The Long-Term Treatment of Depression

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Depression is a recurrent and chronic disorder requiring long-term treatment. Although this fact is generally well accepted, depression remains frequently underrecognized and often undertreated. Recent guidelines recommend that treatment with antidepressants should be continued for at least 4 to 6 months after the initial response and that long-term prophylactic treatment be given to patients who have experienced 2 or more depressive episodes. However, there is little consensus on the duration for which continuation or maintenance treatment should be given. This article reviews the long-term strategy for the treatment of unipolar major depression, particularly in terms of duration of treatment, and which types of patients would benefit from maintenance treatment.

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Depression is a major health problem. Epidemiologic studies carried out in the community estimate that the lifetime risk of depression is 12% to 26% for women and 4% to 12% for men.[1] Of the patients treated for depression, between 75% and 80% experience recurrent depression.[2] Despite the fact that depression has been recognized as a recurrent and chronic disorder requiring long-term treatment, it remains a frequently underrecognized and undertreated disease.[3] When a diagnosis of depression is made, recent guidelines recommend that antidepressant therapy should be continued for at least 4 to 6 months after recovery from the acute episode and that long-term prophylactic therapy be considered in any patient who has experienced 2 or more depressive episodes in the 5 years since the acute episode.[2] In the acute phase of depression, the goal of treatment is to achieve remission of the depressive symptoms (response), whereas the aim of continuation treatment, which comprises the first 4 to 6 months of symptom remission, is to prevent a relapse into depression. The aim of maintenance treatment (prophylaxis) is to prevent another episode of depression (recurrence). There is little opposition to the recommendation that treatment of the acute response should be continued for a period to ensure that the response is stable; however, how long this period should be is less clear.[3] Similarly, prophylactic treatment is accepted as beneficial for some patients, but, again, the duration of treatment remains under debate. The long-term strategy for the treatment of unipolar major depression is reviewed in this article.

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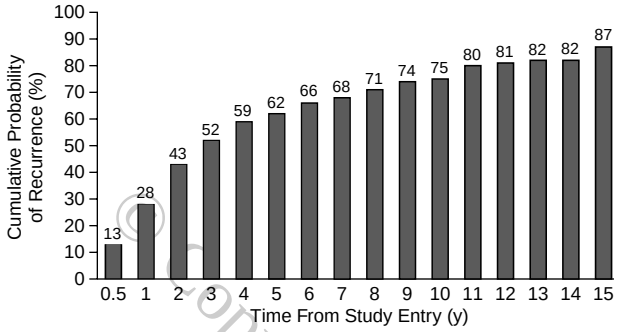
UNIPOLAR MAJOR DEPRESSION

Unipolar major depression has a high rate of occurrence, with approximately a 17% lifetime prevalence.[4] The episodes of depression are often of long duration; one third of patients experience episodes longer than 2 years. In addition, there is a greater than 50% rate of recurrence.[5] The morbidity of major depression has been shown to be comparable with that of angina and advanced coronary artery disease.[6] More specifically, depression was shown to have greater morbidity (measured by disability of daily physical, social, and role functioning, and by bed days) than hypertension, diabetes, and arthritis ($p < .05$).[6] Moreover, up to 15% of hospitalized depressed patients commit suicide.[5]

Patients with major depression have serious psychosocial consequences. Patients with recovery sustained for 2 years of follow-up continue to show severe and widespread impairment in relationships with friends and family, recreational activities, sexual activities, and overall satisfaction with life.[7] An important conceptual shift must be appreciated universally before effective treatment of major depression can prevail. First, major depression is a medical disorder analogous to diabetes or hypertension, and as such, major depression is projected to be the second leading cause of disease burden by the year 2020.[6,8] Second, depression must be recognized as a chronic and recurrent disease that needs maintenance treatment.[5]

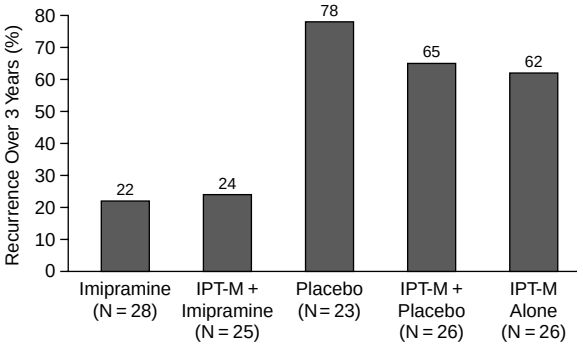
The incidence of recovery from major depression increases with time. A study of 431 patients who were seeking treatment for unipolar major depression examined the probability of recovery from the index episode of major depression.[9] A Kaplan-Meier life table estimated the cu-

Figure 1. Cumulative Probability of Recurrence After Recovery From an Index Episode of Unipolar Major Depression[a]



[a]Data from reference 11.

Figure 2. Maintenance Therapy of Imipramine, Interpersonal Psychotherapy Maintenance (IPT-M), and Placebo in Long-Term Depression: Recurrence Over 3 Years (%)[a]



[a]Data from reference 17.

Table 1. Risk Factors for Recurrent Depression[a]

History of frequent and/or multiple episodes
Double depression (major depression plus preexisting dysthymia)
Onset after age 60
Long duration of individual episodes
Family history of affective disorder
Poor symptom control during continuation therapy
Comorbid anxiety disorder or substance abuse

[a]Based on references 5, 9, and 13–15.

mulative probability of recovery to be 53% at 6 months from entry into the study, 67% at 1 year, 81% at 2 years, and 84%, 87%, and 88% at 3, 4, and 5 years, respectively. From 6 to 15 years, the cumulative probability of recovery remained fairly stable and ranged from 91% at 6 years to 94% at 15 years.[10] Data for years 11 to 15 are as yet unpublished (M.B.K., unpublished data, 1999).

However, the incidence of recurrence of depression after recovery also increases over time. In a study of 359 patients with unipolar depression,[11] the cumulative probability of recurrence after recovery from the index episode of major depression was seen to increase steadily from study entry, to 13% at 6 months, 28% at 1 year, 43% at 2 years, and 62% at 5 years, and continued to increase at a meaningful rate, reaching 75% at 10 years and 87% at 15 years (Figure 1).

MAINTENANCE THERAPY

Maintenance therapy helps prevent the recurrence of depression after recovery. However, when considering the treatment of depression, it is important to differentiate between relapse and recurrence of the disease. *Relapse* is defined as the early return of depressive symptoms following an apparent response, and, ideally in this case, continuation treatment should be administered. *Recurrence* of depression is defined as the appearance of a new episode of depression following response that has been maintained for 6 months. The probability of recurrence of depression as a function of the number of previous episodes is < 60% for 1 previous episode, 60% to 90% for 2 previous episodes, and > 95% for 3 or more episodes,[9,12] and patients who experience a recurrence of depression should receive maintenance therapy. Risk factors for recurrent depression are summarized in Table 1,[5,9,13–15] and patients with these risk factors should also benefit from prophylactic maintenance therapy.[16]

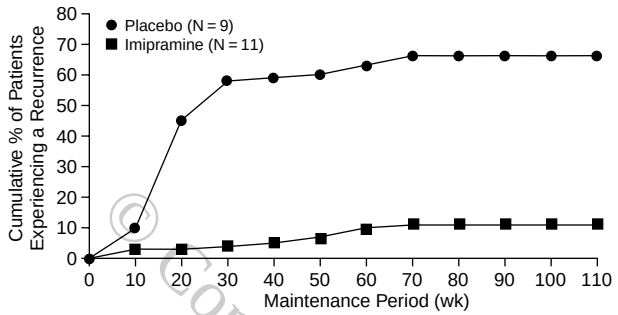
In a study of maintenance therapy in 128 patients, the percentage of recurrence of depression over 3 years in patients who had medication clinic visits with imipramine, placebo, or interpersonal psychotherapy maintenance (IPT-M) on a monthly basis was compared with the percentage in those patients who received combinations of imipramine and IPT-M or of placebo and IPT-M.[17] The results of this study are represented graphically in Figure 2 and show that the maintenance treatment groups that included the antidepressant imipramine experienced substantially fewer recurrences over the 3 years compared with the other maintenance treatments.

A report by Kupfer et al.,[18] from the same study, showed that the subjects recovered for 3 years while taking imipramine. In a random assignment, double-blind study of imipramine or placebo, a highly significantly ($p = .006$) greater likelihood of recurrence was evident in patients randomly assigned to placebo (60%) compared with those taking imipramine (10%) over the subsequent 2 years (Figure 3).

The relapse rates with a number of antidepressants, including fluoxetine, paroxetine, sertraline, citalopram, and mirtazapine, were compared with placebo relapse rates in continuation studies (Table 2).[2,19–22] The relapse rates of patients on antidepressant therapy were significantly lower than those of patients on placebo.

A closer look at the study by Montgomery et al.,[2] which revealed low relapse rates with mirtazapine, shows that the

Figure 3. Five-Year Outcome of Full-Dose Maintenance Therapy in Recurrent Depression: Cumulative Percentage of Patients[a]



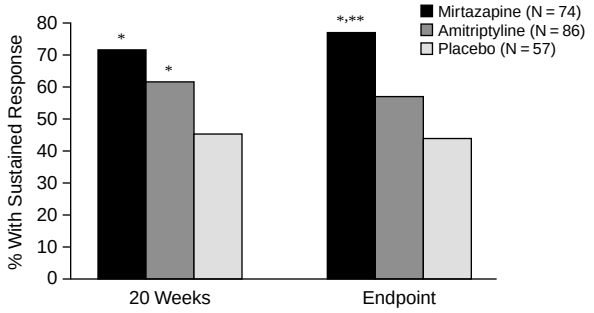
[a]Adapted from reference 18, with permission. Patients with no recurrence during a 3-year full-dose maintenance trial were randomly assigned to 2 years of imipramine or placebo.

Table 2. Relapse Rates of Antidepressants Compared With Placebo in Continuation Studies

Drug	Weeks of Treatment	Relapse (%) Anti-depressant	Relapse (%) Placebo	p Value	Reference
Fluoxetine	52	26	57	p < .01	Montgomery et al, 1988[19]
Paroxetine	52	16	43	p < .001	Montgomery and Dunbar, 1993[20]
Sertraline	44	13	46	p < .001	Doogan and Caillard, 1992[21]
Citalopram	24	11	31	p < .05	Montgomery et al, 1993[22]
Mirtazapine	20	4	23	p < .0001	Montgomery et al, 1998[2]

reduction in the probability of relapses with mirtazapine was significantly greater than with placebo in the short term (20 weeks) and significantly greater than with placebo and amitriptyline in the long term (2 years) as seen by the percentage of patients with a sustained response (Figure 4). The study was a double-blind, placebo-controlled extension study of the efficacy of mirtazapine and amitriptyline in responders to treatment in 4 double-blind, placebo-controlled, 6-week, acute treatment trials of similar protocols (total N = 580). Patients received 5 to 35 mg of mirtazapine, 40 to 280 mg of amitriptyline, or placebo. The baseline characteristics of the treatment groups were comparable with regard to age, gender, and severity of depression (17-item Hamilton Rating Scale for Depression scores) (Table 3). Mean ± SD dose was 22.8 ± 9.4 mg/day in the mirtazapine group and 137.5 ± 70.8 mg/day in the amitriptyline group. The percentage of discontinuations, other than for improvement of the depression, was less in the mirtazapine group (27.1%) than in the amitriptyline group (37.2%) and the placebo group (42.1%) (Table 4). The percentage of discontinuation because of improvement of depression was 10.5% in the mirtazapine group compared with 2.3% in the amitriptyline group and 1.8% in the placebo group.

Figure 4. Mirtazapine Versus Amitriptyline in the Long-Term Treatment of Depression: Sustained Response (HAM-D ≤ 7) for 2 Years[a]



[a]Data from reference 2. Abbreviation: HAM-D = Hamilton Rating Scale for Depression.
*p < .05 vs. placebo.
**p < .05 vs. amitriptyline.

Table 3. Mirtazapine Versus Amitriptyline in the Long-Term Treatment of Depression: Baseline Demographics[a]

Variable	Mirtazapine (N = 74)	Amitriptyline (N = 86)	Placebo (N = 57)
% Female	62.2	58.1	57.9
Age, y			
Mean ± SD	41.6 ± 11.6	42.4 ± 12.2	41.7 ± 12.0
Range	19–66	22–74	19–66
17-Item HAM-D			
Short-term, baseline	24.5	24.1	23.5
17-Item HAM-D			
Long-term, baseline	7.4	7.7	8.9

[a]Adapted from reference 2, with permission.

Table 4. Mirtazapine Versus Amitriptyline in the Long-Term Treatment of Depression: Reasons for Discontinuation (% of patients)[a]

Reason	Mirtazapine (N = 74)	Amitriptyline (N = 86)	Placebo (N = 57)
Other than improvement			
Adverse events	9.5	9.3	3.5
Lack of efficacy	2.7*	3.5	10.5
Other reasons	14.9	24.4	28.1
Total	27.1	37.2	42.1
Improvement	10.5*,**	2.3	1.8

[a]Data from reference 2.
*p < .05 vs. placebo.
**p < .05 vs. amitriptyline.

The proportion of patients complaining of 1 or more adverse events with mirtazapine (78.4%) was significantly lower than that with amitriptyline (95.3%, p < .001), and similar to that with placebo (66.7%). The most commonly reported adverse events were dry mouth and drowsiness; however, the only adverse event reported significantly more often with mirtazapine than with placebo was weight gain (Table 5).

Table 5. Mirtazapine Versus Amitriptyline in the Long-Term Treatment of Depression: Adverse Events (% of patients)[a]

Adverse Event	Mirtazapine (N = 74)	Amitriptyline (N = 86)	Placebo (N = 57)
Dry mouth	31.1**	79.1*	15.8
Weight gain	18.9*	11.6*	0
Headache	12.2	9.3	12.3
Drowsiness	10.8**	30.2*	10.5
Excessive sedation	5.4	3.5	5.3
Constipation	5.4**	25.6*	5.3
Insomnia	2.7	1.2	8.8
Tremor	1.4**	11.6*	0

[a]Reprinted from reference 2, with permission.
*p < .05 vs. placebo.
**p < .05 vs. amitriptyline.

UNRESOLVED ISSUES

Although antidepressants are available that appear to be effective in the long term and have improved tolerability profiles, similar to that of placebo in some instances, still fewer than 10% of patients with major depression receive the correct treatment in terms of adequate dosage or sufficient duration of treatment.[23] Some of the reasons that patients do not receive adequate dosages of antidepressants may be basic, such as a failure of physicians to diagnose depression or, if the diagnosis is made, refusal of treatment or failure to comply with treatment by patients as a result of either their condition or the stigma attached to depression. In addition, some clinicians also have a preference for psychosocial treatments rather than medication. Finally, low dosages of the antidepressant may be given as a result of concern over side effects, contraindications to particular antidepressants, or the possibility of overdose.[15] Unresolved issues also exist concerning the treatment of recurrent major depression, such as what the correct maintenance dose should be and how the maintenance dose should be tapered off when appropriate. Unfortunately, as maintenance therapy continues to be studied far less adequately than treatment directed at the acute episode, questions concerning whether long-term use of maintenance therapy increases the rate of recurrence after cessation of use or whether maintenance therapy loses its efficacy and/or potency over time remain unanswered. Moreover, the role of psychotherapy in the maintenance treatment of recurrent major depression and the optimum duration for the maintenance antidepressant medication still have to be defined.

RECOMMENDATIONS

Treatment with antidepressants for a duration of 4 to 6 months for a first episode of depression often achieves remission of the depressive symptoms. However, depression is a chronic and recurrent disease with a morbidity analogous to diabetes or hypertension. Maintenance treatment for depression should therefore be viewed as a chronic disease management program, not just as a drug treatment. For those patients who experience relapse, continuation treatment should be administered, whereas for those patients with recurrent depression, maintenance therapy should be instituted. Patients with ≥ 3 episodes of major depression or ≥ 2 episodes plus a family history of mood disorders, rapid recurrence, older age at onset, or severe episodes would also benefit from maintenance therapy. Maintenance treatment for recurrent major depression should consist of the same drug treatment, given at the same dose, as that administered for the initial response. The duration of maintenance therapy should be 2 episode cycles, possibly in the range of 4 to 5 years.

Drug names: amitriptyline (Elavil and others), citalopram (Celexa), fluoxetine (Prozac), mirtazapine (Remeron), paroxetine (Paxil), sertraline (Zoloft).

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