Evolution of Remission as the New Standard in the Treatment of Depression

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Epidemiologic and clinical data support the goal of treating depressed patients to wellness or full remission. Many patients improve but fail to achieve full remission with antidepressant treatment and continue to have residual symptoms, which cause distress and dysfunction. These residual symptoms may meet criteria for subsyndromal and minor depression. Patients who have these milder syndromes after treatment have a greater risk of relapse and recurrence than do those who remain symptom-free. Clinical trials of antidepressants have shown lower rates of remission than of responses that fall short of remission, although some dual-acting antidepressants (e.g., serotonin-norepinephrine reuptake inhibitors) may have higher remission rates than other agents. Treatment with such robust dual-acting antidepressants may result in higher rates of remission and fewer residual symptoms than treatment with selective serotonin reuptake inhibitors. *(J Clin Psychiatry 1999;60[suppl 22]:7–11)*

Between the mid-1950s and the late 1960s, in an era of great skepticism about the use of drugs to treat psychiatric disorders and when psychoanalytically oriented psychotherapy was predominant, randomized clinical trials were used to assess the efficacy of new psychopharmacologic agents. Subsequent placebo-controlled trials in many[1] but not all studies[2] indicated that active antidepressants were more effective than placebo. Continuous measures such as the Hamilton Rating Scale for Depression (HAM-D)[3] showed greater statistical improvement from baseline with active medications than with placebo. The challenge, however, in the absence of precedent, was for researchers to choose clinically interpretable categorical outcome variables to define responders. A 50% improvement in baseline measures of psychopathology became the norm for the definition of response,[4] even though Hamilton's precedent was 60% improvement. Since those heady times of discovery, epidemiologic studies[5] and extensive clinical trials have shown that the original standard of a 50% improvement is insufficient: subthreshold depressive symptoms are associated with dysfunction,[5–7] residual symptoms may increase the risk of developing further episodes of both subthreshold and threshold psychopathology,[8] residual symptoms are an important outcome of treatment,[9–11] and a minority of those who are treated achieve and maintain symptom-free states of full remission.[12]

This article reviews the epidemiologic studies and clinical trials that examined the importance of residual symptoms and the treatment goal of full remission.

EPIDEMIOLOGY: FROM WELLNESS TO SYMPTOMS TO DISORDER

Psychiatric wellness could be defined as the absence of any recognizable psychiatric disorder. In the National Comorbidity Survey (NCS),[13] about half of the community cohort were free of lifetime psychiatric disorders, and about 70% had had no psychiatric disorder during the previous 12 months. Peter Kramer, in his landmark book in the lay press, *Listening to Prozac*, describes patients who were in distress but free of a recognizable mood disorder who became "better than well" when treated with fluoxetine.[14] It is possible, but speculative, that Dr. Kramer's patients had unrecognized subsyndromal depressive states that responded to antidepressant treatment.

It has become increasingly recognized that the presence of even a few psychiatric symptoms is associated with dysfunction. Minor depression has the same symptoms as major depression—either decreased mood or decreased interest and pleasure—but with fewer than 5 *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV)–defined symptoms of major depressive disorder (MDD).[15] Subsyndromal depression is defined as 2 DSM-IV–defined symptoms of MDD with no complaint of decreased mood or lack of pleasure or interest. Reanaly-

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sis of the Epidemiologic Catchment Area (ECA) study data by Judd and colleagues[5] revealed 1-month point prevalence rates of 3.9% for subsyndromal depression and 6.1% for other syndromal depressive disorders. Patients with these depressive-spectrum disorders were more likely to use medical outpatient services and emergency rooms, to be supported by public assistance and disability benefits, and to have more suicidal thoughts and behavior than were those without any symptoms.[5] The naturalistic ECA study also found that those patients who had recovered from an index depressive episode but who met criteria for either minor or subsyndromal depression were much more likely to experience a relapse or recurrence than were those who had recovered fully.[8] Those with residual symptoms were not only likely to experience another episode sooner than were those who were symptom-free, they were also more likely to have a depressive relapse or recurrence than were those with recurrent depression.

The NCS found 12-month prevalence rates of 10.3% for major depression and 2.5% for dysthymia, with lifetime prevalence rates of 17.1% and 6.4%, respectively.[13] For minor depression, the lifetime prevalence rate was 10% with similar levels of dysfunction, similar proportions of recurrences, similar durations of first episodes, and similar patterns of comorbidity, dysfunction, and parental history of psychopathology, compared with those who had MDD with no more than 6 symptoms.[16] Greater discontinuity was found between those with minor depression and those with MDD who had 7 to 9 symptoms, but the difference between the probands with severe depression and those with minor depression was about as large as the difference between those with severe MDD and those with MDD but with only 5 or 6 symptoms.

The prevalence of depressive symptoms occurred in as many as 24% of subjects in an epidemiologic sample with no prior or current MDD or dysthymia.[6] Just 2 to 4 depressive symptoms were a risk factor for the development of first-episode MDD within a year of follow-up. Those with depressive symptoms were 4.4 times more likely to develop MDD than were those without symptoms. Of those who developed MDD without ever having a history of MDD or dysthymia, more than half had had depressive symptoms a year earlier. These data support the concept of prodromal depressive symptoms.

Even in patients who do not meet the criteria for MDD or dysthymia, the presence of depressive symptoms is associated with increased numbers of suicide attempts, increased visits to physicians, and more antidepressant use than in people without any symptoms.[17] In an epidemiologic study from Germany,[7] between 1 and 4 symptoms of MDD were associated with disability and suicide attempts. Also, a clinical trial of fluvoxamine in depressive-spectrum disorders found that patients with subsyndromal depression had worse functioning in the domains of emotional well-being, energy, social functioning, and overall sense of well-being, whereas those with minor depression had even more severe levels of dysfunction in the same domains.[18]

Overall, the epidemiologic evidence strongly supports the hypothesis that depressive symptoms lie along a spectrum that ranges from subsyndromal depression to minor depression to full MDD that is associated with disability. Depressive symptoms can be a prodrome of MDD, a subsyndromal disorder associated with disability, an outcome of MDD associated with a high rate of relapse, or a combination of these. The clinical importance of these data is that the ultimate goal of treatment of depression should be full remission, i.e., elimination of symptoms, and aggressiveness of treatment should increase until this goal is achieved.

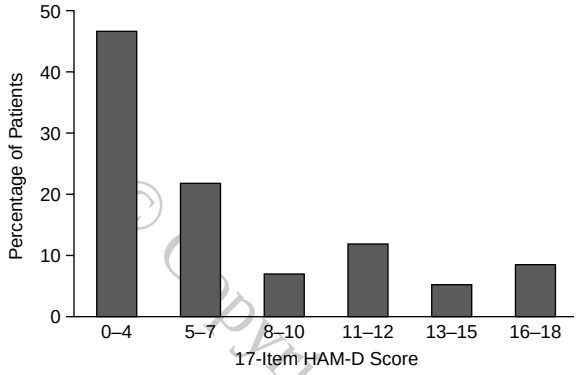
CLINICAL TRIALS OF ANTIDEPRESSANTS FOR MAJOR DEPRESSIVE DISORDER AND THE IMPORTANCE OF FULL REMISSION

Compelling epidemiologic evidence in support of the importance of residual symptoms begs the question of treatment outcomes and realistic goals of treatment. Few probands in epidemiologic studies underwent controlled or optimized treatment. What, then, is the outcome of patients treated rigorously in clinical trials? How many achieve remission? How many experience persistent residual symptoms? What should clinicians expect to achieve with pharmacologic or psychotherapeutic interventions?

Various definitions for outcomes of the treatment of depression have been used in clinical research.[4] "Response" has most often been defined as a 50% decrease from a baseline score on a depression rating scale (e.g., HAM-D[3] or Montgomery-Asberg Depression Rating Scale [MADRS][19]). Definitions of "remission" have been more elusive, with final 17-item HAM-D scores ranging from as low as 7 to as high as 11. Using these definitions, about 50% to 70% of patients in clinical trials respond to antidepressants but fail to remit, whereas perhaps 25% to 35% experience full remission.[1,20] As the epidemiologic evidence shows, full remission is the desired goal, both to decrease distress and disability and to lower the probability of subsequent relapse,[8,21–24] as well as to minimize impairment at work.[25] A problem exists for most patients, however, if less than half are expected to achieve full remission and if most will experience at least some residual symptoms after a reasonable duration of treatment.

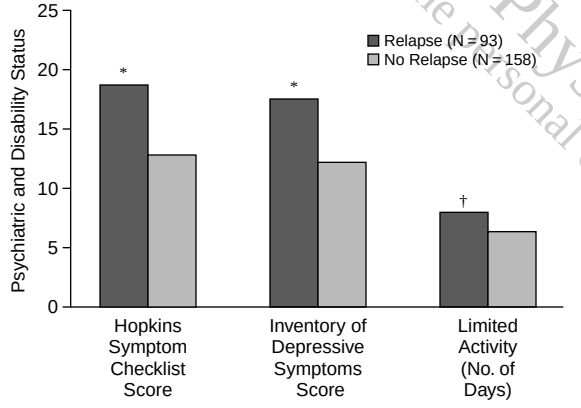
In contrast with the assertion that remission should be the goal, Angst and colleagues[26] have argued that a 50% reduction in depression scores is reasonable within the confines of a clinical trial. They note that patients appear to improve at the same parallel rate even when they start out with different levels of baseline severity. This means that those who start out with higher levels of baseline se-

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]



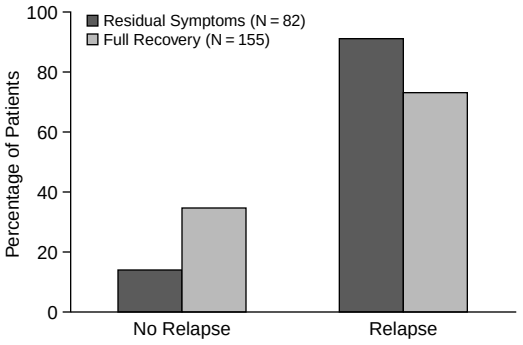
[a]Adapted with permission from Paykel et al.[10]

Figure 2. Prevalence of Depressive Symptoms and Disability Among Patients With or Without Relapse at 7-Month Follow-Up[a]



[a]Data from Lin et al.[24] All data are presented as mean.
*p ≤ .001. †p ≤ .008.

Figure 3. Outcome Among Patients With Major Depressive Disorder With Full Recovery Versus Those With Residual Symptoms[a]



[a]Data from Judd et al.[8] p < .001 for comparisons between groups.

verity will take longer to cross any threshold that defines response. The problem remains, however, to define an adequate duration of a clinical trial. For example, Keller and colleagues[27] found that for patients with chronic depression, 103 (20%) of 500 patients who failed to respond to treatment with sertraline or imipramine at week 8 eventually responded by week 12. Of the entire group of subjects, about half responded and about a third remitted. Of those who responded, more than half were also considered to have remitted.

Regardless of how the level of response is defined, the persistence of residual symptoms after treatment is a sign of a poor prognosis. For example, Paykel and colleagues[10] found that patients who experienced partial remission had a greater initial severity of depression, had more psychological symptoms, were female, had an increase in passive-dependent behavior, and had deteriorating self-esteem. Using Research Diagnostic Criteria to define remission, those investigators found that 68% of the subjects had attained remission (i.e., HAM-D_{17} total score ≤ 7), while 32% of the subjects had total scores ≥ 8 and exhibited residual symptoms (Figure 1).[10] A study[24] of the rate and clinical predictors of relapse among patients with MDD found a 37.1% rate of relapse at 7 months among patients treated in primary care (Figure 2). The presence of persistent symptoms of depression was a primary risk factor for relapse, consistent with the data cited earlier from Judd and colleagues[8] (Figure 3). Paykel et al.[10] found that the presence of residual symptoms of depression (i.e., a HAM-D score ≥ 8) was associated with a relapse rate of 76%, compared with a rate of 25% among patients without residual symptoms. In another study[11] among a group of 56 outpatients with MDD, relapse or recurrence occurred in 41% over 5 years, and the presence of residual symptoms was significantly associated with relapse within the first 4 months after attaining remission.

Thus, these clinical data support the goal of treating depressed patients to full remission.

MANAGEMENT OF RESIDUAL SYMPTOMS

The ideal approach to managing residual symptoms is that of prevention. Aggressive initial treatment should be implemented with drugs that offer robust efficacy and the best chance to induce a full remission. Clomipramine is widely accepted in European countries as a potent antidepressant with exceptional activity in patients with severe melancholic depression.[28,29] However, the routine use of clomipramine is often limited by dosage-related adverse events and the potential for overdosage and toxicity. Recent data also suggest that drugs with more than 1 mechanism of action, such as venlafaxine extended release (XR)[30,31] and mirtazapine,[32] may offer more robust efficacy than do single-action drugs.[33]

For patients who experience a partial remission, the optimal approach is to ensure that they are given an adequate dosage and duration of drug therapy.[1] Alternative strategies are to switch to a different drug, use augmentation or drug-combination strategies, or resort to other treatment strategies, such as psychotherapy or electroconvulsive therapy. Antidepressant agents that exhibit a dose-response effect, such as venlafaxine XR,[34] may have an advantage over other agents, because the ability to increase the dosage may obviate the need to switch or augment therapy.

Another approach that is undergoing evaluation in clinical trials is the use of cognitive-behavioral therapy (CBT) alone or in combination with drug therapy. Patients with major depression who had responded during acute therapy had a lower rate of relapse when they were given continuation therapy, consisting of CBT alone or combined with drug therapy, than did patients who were not given such continuation therapy.[23] In an earlier study of patients with residual symptoms of depression despite antidepressant treatment, CBT was associated with a 20% reduction in the recurrence of depression, compared with similar patients not given CBT.[35] Most recently, Fava and colleagues[36,37] found significantly lower relapse rates among patients with recurrent depression or primary MDD who received continuation therapy with CBT during follow-up that extended to 2 years and 6 years, respectively.

CONCLUSIONS

The goal of remission is strongly supported by data from both epidemiologic and clinical studies. Responses that fall short of remission are associated with residual symptoms and depressive-spectrum disorders. The persistence of even a few depressive symptoms causes distress and disability and puts patients at a high risk of subsequent relapse and recurrence. Treatment with robust antidepressants that have dual actions, such as clomipramine, venlafaxine XR, and mirtazapine, may result in higher rates of remission and fewer residual symptoms than does treatment with SSRIs. More comparative studies would be useful to assess relative rates of remission.

Drug names: clomipramine (Anafranil and others), fluoxetine (Prozac), fluvoxamine (Luvox), mirtazapine (Remeron), sertraline (Zoloft), venlafaxine XR (Effexor XR).

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