New Standard of Depression Treatment: Remission and Full Recovery

David Bakish, M.D.

Major depressive disorder (MDD) is a chronic disorder that substantially impairs a patient's psychosocial and occupational functioning. Lifetime prevalence rates for MDD vary widely, ranging from 4.4% to approximately 20%, and it is predicted to become the second leading cause of disability by the year 2020. The magnitude of this public health problem, with its associated decreased quality of life, increased risk of suicide, loss of productivity, and increased health care use, underscores the importance of treating depressed patients to full remission. The presence of residual depressive symptoms due to partial or incomplete remission is associated with significant morbidity and mortality. Hence, complete remission should be the goal in the treatment of patients with MDD because it leads to a symptom-free state and a return to premorbid levels of functioning. Full remission and improved long-term prognosis can be achieved with long-term antidepressant therapy with newer agents that work through multireceptor mechanisms, especially through the serotonergic and noradrenergic systems (i.e., dual action). Robust efficacy and greater remission rates have been associated with dual-action agents.
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Major depressive disorder (MDD) is a chronic disorder that substantially impairs a patient's psychosocial and occupational functioning. Epidemiologic data indicate that MDD is a significant health care problem. Lifetime prevalence rates for MDD vary widely, ranging from 4.4% to approximately 20%.[1] According to the 1990 Global Burden of Illness list, depression is the fourth leading cause of disability in terms of the physical, social, and mental impact of disease, and it is predicted to become the second leading cause by the year 2020.[2,3]

Obtaining an early and accurate diagnosis of depression and providing effective treatment options are primary challenges in the management of this highly prevalent disease. Data from the Australian National Survey of Mental Health and Well-Being showed that patients who had met the *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10)[4] diagnostic criteria for MDD experienced an average of 7 days in the previous month during which depressive symptoms interfered with their daily activities.[5] The same study revealed that, despite significant disability, 35% of patients with depression had not sought medical care at any time in the previous 12 months, and only 52% of those individuals who did visit a physician were offered effective treatment.[5] The Depression Research in European Society (DEPRES) study,[6] which involved 78,463 patients, found that more than two thirds (69%) of depressed patients were not prescribed any treatment medication, and when drug therapy was prescribed (31% of cases), only about one fourth of such patients were given antidepressant agents.

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THE NATURAL COURSE OF DEPRESSION

Often chronic, MDD is characterized by varying levels of psychopathology over the long term, with some patients remaining fully symptomatic over time and others experiencing continuous fluctuations in symptom severity over time.[7–9] Once an individual suffers a first episode of MDD, the probability of the occurrence of a second episode ranges from 50% to 80%, and after the second episode the likelihood of a third one increases to 90%.[10] In addition, the longer a patient remains symptomatic, whether at a level of full diagnostic psychopathology or at a subsyndromal level, the lower the chances of a complete recovery.[9]

From the Ottawa Psychopharmacology Clinic, Ottawa, Ontario, Canada.

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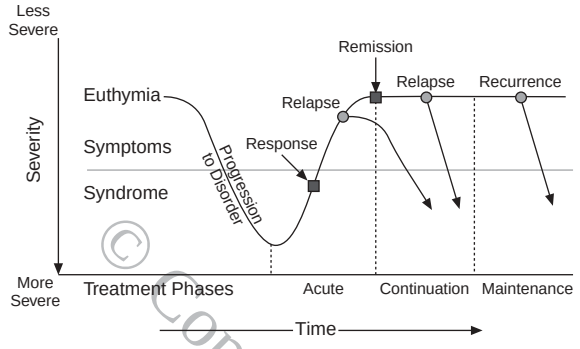
Reprint requests to: David Bakish, M.D., Ottawa Psychopharmacology Clinic, 1929 Russell Rd., Suite 328, Ottawa, Ontario, Canada K1G 4G3.

Figure 1. Fluctuations in Symptom Severity Over Time and Long-Term Treatment of Major Depressive Disorder[a]



[a]Adapted, with permission, from Kupfer.[10]

A better understanding of the course of MDD provided by prospective longitudinal follow-up studies suggests that subsyndromal conditions are an active state of a depressive episode from which the patient has not fully remitted. A prospective 12-year study of patients with MDD showed the dynamic and changeable symptomatic course of MDD, with major, minor, and subsyndromal depressive symptoms commonly alternating as different manifestations and levels of disease.[8] Subsyndromal and minor depressive symptoms combined appeared as the most common clinically active states of MDD in the study population. Moreover, similarly to MDD, subsyndromal or residual symptoms were associated with significant psychosocial dysfunction.[8]

Residual symptoms are often similar to but milder than those seen in MDD and commonly include depressed mood, guilt, weight loss, early insomnia, and hopelessness accompanied by significant occupational and psychosocial dysfunction.[11] Furthermore, residual symptomatology has been found to be associated with early relapse and increased rates of recurrence.[8,11] A relapse of depression is defined as the return of symptoms meeting the full syndrome criteria that occurs during an asymptomatic period of incomplete recovery from the index episode.[12] Recurrence refers to the occurrence of a new episode after full remission of an index episode has been reached. The implementation of long-term treatment, consisting of an acute, a continuation, and a maintenance phase (Figure 1),[10] is instrumental in preventing relapse and recurrence of MDD. Treatment phases are discussed below.

TREATING MDD: REMISSION VERSUS RESPONSE

As for the treatment of most medical ailments, the goal for the therapeutic management of MDD should be remission, i.e., the complete resolution of symptoms and dysfunctions. In clinical trials, however, treatment efficacy has generally been measured by a patient's response to therapy. The most frequently employed criterion to measure response to antidepressant therapy is a 50% reduction from baseline scores in the Hamilton Rating Scale for Depression (HAM-D) or in the Montgomery-Asberg Depression Rating Scale.[13–15] Response to therapy is a useful treatment endpoint in short-term clinical trials. However, it should not be the endpoint in long-term trials or the goal of treatment in clinical practice because, under that criterion, patients that respond to a given therapy may still present a significant level of residual symptomatology. Remission is a more meaningful treatment endpoint and goal.

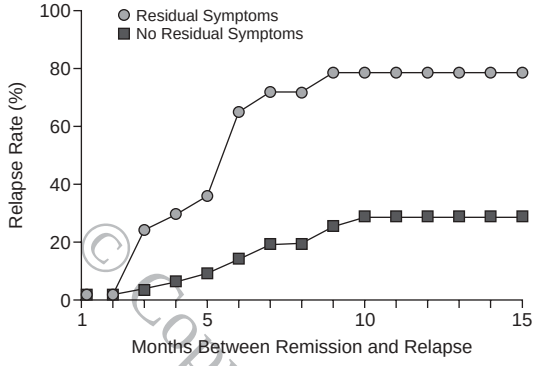
Achieving remission of MDD provides the best opportunity for improving long-term prognosis and preventing relapse and recurrence. A patient in full remission is completely symptom-free and has returned to premorbid levels of psychosocial and occupational functioning.[16] The criteria used to define remission in clinical trials include a final score ≤ 7 on the 17-item HAM-D scale, a final score of < 10 on the 21-item HAM-D scale, or a score of 1 on the Clinical Global Impressions (CGI) scale.[13,14] The distinction between obtaining a treatment response and reaching full remission has important implications in the selection of antidepressants, as many of these agents are effective in producing a response in 50% to 60% of patients but elicit much lower remission rates.[13]

The clinical consequences of a treatment response without full remission have been described by a number of investigators.[7,8,11,17,18] In a 2-year prospective study, Paykel[17] followed longitudinally the course of illness in 64 patients with MDD, the majority being inpatients with a history of recurrence. Seventy percent of the patients achieved remission by month 6. At the time of remission (at least 2 months with symptoms below the Research Diagnostic Criteria [RDC] threshold for MDD),[19] however, 32% of patients were experiencing residual symptoms ($HAM\text{-}D_{17}$ score ≥ 8).[17] Most significantly, the presence of residual symptoms was a strong predictor of early relapse: 76% of patients experiencing symptoms compared with 25% of those without symptoms had a relapse of the index depressive episode (Figure 2).[11]

In addition to an increased risk of disease chronicity, patients with residual depressive symptoms have a significantly higher lifetime prevalence of suicide[7] and significantly greater psychosocial impairment[8] than patients who fully remit. Residual symptoms reflect a partial or incomplete remission, which increases the risk of chronicity in the course of MDD.[8]

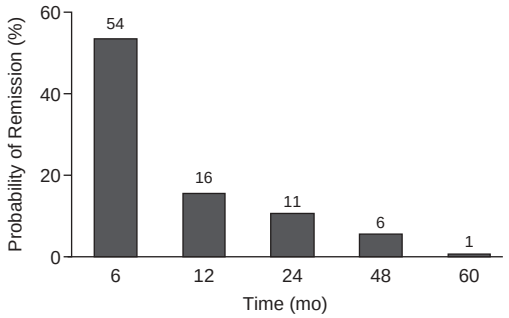
There are a number of patient- and treatment-related factors that may affect treatment outcome. Patient-related factors include the severity of illness, the presence of comorbid illnesses or disorders, lifestyle stressors, and attitudes toward depressive illness and treatment compliance.[9,11,16,20] Several treatment/drug characteristics may

Figure 2. Effect of Residual Depressive Symptoms on Relapse Rates[a]



[a]Adapted, with permission, from Paykel et al.[11] $p < .001$, relapse rates in patients with residual symptoms versus those with no residual symptoms.

Figure 3. Likelihood of Achieving Remission Over Time[a]



[a]Data from Keller et al.[9]

also be important for ensuring optimal therapeutic outcome, such as the class and efficacy of antidepressants,[13,14] dosage level and treatment duration,[9,10] and the incidence and severity of adverse events.[21]

STRATEGIES FOR REACHING AND SUSTAINING REMISSION

Clinical studies indicate that the chances of achieving full remission are greatest during the first 6 months of antidepressant therapy.[9,18] In a 5-year prospective follow-up study, Keller and colleagues[9] observed rates of recovery in 431 patients with MDD participating in the National Institute of Mental Health Collaborative Depression Study. Recovery rates, defined as beginning the first of 8 consecutive weeks at a Psychiatric Status Rating score of 1 or 2, were highest (54%) within the first 6 months of follow-up and declined markedly over time (Figure 3).[9] Similarly, a 2-year prospective study[18] that followed the course of illness in 64 patients with MDD showed that remission rates (at least 2 months with symptoms below the RDC threshold for MDD) were greatest at month 3 (33%) and substantially declined during the 4- to 6-month (17%), 7- to 9-month (17%), and 10- to 12-month (8%) intervals. These data underscore the importance of treating patients early and aggressively to maximize the chances of eliciting full remission.

Clinical guidelines to maximize the benefits of treatment evolved as the need to treat patients to full remission became apparent. Treatment of depression should focus not only on single symptoms but also on the global aspects of the disorder, addressing a variety of symptomatologies and disparate symptom domains.[22] The treatment endpoint should be clinically relevant, and the assessment tools employed should allow physicians to distinguish the presence of residual symptoms.[16] The HAM-D, the most commonly used tool in research trials, is recommended[22]; however, it may be somewhat less practical in the clinical setting because of its length. The Sheehan Disability Scale, which measures global impairment in family, work, and social functioning, is also a reliable and valid tool for assessing the effectiveness of antidepressant treatment.[22] A score of 1 or less on this scale is correlated with remission. Objective evaluation employing physician-rated scales such as the HAM-D and the Sheehan Disability Scale should be used in concert with patient-rated scales, such as the CGI. A score of 1 (very much improved) on the CGI is associated with remission.[13]

Three distinct treatment phases should be implemented in the management of MDD: acute, continuation, and maintenance (Figure 1, Table 1).[10,22] During the acute phase, the goal of treatment is to elicit a response and decrease symptoms to a nonpathologic level. The acute phase may last up to 6 to 8 weeks. Once a return to normalcy is achieved, a continuation phase of 4 to 9 months should follow. The goal of this treatment phase is to maintain the improvements, resolve remaining symptoms and functional impairments, and prevent relapse. Next, a maintenance phase to prevent the recurrence of a new depressive episode begins. The length of this phase may vary depending on the number of previous depressive episodes and the presence of a comorbid anxiety disorder, but it should consist of at least 4 to 5 additional months of treatment.[22]

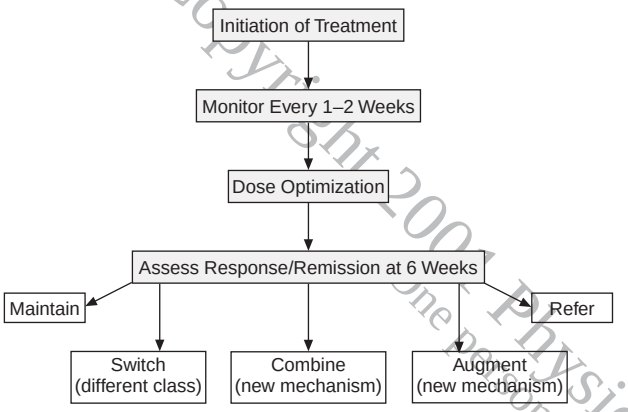
An individualized treatment approach is often required to optimize treatment outcome.[21] Once treatment is initiated, the patient should be monitored on a weekly or biweekly basis (Figure 4). During this period, it is important to optimize the medication dosage and to begin the process of patient education in regard to the nature of the disorder, the goals of therapy, and the importance of compliance. Gradually adjusting medication dosage according to the patient's clinical response is of utmost importance to obtain the best outcome possible early in the treatment. The use of suboptimal dosages may limit the efficacy of the medication, delaying the resolution of the depressive epi-

Table 1. Treatment Guidelines for Major Depressive Disorder[a]

Phase	Goals	Time Course	Physician Scale	Patient Scale[b]
Acute	Reduce symptoms to nonpathologic level	6–8 wk	HAM-D_{17} score ≤ 7	CGI score = 1
Continuation	Maintain improvement and induce remission; resolve functional impairments	Additional 4–9 mo	HAM-D_{17} score ≤ 7; Sheehan score ≤ 1	CGI score = 1
Maintenance	Maintain remission and reduce recurrence	Additional 4–5 mo	HAM-D_{17} score ≤ 7	CGI score = 1

[a]Adapted with permission from Ballenger.[22] Abbreviations: CGI = Clinical Global Impressions scale, HAM-D_{17} = 17-item Hamilton Rating Scale for Depression, Sheehan = Sheehan Disability Scale.
[b]Alternatively, a 70% improvement on another patient-rated scale could be used.

Figure 4. Treatment Strategies for Achieving and Sustaining Remission in Patients With Major Depressive Disorder



sode and possibly inducing only a partial response or premature discontinuation for insufficient treatment efficacy. Agents like the selective serotonin reuptake inhibitors, however, do not show a clear dose response, so increasing dosages may only raise the incidence or severity of side effects such as sexual dysfunction. In this regard, agents that demonstrate a clear dose response, such as dual-action venlafaxine, have a therapeutic advantage. Treatment-resistant depression has been shown to respond to increasing dosages. If remission is not achieved through increasing drug dosage, the treatment strategy should be reassessed.[21] The options available to the clinician to treat a partial response include maintaining the current regimen for a longer period, switching medications, combining antidepressant medications,[16] or augmenting treatment with adjunctive cognitive-behavioral therapy, lithium, thyroid hormone, or anxiolytic agents. Switching to another agent within the same class may prolong the patient's suffering unnecessarily, although, unfortunately, it is commonly done in clinical practice. Switching to a different class of antidepressant may be the most rational approach if the patient fails to respond adequately to therapeutic levels of the initial medication. Patients who have failed therapy with several different classes of antidepressants may be more appropriate candidates for augmentation strategies.[16]

CONCLUSION

U.S. and global evidence-based guidelines for treating MDD underscore the importance of treating patients to full recovery and, in that context, indicate the greater efficacy of agents with a dual mechanism of action.[23] Complete remission should be the goal in the treatment of patients with MDD. This outcome allows a patient to regain full functioning in all aspects of life and to return to a symptom-free state. Residual depressive symptoms, which reflect partial or incomplete remission, are considerably common in clinical practice and are associated with significant morbidity and mortality. In addition, the longer a patient remains ill, whether experiencing syndromal or subsyndromal symptomatology, the less likely he or she is to recover. Full remission and improved long-term prognosis can be achieved with long-term antidepressant therapy with newer multireceptor agents that demonstrate robust efficacy and remission to full recovery.

Drug name: venlafaxine (Effexor).

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