

Long-Term Treatment of Recurrent and Chronic Depression

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Depression is associated with high rates of impairment and comorbidity with other disorders and has a devastating effect on those who suffer from it. Treatment options are available and can greatly improve functioning; however, undertreatment still persists. Undertreatment may result from incorrect or incomplete diagnoses or inadequate treatment duration. In addition, when treating depression, clinicians must identify underlying conditions, life-span issues, and proper treatment duration to maximize outcome. This article provides an overview of the underlying implications of depression, reviews issues in treating chronic depression that are still unresolved, and recommends standards for maintenance therapy. *(J Clin Psychiatry 2001;62[suppl 24]:3-5)*

Major depression is a devastating disorder with a high lifetime prevalence of 17%¹ for major depressive episode and high rates of comorbidity and impairment. One third of patients have episodes that last longer than 2 years, and the rate of recurrence is over 75%.² Morbidity of major depression is comparable to that of angina and advanced coronary artery disease.³ In addition, a high suicide rate (15%) among hospitalized depressed patients has been reported.⁴

Treatment options are readily available and can greatly improve functioning, but inadequate treatment still persists, in detriment to both the afflicted individual and society at large. Undertreatment may be the result of incorrect or incomplete diagnosis or inadequate duration of treatment. The clinician must be able to identify underlying conditions, life-span issues, and proper treatment duration to maximize outcome. This article provides an overview of the underlying implications of depression, reviews issues in treating chronic depression that are still unresolved, and recommends standards for maintenance therapy.

RECURRENCE AND CHRONICITY

Data show that among patients seeking treatment for depression, only half can be expected to recover within 6 months, and two thirds within a year (references 5 and 6 and M.B.K., unpublished data). Even 10 to 15 years after

the index episode, 6% to 7% of patients will still be depressed. Among those patients who have recovered, most will have a recurrence of depression—87% by 15 years after recovery from the index episode (M.B.K., unpublished data)—making recurrence of depression the rule rather than the exception.

The DSM-IV⁷ defines chronic depression as a major depressive episode that has lasted at least 2 years. A number of predictors of chronic outcome in major depression have been identified.⁸ For example, long duration of the index episode foretells a chronic course, as do previous depressive episodes that required inpatient hospitalization and the presence of a comorbid anxiety disorder or substance abuse. Other factors associated with chronic depression are an intact marriage and low family income.⁸ In addition, we have identified risk factors for recurrent depression, including a history of frequent and/or multiple depressive episodes, presence of double depression, onset after the age of 60 years, long duration of individual episodes, family history of affective disorder, poor symptom control during continuation therapy, and comorbid anxiety disorder or substance abuse.^{5,7,9-11}

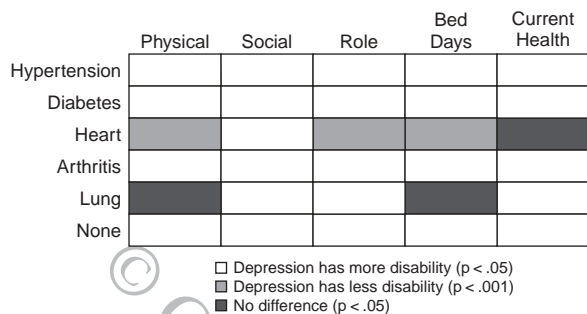
DISABILITY

A significant amount of disability is associated with depression in the work, social, and personal arenas. As Figure 1 shows,¹² depression causes a comparable amount of disability as several common medical diseases, such as hypertension and diabetes, in ratings of physical and social well-being, role functioning, bed days, and current health. This disability literally adds up: in 1990, the estimated annual cost of depression in the United States was \$43.7 billion.¹³ Less than a third of that total was attributed to direct medical costs, and close to one fifth of the total cost

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Figure 1. Disability in Daily Functioning: Depression Versus Chronic Medical Conditions^a



^aData from Wells et al.¹²

Table 1. Relapse of Depression: Long-Term Antidepressant Treatment Versus Placebo

Drug	Weeks of Treatment	Relapse Rate, %		p Value
		Drug	Placebo	
Fluoxetine ^a	52	26	57	< .01
Paroxetine ^b	52	16	43	< .001
Sertraline ^c	44	13	46	< .001
Citalopram ^d	24	11	31	< .05
Nefazodone ^e	36	17	33	< .05
Mirtazapine ^f	20	4	23	< .0001

^aData from Montgomery et al.¹⁸

^bData from Montgomery and Dunbar.¹⁹

^cData from Doogan and Caillard.²⁰

^dData from Montgomery et al.²¹

^eData from Feiger et al.²²

^fData from Montgomery et al.²³

was related to mortality costs from depression-related suicides, whereas over half was derived from the indirect costs of lost time from work and reduced productivity while at work due to depression. It has also been reported recently that cardiac patients with depression have an increased risk of death compared with nondepressed cardiac patients.¹³

In addition, the individual suffers long-lasting psychosocial consequences from a depressive episode. Coryell and coworkers¹⁵ found that patients who had been recovered from depression for 2 years continued to experience severe impairment in a variety of areas at 5-year follow-up. These patients still showed impairment in relationships with friends and family, recreational activities, sex, and overall satisfaction with life. Clearly, a depressive episode has far-reaching adverse effects on the individual's quality of life.

TREATMENT

A variety of effective treatments exist for major depression. For example, a recent study¹⁶ of nefazodone, cognitive-behavioral analysis therapy, and the combination of the 2 for the acute treatment of chronic depression found that each of the individual therapies had a response rate of around 50%, whereas the combination therapy had a response rate of 85% in completers and 73% in the intent-to-treat group. A study¹⁷ comparing sertraline with imipramine for the treatment of chronic and double depression also found similar acute-phase response rates for each agent. Sertraline was associated with a 59% response rate (including remitters) and imipramine was associated with a 61% response rate among those who completed the study. In the intent-to-treat analysis, the response rate was 52% for sertraline and 51% for imipramine.

However, a long duration of treatment is often necessary in chronic depression to protect against relapse. Table 1 shows results from continuation studies comparing antidepressants with placebo. These studies varied in duration from 20 weeks to 1 year, and in all of them, the rate of relapse with placebo was significantly greater than that with antidepressant treatment.¹⁸⁻²³

In a study of long-term management of depression, Frank and colleagues²⁴ compared the efficacy of imipramine, interpersonal therapy, and the combination. Their design included 5 groups of patients: those receiving imipramine only, interpersonal therapy only, interpersonal therapy plus imipramine, interpersonal therapy plus placebo, and placebo only. Placebo had the highest rate of recurrence over the 3-year follow-up period at 78%, whereas imipramine treatment, either alone or in combination with interpersonal therapy, had the lowest rate of recurrence (22% alone, 24% in combination).

At least 1 flexible-dose study has investigated maintenance treatment of chronic depression for longer than 1 year and found that prophylaxis SSRI treatment protects against the recurrence of depression.²⁵ A total of 161 outpatients who responded to sertraline during a 16-week study were randomly assigned to up to 200 mg/day of sertraline or placebo and followed for 76 weeks. Recurrence occurred in only 5 (6%) of the 77 sertraline-treated patients versus 19 (23%) of the 84 placebo-treated patients ($p = .002$ for the log-rank test of time-to-recurrence distributions), while clinically significant depressive symptoms reemerged in 20 (26%) of the sertraline-treated patients as opposed to 42 (50%) of those who received placebo ($p = .001$).

Long-term therapy, then, can protect the patient against relapse and recurrence of depression. The question becomes, how long should maintenance treatment last? Kupfer and coworkers²⁶ found comparable results in favor of imipramine treatment in their 5-year study of full-dose maintenance treatment comparing imipramine and placebo. Patients who had received treatment for 3 years without relapse or recurrence were asked to continue treatment for 2 more years; imipramine was found to protect against relapse for the majority of patients for this time period. The authors recommend prophylaxis treatment of recurrent depression for at least 5 years.²⁶ The recurrence of depression tends to increase dramatically during the first several years after recovery from the index episode, reinforcing the necessity of long-term maintenance treatment lasting several years.

Table 2. Possible Explanations for the Undertreatment of Depression^a

Diagnosis of depression is missed by the clinician
Patient refuses or does not comply with treatment
Clinician prefers psychosocial treatments to somatic treatments
Clinician and/or patient have concerns about side effects, contraindications to treatment, and overdose
Patient fears stigma of depression
Patient lacks adequate access to the health care system

^aFrom Keller et al.¹¹ and Hirschfeld et al.²⁷

UNRESOLVED ISSUES AND RECOMMENDATIONS FOR TREATMENT

Fewer than 10% of patients with major depression receive the correct treatment, a high enough dosage, or a sufficient duration of treatment. Some possible explanations for undertreatment are listed in Table 2.^{11,27} Chronic or recurrent depression calls for long-term treatment, as we have seen, but there are many unresolved issues. First and foremost is the duration of treatment. Kupfer et al.²⁴ recommend maintenance treatment for at least 5 years, but that guideline is still open for debate. Concerns about the effects of maintenance treatment exist, such as the possibility that the risk of relapse or recurrence might increase after the cessation of long-term pharmacologic treatment or that antidepressants might lose efficacy over time. In addition, it can be difficult to determine the optimal maintenance dose, rate of tapering (when tapering is needed), or the role psychotherapy should play.

The goal of maintenance therapy, though, is clear: to prevent new or recurrent episodes of depression. Candidates for maintenance therapy include patients who have had 3 or more episodes of major depression or those who have had 2 or more episodes and have a family history of mood disorder, a rapid recurrence of depressive episodes, an older age at onset, or severe episodes. The maintenance regimen should consist of the same dose of the same drug to which the patient initially responded and should last as long as 2 episode cycles, which at times can be up to 4 or 5 years. At the end of this period, pharmacotherapy should be slowly tapered off only if the patient is strongly opposed to continuing medication. Although the role of psychotherapy in chronic depression holds promise, its use has not yet been established. More research is needed to answer the questions still surrounding the treatment of depression, especially in its chronic and recurrent forms.

Drug names: citalopram (Celexa), fluoxetine (Prozac), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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