an entirely new depressive episode.

Relapse: Therapeutic Issues

The continuation phase of treatment spans the period between response and recovery. Patients who remit completely have about a 2% to 4% risk of relapse per month during continuation phase therapy. Studies[23] involving the double-blind discontinuation of active antidepressants after 6 or 8 weeks of therapy suggest that up to 50% of patients withdrawn from antidepressant medication will relapse within 6 months.[24] Continuation phase therapy thus conveys a 2- to 3-fold reduction in relapse risk. For this reason, 6 to 9 months of continuation phase pharmacotherapy is considered the standard of care for virtually all antidepressant responders.

Relapse rates in patients taking active antidepressant medication are significantly higher among those who do not obtain a complete remission during acute phase therapy. In the naturalistic study of Paykel et al.,[25] the relapse risk of incompletely remitted patients receiving continuation phase therapy was about as large as the aforementioned risk of premature discontinuation of antidepressants. Several studies[24,26,27] have demonstrated that incomplete remission similarly increases relapse risk after termination of time-limited psychological treatments of depression.

The most common causes of relapse during continuation phase therapy for patients who are fully remitted are nonadherence and apparent loss of therapeutic efficacy. If a patient who has been in full remission suddenly relapses, the odds are that he or she has stopped taking the medication or is taking the medication irregularly. Informative data from a wide range of sources document just how common nonadherence is during longer-term treatment of common medical disorders.[28] For most antidepressants, anything less than 80% or 85% adherence with

a prescribed medication regimen places the patient at risk for relapse.

Some relapses occur despite full adherence and thus appear to represent failure of an effective treatment. However, the principal cause of such drug "failure" is probably the loss of the placebo response. As controlled studies[29] have consistently found that 20% to 40% of depressed patients will respond to treatment with a placebo, it can be assumed that at least one half of those who appear to respond to an antidepressant actually benefited from the passage of time or the nonspecific elements of treatment. Such placebo responses are less durable than "true" antidepressant responses and, hence, patients who did not actually respond to the active medication will not be protected by it during the continuation phase.

In a 12-week, double-blind, randomized study,[29] relapse attributable to loss of placebo effect was studied among 507 patients who were initially treated for 6 weeks with placebo, imipramine, or phenelzine. Two different assumptions are used in models for estimating relapse attributable to placebo effects during drug treatment. The independent model argues that the 2 effects are independent, that is, patients who respond when taking a drug include those whose improvement is due to the effects of the drug, those who improve as a result of placebo effects only, and patients whose response is a combination of both effects. The exclusive model, on the other hand, posits that placebo response and drug response are mutually exclusive and those who respond to placebo are incapable of a drug response. During the 7 to 12 weeks, more patients relapsed in the placebo group (31.3%) than in the imipramine (11.8%) or phenelzine (8.8%) groups. Results for imipramine and phenelzine under the exclusive model and results for imipramine under the independent model showed that, in the most conservative estimates, a substantial majority of relapses were due to loss of placebo effect.

The physician also needs to be attuned to changes in the patient's life or medical status that could contribute to relapse. Problems that did not exist during the acute phase of treatment can arise during the continuation phase. For example, strong marital support may have been a critical asset during early treatment, but if the marriage fails, the loss of social support may provoke emergence of depressive symptoms.

Another possible cause of relapse is sometimes called the "poop-out syndrome" or, more properly, antidepressant tachyphylaxis. These terms refer to the theoretical possibility that there may be adaptations in the nervous system that result in an antidepressant that no longer produces the neurochemical changes needed to counteract or control dysregulated serotonin, norepinephrine, or other stress-responsive systems. However, whereas the concept of tachyphylaxis has been established in disorders such as asthma[30] and epilepsy,[31] it has not yet been proved in depression.

Strategies to Prevent Recurrent Depression

Patients who have suffered 3 or more lifetime episodes of depression face a risk of recurrence of at least 50% (and possibly as high as 90%) within 3 years of stopping continuation pharmacotherapy.[32] The best way to prevent recurrence is to continue an effective medication at full therapeutic dosage for an indefinite period after completion of the continuation phase.[32] The findings of Kupfer et al.[33] suggest that maintenance phase antidepressant therapy may need to be lifelong. There are, however, virtually no data from controlled studies on the benefits of such longer-term (> 3 years) antidepressant therapy. In one small study[34] conducted by the Pittsburgh group, patients who had completed a 3-year randomized maintenance trial were asked to continue in an additional 2-year randomized trial in which they would either continue active medication (N = 9) or be switched to placebo (N = 11). Six (55%) of the patients switched to placebo relapsed, compared with only 11% (1/9) of those who remained on active medication.

Interpersonal psychotherapy has been shown to provide some prophylaxis against recurrent depression after withdrawal of antidepressants.[34,35] When applied in sequence, some forms of focused psychotherapy may be able to produce an even more enduring reduction of risk. Fava et al.[36] studied 40 patients with recurrent major depression who were receiving continuation or maintenance antidepressant pharmacotherapy. Patients had to have had 3 or more previous episodes of depression, a minimum of 10 weeks' remission on antidepressants according to the Research Diagnostic Criteria, and minimal symptoms on a modified version of the Paykel Clinical Interview for Depression. Patients (N = 40) were randomly assigned to receive either continued clinical management or CBT focusing on enhancing well-being and relapse prevention strategies. After 20 weeks, antidepressant treatment was tapered and discontinued. During the subsequent 2-year follow-up period, only 5 of the 20 patients in the CBT group relapsed compared with 16 of the 20 patients in the clinical management group.

CONCLUSION

While remission is the first goal of treatment, it is sometimes the most difficult to achieve. Effective strategies to achieve remission include an increase in dose, augmentation of medication, combination of psychotherapy and antidepressant treatments, or using medications with more than one mechanism of action. Many patients who do not achieve remission or who relapse are simply not adhering to their medication regimen. Clinicians should emphasize the importance of proper adherence to medication regimens and should suggest helpful strategies to remind patients to take their medication.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin and others), buspirone (BuSpar and others), clomipramine (Anafranil and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), methylphenidate (Concerta, Ritalin and others), mirtazapine (Remeron and others), modafinil (Provigil), paroxetine (Paxil and others), phenelzine (Nardil), pramipexole (Mirapex), sertraline (Zoloft), venlafaxine (Effexor).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, buspirone, fluvoxamine, lithium, modafinil, and pramipexole are not approved by the U.S. Food and Drug Administration for the treatment of depression.

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