Key Words: depression, treatment duration, antidepressants, serotonin, SSRI, SNRI, venlafaxine, maintenance pharmacotherapy

Depression Treatment: A Lifelong Commitment?

By Martin B. Keller, MD, and Ernst R. Berndt, PhD

ABSTRACT *~ Depression is associated with considerable disability, morbidity, and mortality. In many patients, depression follows a course of relapse and/or recurrence. However, there is significant evidence that the majority of patients with depressive disorders are undertreated and this imposes a substantial economic burden on society. The reasons for undertreatment include patient, provider, and healthcare system factors. It is vital that treatment be targeted appropriately to break the cycle of relapse/recurrence. Rather than short-term improvement of symptoms, the optimal outcome of treatment of depressive disorders should be full symptom resolution (remission) and long-term recovery. Patients with histories of recurrent depressive episodes may require long-term, indefinite treatment with antidepressants. Currently, few data exist on the outcome and appropriate duration of maintenance pharmacotherapy. The benefits of psychotherapy have recently been demonstrated in a 12-week, randomized, controlled study, which also includes a maintenance phase that has not yet been completed. Additional well-designed studies addressing these issues are urgently needed.* Psychopharmacology Bulletin. *2002;36(suppl 2):133-141*

Introduction

It is now well recognized that depression causes substantial impairment of social and physical functioning, decreased quality of life, increased morbidity, and higher rates of suicide.[1] Indeed, the level of disability caused by depression is greater than that associated with chronic medical conditions such as diabetes, arthritis, and lung disease.[2] Furthermore, depressive disorders are among the most frequent of all medical illnesses,[3] with the lifetime prevalence rate in the United States estimated at 19.3%.[4]

The level of depressive illness and associated disability in the general population has considerable economic implications. Estimates developed by Greenberg

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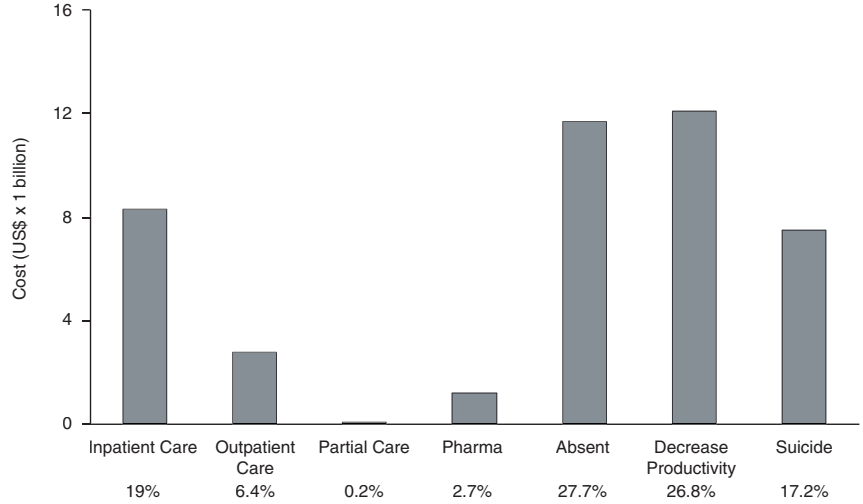
and colleagues[5] suggest that the economic burden of depression in the US in 1990 was $43.7 billion. This amount includes the costs of medical treatment, mortality, morbidity, and lost work productivity (Figure 1). Allowing for inflation and converted into 2001 dollars (using an arithmetic mean of the relative 2001 and 1990 values of the Consumer Price Index-All Items and the Consumer Price Index-Medical care), this economic burden in 2001 becomes $66.2 billion.[5,6] The World Health Organization (WHO) has calculated that depression is the most costly of all medical illnesses in developed countries.[7] There is increasing recognition and acceptance that depression may be a chronic or recurrent medical illness. However, historically, the emphasis of treatment has been on the acute phase of depression. Given the enormous economic consequences of depression, it is clearly vital that treatment strategies should reflect the long-term nature of the disorder. The purpose of this article is to review the clinical course of depression in terms of time to recovery and the incidence of relapse and recurrence; to identify the risk factors for long-term depression; and to give practical guidance for the management of patients with chronic depressive disorders.

The Clinical Course of Depression

Much of the evidence signifying that depression is a chronic and recurrent condition is derived from the National Institute of Mental Health Collaborative Study of the Psychobiology of Depression (CDS).[8] This was a prospective, longitudinal, long-term study of patients with mood disorders that was initiated in the late 1970s and is still ongoing.

FIGURE 1

Direct and Indirect Costs of Depression in the United States in 1990



Keller MB, Berndt E. *Psychopharmacology Bulletin*. Vol 36. Suppl 2. 2002.

Recovery From Acute Episode

There is a widely held belief that depressed patients tend to make complete recoveries from acute depressive episodes. However, data from the CDS demonstrate that a significant percentage of patients with major depression remain chronically ill, and that the longer they remain ill the less likely recovery becomes.[8] Only 53% of patients in the CDS made a full recovery from their index episode of major depression within 6 months. Even after 2 years, 20% of patients had not yet fully recovered and, in a small minority of patients, the index episode of depression persisted for longer than 15 years.[9] These findings are supported by other short- and long-term prospective data and are not a reflection of an unusually treatment-resistant patient population.[8]

The estimated probability of chronicity (defined as remaining ill for at least 5 years) in the CDS was 11.5%.[9] In general, most of these patients had chronic minor depression or dysthymia with episodes of major depression rather than chronic major depression alone; only about 30% of the patients with chronic depression met the full criteria for major depression for more than half of the 5-year period.[9]

Six factors were found to be significantly associated with a chronic course of major depression in the CDS.[10] These predictors were long episode duration before entry into the study, the admitting research center, marital status (married), inpatient hospitalization status at intake, low family income, and comorbid psychiatric disorders (eg, schizophrenia, alcoholism, phobia). The presence of comorbid anxiety disorders had a dramatic effect on the course of depression; the median time to recovery in comorbid patients was 26 weeks compared to 13 weeks in those with pure depression ($P<.01$).[11]

Relapse

Relapse is defined as the early return of depressive symptoms in the months following a response to treatment or a spontaneous remission, and is presumed to represent a reactivation of the pathophysiology of the index episode. The risk of relapse of depression is highest in the first 4–6 months after the initial response.[1] The results of clinical trials in which patients were randomized to placebo after the acute phase of pharmacotherapy suggest that the risk of relapse during this time can be as high as 50%.[1] Patients in the CDS who had had three or more previous episodes of depression had a markedly higher risk of early relapse, compared with those with fewer previous episodes.[8] The high risk of relapse after acute treatment clearly demonstrates that pharmacotherapy should be continued beyond the acute phase of the depressive illness.

Recurrence

Recurrence is defined as a new episode of depression occurring after a sustained period of remission, which may or may not occur while the patient is receiving treatment. The risk of recurrent episodes of depression increases with time, with 60% of patients with major depression in the CDS experiencing recurrence after 5 years, 75% after 10 years, and 87% after 15 years.[8] The median length of time to recurrence following recovery from the index episode was 20 months. There is evidence to suggest that the risk of recurrence increases with each episode. The risk of recurrence within 2 years in patients with three or more previous episodes is greater than 95%.[7] Moreover, subsequent episodes of depression often occur sooner, are of longer duration, are more severe, and are less responsive to treatment than the index episode. Other risk factors for recurrent depression include double depression (major depression plus dysthymia), long duration of episodes, comorbid substance abuse or anxiety disorder, and age of onset >60 years. Data from the CDS strongly suggest that many patients with depression should receive long-term antidepressant therapy. Indeed, some of these patients will require lifelong therapy.[1,12,13]

CURRENT TREATMENT OF DEPRESSION

Despite considerable evidence demonstrating the chronic nature of depression and the disability associated with the illness, it has been extensively documented that patients with depression are undertreated. Data presented in 1996 at a consensus conference of the National Depressive and Manic Depressive Association showed that less than 10% of people with unipolar major depression were likely to receive adequate treatment for a sufficient period of time.[3] Reasons for such low levels of treatment have been attributed to patient, provider, and health-care system factors.[3] Many patients do not seek treatment for depressive symptoms. Among patients who do seek treatment, some are not diagnosed with depression, while others may be offered psychosocial treatments rather than pharmacotherapy because of concerns about drug-related adverse events, contraindications, and overdose attempts.

When patients are prescribed antidepressants, lack of compliance is a major barrier to successful therapy. Data suggest that more than 20% of patients with major depression do not even fill their first prescription.[14] Most patients who do begin treatment continue with their medication for less than 14 weeks. The main reasons for the generally short duration of antidepressant therapy are medication adverse events and lack of appreciation, both by the patient and the physician, of the need to continue therapy long-term.[3]

Guidelines on the Pharmacotherapy of Depression

Consensus recommendations on the pharmacotherapy of depressive disorders were made in 1989 by the heads of centers in biological psychiatry and psychopharmacology collaborating with the WHO.[15] These included guidelines on acute treatment, continuation treatment, and long-term maintenance treatment.

The acute phase of treatment is defined as the period required for a response and lasts approximately 12 weeks.[16] Regarding acute treatment, the WHO guidelines recommended changing dosage or trying alternative medication if a patient failed to respond within 3 weeks. The guidelines also noted that for all patients suffering from depressive disorders, psychotherapy might be useful in conjunction with pharmacotherapy.

Following recovery from the acute episode, the WHO treatment guidelines recommend that medication should be continued for at least 6 months. The aim of this stage of treatment (the continuation phase) is to produce a remission and to prevent relapse. At the end of the continuation phase, the guidelines recommended that therapy should be gradually discontinued and the patient's mental status checked about 3 weeks after complete cessation. The patient should be followed up regularly for at least 6 months. The WHO guidelines also recommended that long-term maintenance (prophylactic) therapy should be considered for patients who have had more than one severe episode of depressive illness in the past 5 years.

The successful implementation of these guidelines in individual patients necessitates the proactive management of compliance issues. The identification and management of adverse events associated with antidepressant therapy is vital to prevent the premature discontinuation of an otherwise optimal therapy, and needs to be combined with early and ongoing educational messages to the patient about the importance of sustaining remission. Clinically, treatment decisions are generally based on patient response to therapy (Figure 2).

Recent Long-Term Clinical Studies of Antidepressants

Several continuation studies of traditional antidepressants were conducted in the 1980s.[17] More recently, long-term studies have been conducted with newer antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and the serotonin and norepinephrine reuptake inhibitor (SNRI) venlafaxine, which tend to be tolerated better than tricyclic antidepressants.

The design of these trials varied, but generally patients received either the active drug or placebo after recovery from the acute symptoms of depression. The majority of the studies addressed continuation therapy

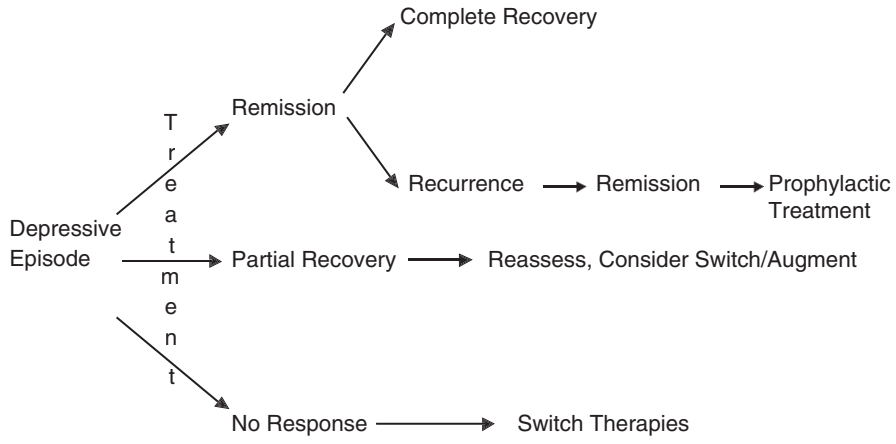
only. However, in one study, therapy was continued for 1 year following an 8-week course of the SSRI, paroxetine, and it therefore included the early maintenance phase as well as the continuation phase of treatment (up to 6 months).[18] The SNRI, venlafaxine, has also been evaluated in both the continuation and maintenance phases.[19] Another study addressed early maintenance therapy only, when patients who had responded to a 6-month course of the SSRI, fluoxetine, were followed for a 1-year period after randomization to fluoxetine or placebo.[17] In general, the dose of antidepressant used for the continuation phase was identical to that used in the acute phase of treatment.

In studies evaluating continuation therapy, relapse rates in the placebo group ranged from 31% to 52%, whereas relapse rates on active compounds were significantly lower (4% to 28% [Keller, pages 36-48]). Thus, the results of these studies consistently show that the SSRIs paroxetine, citalopram, and sertraline, and other newer agents, such as nefazodone, mirtazapine, and the SNRI venlafaxine, are effective in preventing relapse after recovery. The data demonstrate the validity of the recommendations for the continuation of antidepressant treatment following acute recovery.

Those studies that continued into the maintenance phase of antidepressant therapy also showed a clear reduction in recurrence rates. For example, after 1 year of maintenance fluoxetine, 26% of patients experienced a recurrence of symptoms compared with 57% of patients in the placebo group.[17] The benefits of long-term therapy with paroxetine

FIGURE 2

SCHEME OF TREATMENT DECISIONS



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were also apparent during the maintenance phase of the study.[19] Likewise, venlafaxine extended release reduced relapse rates compared with placebo (28% versus 52%, respectively),[19] and venlafaxine improved recurrence rates (22% versus 55% for placebo).[19]

Few data exist on the maintenance phase of antidepressant therapy beyond 1 year, with only one randomized, placebo-controlled trial continuing for up to 3 years.[20] In this study by Frank and colleagues,[20] patients in at least their third episode of major depression who had successfully completed continuation therapy (17 weeks) were randomized to one of five groups: visit to the clinic and imipramine; interpersonal psychotherapy and imipramine; visit to the clinic and placebo; interpersonal psychotherapy only; and interpersonal psychotherapy and placebo. The percentage of patients in the imipramine and placebo groups who completed the 3-year study without recurrence was 46.4% and 8.7%, respectively. Although these data clearly demonstrate a reduction in recurrence with active medication, the optimal duration of maintenance therapy remains to be established. Data from an extension of this study demonstrate a high risk of recurrence soon after the discontinuation of maintenance therapy, which suggests that treatment may need to continue indefinitely for some patients.[8,21]

Current Status of Psychotherapy for Treating Depression

For most patients, psychotherapy should be regarded as an adjunct to pharmacotherapy. Three psychotherapeutic approaches have been modified or developed specifically for the treatment of depression: cognitive therapy, behavioral therapy, and interpersonal therapy.[11] Cognitive therapy views depression as resulting from impaired cognition, which leads to an unrealistic outlook and set of expectations. Behavioral psychotherapy is based on the premise that depression is the result of the loss of positive reinforcement, whereas interpersonal psychotherapy views difficulties in interpersonal relationships as the cause or result of depression.

There is still a major research gap in the area of psychotherapy, as there have been few systematic, controlled clinical studies in chronic major depression—open studies are promising.[11] The randomized study by Frank and colleagues[20] described above also evaluated interpersonal psychotherapy. Psychotherapy alone was less effective than imipramine, but more effective than placebo in preventing recurrence. However, there was a significant advantage observed in groups that combined interpersonal psychotherapy with pharmacotherapy, compared with either approach alone. A more recent study has also shown that concomitant treatment with nefazodone and psychotherapy (cognitive behavioral-analysis system of psychotherapy) was significantly more efficacious than either nefazodone or psychotherapy alone.[21]

CONCLUSION

Depression, a chronic disorder associated with considerable disability, morbidity, and mortality, is often not recognized. Even when depression is properly diagnosed, many patients receive inadequate treatment. Rather than just short-term improvement of symptoms, the optimal outcome from antidepressant therapy should be full remission and long-term recovery. In some patients, this will necessitate long-term, possibly life-long, treatment. However, only an antidepressant that achieves a high remission rate can be expected to provide a lasting symptom-free state. ✤

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