

Depression: The Benefits of Early and Appropriate Treatment

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Abstract

Depression has a profound impact on patient health, individual and family quality of life, activities of daily living, and daily functioning, as well as on healthcare providers, payers, and employers. Persons with depression tend to have multiple comorbidities that compound the negative effects and increase costs. The economic burden of the disease is significant, with direct medical costs estimated at \$3.5 million per 1000 plan members with depression. Depression is significantly underdiagnosed and undertreated, particularly in primary care where the majority of patients with depression seek care. Effective strategies to achieve remission have been identified and have proven effective in clinical trials. Early detection, intervention, and appropriate treatment can promote remission, prevent relapse, and reduce the emotional and financial burden of the disease.

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Burden of Depression

An estimated 19 million Americans suffer from depression.¹ Left untreated, depression can have a significant negative impact on a person's social, physical, and mental well-being, and place an enormous burden on society. Patients with depression experience a higher incidence of premature death related to cardiovascular disease^{2,3} and are 4.5 times more likely to suffer a myocardial infarction than those without depression.³ Depression is also very costly. In the United States, the total cost of depression was estimated to be \$83.1 billion in 2000⁴ with lost productivity and direct medical costs accounting for \$30 billion to \$50 billion each year.⁵ Health service costs are 50% to 100% greater for depressed patients than for comparable patients without depression primarily because of higher overall medical utilization.^{6,7} Overall, the economic burden of the disease is significant to managed care organizations, with direct medical costs estimated at \$3.5 million per 1000 plan members with depression.^{2,7}

Persons who are depressed miss work because of illness at twice the rate of the general population.⁸ This lost productivity translates into \$44 billion in annual wages alone.⁹ Additional intangible costs associated with depression include impaired concentration, failure to advance in educational and vocational endeavors, increased substance abuse, and impaired or lost relationships.^{10,11}

Despite its prevalence, depression remains a significantly underrecognized and undertreated condition in all practice settings, including managed care. Less than one third of adults with depression obtain appropriate professional treatment.¹² Denial of illness and fear of social stigma are 2 primary barriers to proper identification and treatment of depression. Many individuals with depression are ashamed to seek out a mental health professional and consider depression a sign of personal "weakness." When patients seek help, it is estimated that two thirds will present to a primary care physician (PCP).¹³ In fact, PCPs are the sole contacts for more than 50% of patients with mental illness.^{14,15} Prevalence of major depression is 2 to 3 times higher in primary care patients than in the overall population because patients with depression use healthcare resources more frequently.^{14,16} Several studies have demonstrated that early recognition and treatment of depression in the primary care setting can improve social function, increase productivity, and decrease absenteeism in the workplace.^{17,18}

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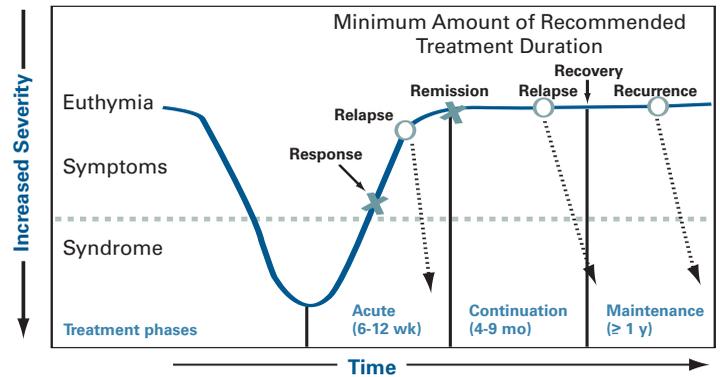
Treatment of Depression

Usual care for depression typically consists of a prescribed antidepressant, psychotherapy, or both. However, mental health specialists encourage earlier and more aggressive therapy to help increase the likelihood of achieving remission and therefore lead to a lower overall cost of care. Accepted clinical practice guidelines state that patients with depression should progress through 3 phases of antidepressant medication treatment (ie, acute, continuation, maintenance), culminating in remission characterized by full restoration of normal capacity for psychosocial and occupational function with no residual symptoms (Figure 1).^{19,20} Treatment begins with the acute phase for a patient who has been diagnosed with a major depressive episode.^{19,20} The primary goal of treatment in the acute phase is to achieve a response or significant improvement in depressive symptoms through medication or psychotherapy, eventually culminating in remission or absence of all residual symptoms. The recommended acute phase of treatment generally lasts a minimum of 6 to 12 weeks.²⁰ It is important to note that if symptoms improve during this period but do not return to normal functional levels, the course of therapy should be modified toward aggressive measures (ie, maximum dosing of the primary agent) in an attempt to achieve remission.¹⁹ Patients with residual symptoms at the end of the acute phase have a 76% relapse rate compared with a 25% relapse rate for patients who reach remission.²¹

After remission has been achieved and physical and emotional functions have been restored, the continuation phase of treatment begins. At this point in the treatment process, the main goal is to prevent relapse, defined as a regression of the patient's condition to less than optimal physical and psychological status, or, more simply, a return of depressive symptoms. Relapse may occur before remission is achieved; however, the continuation phase does not begin until remission has been achieved.²⁰ The minimum recommended duration of treatment in the continuation phase is 4 to 9 months.²⁰

The maintenance phase of treatment is essentially long-term management of the depressive disorder. In this phase, treatment is continued with the desired goal of preventing recurrence of a depressive episode.¹⁹ Recurrence, like relapse, is characterized by a regression of the patient's condition or a return

■ **Figure 1.** Longitudinal Course of Treated Depression



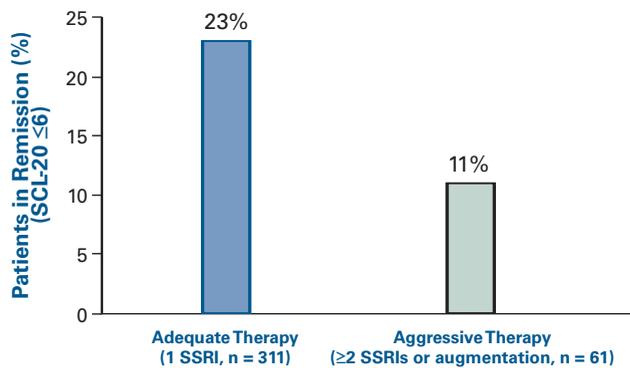
Kupfer DJ. *J Clin Psychiatry.* 1991;52(suppl 5):28-34. Copyright 1991, Physicians Postgraduate Press. Adapted with permission.

of depressive symptoms. Recurrence, however, is only considered to have occurred after recovery has been achieved. The maintenance phase of treatment may continue indefinitely, depending on an individual's risk of recurrence, but for the first episode of depression, it is usually recommended to continue for 12 months.

Considering the long-term and progressive nature of depression, achieving remission is crucial for predicting future outcomes in the severity of the disease or in the emergence of new depressive episodes. Current data predict a greater than 50% probability that an individual who has had 1 episode of depression will experience a second episode within 5 years. After a second episode of depression, the likelihood of recurrence increases to roughly 70%. The risk of recurrence is greater than 90% after a patient has a third episode of depression.²²⁻²⁴ Unfortunately, less than one third of adults with depression obtain appropriate professional treatment,¹² and a majority are not treated sufficiently to achieve remission.²⁵ Patients who do not achieve remission are at greater risk for relapse and recurrence, more long-term depressive episodes, and a shorter duration between depressive episodes.

Presence of residual symptoms after treatment is a predictor of poor outcomes. Results of the National Institute of Mental Health's Collaborative Depression Study demonstrated that patients with residual symptoms during recovery had significantly more severe and long-term future courses of disease than those with no residual symptoms.²⁶ Likewise,

■ **Figure 2.** Open-label Data Suggest that Multiple SSRI Trials May Not Achieve High Levels of Remission



SCL-20 indicates Symptom Checklist-20; SSRI, selective serotonin reuptake inhibitor.

Corey-Lisle PK, et al. *Arch Intern Med.* 2004;164:1197-1204.

those with residual symptoms experienced a relapse more than 3 times faster and had more recurrences, and fewer symptom-free weeks during follow-up than asymptomatic patients.²⁶

Individuals who fail to achieve remission also tend to use more healthcare resources as suggested by a report that employees with a history of treatment-resistant depression (TRD) used more than twice as many medical services as those without TRD.²⁷ In the TRD patients, the average annual medical cost was \$14 490 per employee versus \$6665 for employees who were depressed, but not considered treatment-resistant.²⁷ Similar results were found by a second study that demonstrated that patients with persistent depression had nearly twice the annual healthcare costs of those who had achieved remission.²⁸

Choice of Antidepressant Therapy

The choice of an antidepressant should be based mainly on the unique medical-historical profile of the individual patient. Drug safety, side effect profile, tolerability, and the potential for drug interactions should be considered because these variables can affect adherence to treatment. Several different classes of medications are currently used to treat depression. First-line medications typically used in the treatment of depression include the selective serotonin reuptake inhibitors (SSRIs), which have reasonable efficacy and a relatively low rate of adverse events. There are a number of agents in this

class available as generics. Although effective, older agents, such as monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs), are associated with cardiac, anticholinergic, and hypotensive side effects, as well as the potential for severe toxicity. Consequently, these agents are more frequently used as secondary or adjunctive therapies. Several different combination and augmentation strategies are also employed in an effort to improve outcomes.

Despite the existence of multiple classes of pharmacotherapies, many patients experience an inadequate response to initial antidepressant treatment. One study reported that two thirds of patients treated with fluoxetine, paroxetine, or sertraline were nonresponders (ie, failed to exhibit a clinically significant symptom reduction) to initial SSRI therapy (Figure 2).²⁹ These patients who failed to achieve an adequate response on initial therapy often continued to cycle through several other antidepressants without reaching the treatment goal of remission. This inadequate response often results because of insufficient dosing for an inadequate duration and/or drug intolerance. The positive dose-response relationship observed with antidepressant therapy dictates that the dose should be pushed to the highest tolerable levels to achieve remission and prevent relapse. If a patient does not demonstrate adequate response with a particular antidepressant after 4 to 6 weeks of therapy at the initial dose or after 2 to 4 additional weeks at the maximum dose, therapy should be adjusted by either treatment substitution using another antidepressant, adding another antidepressant to the current therapy, or augmenting therapy with another agent.^{30,31}

Although the optimal therapeutic strategy has yet to be determined, findings of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D), a multisite, prospective, sequentially randomized controlled trial of outpatients (n = 4041) with nonpsychotic major depressive disorder that compared various switching or augmenting strategies, have provided significant new insights.³² The STAR*D trial was designed to achieve remission from depression rather than only partial improvement. All patients began with a 12-week course of the SSRI citalopram (phase 1). Patients who did not achieve remission or could not tolerate

citalopram during this period were enrolled in phase 2. Phase 2 compared several different strategies that entailed either replacing citalopram with a different treatment or augmenting citalopram with an additional treatment, including cognitive therapy. Those without sufficient improvement in phase 2 were offered up to 2 additional levels of treatment. Those patients who achieved an adequate response were followed for 1 year to evaluate long-term outcomes with these various treatments.³²

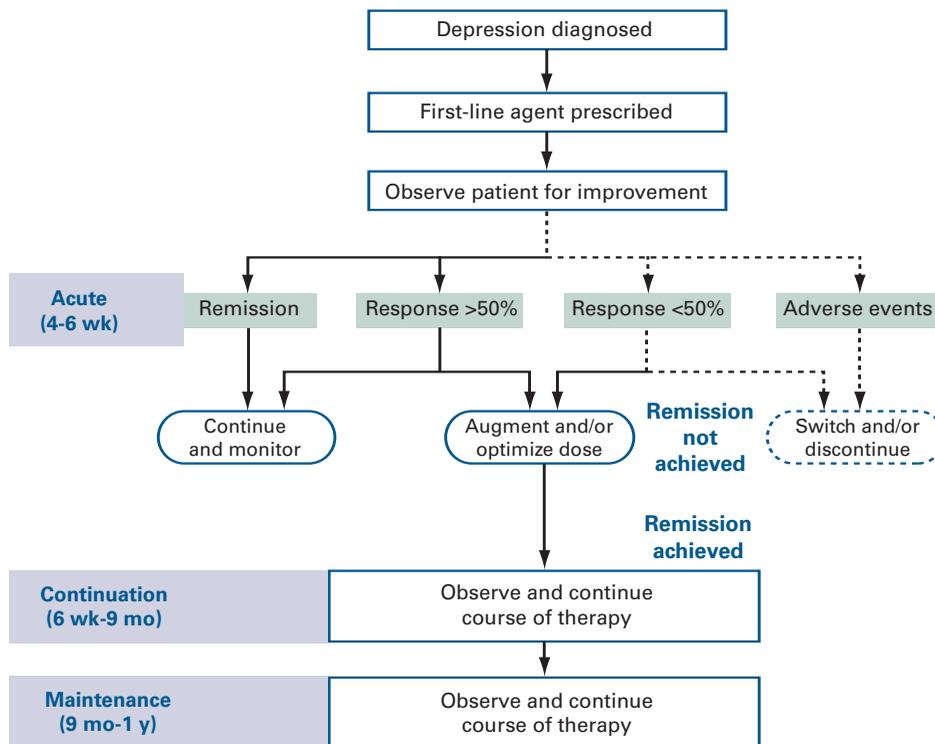
Phase 1 results (n = 2876) indicated that only approximately 30% of patients met the criteria for remission during initial citalopram treatment. Response rates did not differ between patients treated in primary and psychiatric care settings. Remission, when it occurred, did so only after 8 weeks or more of treatment.³² In phase 2, augmentation of citalopram with sustained-release bupropion or buspirone led to similar rates of remission (39.0% and 32.9%, respectively). In those patients switched to another antidepressant therapy, approximately 25% had remission of symptoms after

switching to sustained-release bupropion, sertraline, or extended-release venlafaxine, a serotonin norepinephrine reuptake inhibitor (SNRI).³³

There are economic implications to switching between antidepressants. An analysis of a national pharmacy claims database indicated that switching from a failed antidepressant to another agent with a different mechanism of action (eg, SSRI to SNRI) resulted in reduced total healthcare costs, regardless of which drug class was attempted first.³⁴ Costs declined after switching, but SSRI to SNRI switchers experienced a greater decline in total cost compared with SNRI to SSRI switchers.

To help clarify the selection of antidepressants in a managed care setting, Dunn and Tierney developed a step-therapy algorithm modeled partially after the STAR*D trial and based on trial data and the consensus statements of a panel of clinical and managed care professionals (Figure 3).²⁵ The algorithm begins with the trial of an initial agent, followed by observation to determine the patient's response. If an inadequate response is achieved or if

■ **Figure 3.** Treatment Algorithms May Be Beneficial in Guiding the Management of Treatment-resistant Depression



Dunn JD, Tierney JG. *Am J Manag Care.* 2006;12(suppl 12):S335-S343. Adapted with permission.

intolerable adverse events occur, options exist for dose escalation and/or augmentation as well as switching and/or discontinuation.²⁰ In keeping with the body of evidence in depression treatment, remission is the end goal of the treatment outlined in the algorithm. Frequent follow-up visits or calls are promoted in the algorithm to continuously monitor progress in patients being treated for depression. When switching is deemed appropriate following 1 or 2 therapeutic failures in the same class, the panel recommends switching to an agent from a different class than the initial agent, in keeping with the body of evidence.²⁰

Summary

Depression is a long-term and progressive condition that when not treated adequately can lead to severe morbidity and mortality and increased costs for payers, employers, and patients. Despite the significant burden of depression, the majority of patients do not receive treatment adequate enough to achieve remission. While remission is the primary 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 1 mechanism of action. These strategies may be most easily applied through the use of a treatment algorithm. Patients who do not achieve remission, including those cycling on ineffective therapies, are at greater risk for relapse and recurrence, more long-term depressive episodes, and a shorter duration between depressive episodes. SSRIs are widely used first-line agents for the treatment of depression because of their efficacy, tolerability, and generic status, but when treatment fails, another class of antidepressants, such as an SNRI, should be attempted. Clinical trials provide good evidence to show that achieving and sustaining the fully remitted state is an attainable goal in the management of patients with depression.

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