

Prevention of Relapse and Recurrence in Depression: The Role of Long-Term Pharmacotherapy and Psychotherapy

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Major depressive disorder is a chronic disorder, frequently characterized by relapses and recurrences. One of the major risk factors for additional episodes of depression is the presence of residual symptoms that persist after a depressive episode ends; these residual symptoms tend to progress to another depressive episode. Although relapse or recurrence may be prevented with long-term pharmacotherapy, this approach is recommended only for patients at high risk of relapse or recurrence. Patients not at high risk who are effectively treated to full remission have a substantially lower risk of developing another depressive episode. In addition, psychotherapy, alone or combined with medication, has been shown to be effective in preventing further episodes of depression.

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Major depressive disorder was once considered an acute episodic disorder with a clear onset and offset, with some episodes clearly linked to environmental stressors (reactive) while others appeared spontaneously with no apparent precipitant (endogenous). Data collected since the late 1980s, however, have shown that the majority of patients who have major depressive disorder will experience relapses and recurrences, with the first few episodes linked to unequivocal stressors and later episodes appearing more spontaneously.^{1,2} The model of acute reactive versus endogenous depression is, therefore, oversimplified, and the distinctions between the two have not stood the test of time. What is clear, however, is that major depressive disorder is a chronic disorder, most frequently characterized by relapses and recurrences. One of the major risk factors for repeat episodes (either relapse or recurrence) is the presence of residual symptoms that persist after an episode ends; these residual symptoms tend to progress over time to another full-blown depressive episode.³ This article reviews the course of major depressive disorder and the role of long-term antidepressant treatment and psychotherapy in the prevention of relapse and recurrence.

REMISSION, RELAPSE, RECURRENCE

As a result of the U.S. Food and Drug Administration procedures to approve antidepressants, the field has long accepted the outcome of response as a sufficient endpoint for an antidepressant trial. Response is defined as a 50% improvement in a baseline depression rating scale score. Recently, the outcome of choice has become remission, such that patients are asymptomatic, no longer meet criteria for major depressive disorder, and have no more than minimal residual symptoms. Beyond the lack of symptoms, it has become apparent that remission translates into full restoration of functioning.^{4,5}

Many readers will be aware that depressive relapse is defined as an episode of major depressive disorder that occurs within 6 months after either response or remission, while recurrence is defined as another depressive episode that occurs after 6 months have elapsed. Interestingly, however, no widely accepted definition of recovery exists (i.e., the duration of remission required to define full recovery from the depressive episode).^{6,7} Naturalistic studies have found that most patients will eventually experience either a relapse or recurrence if followed for a long enough period without sustained treatment.⁸ After 15 years, almost 90% of patients could be expected to become depressed again after experiencing an acute depressive episode.⁹

Rather than treating and managing relapse or recurrence, for which minimal data exist to guide clinicians, the best strategy may be to prevent these repeat depressive episodes from occurring in the first place. Compelling

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epidemiologic and clinical data suggest that those who are treated to full remission have a substantially lower risk of eventually developing a depressive relapse or recurrence compared with those who continue to demonstrate residual symptoms.^{3,10,11}

One widely accepted method for preventing relapse or recurrence is long-term pharmacotherapy. To prevent relapse during the continuation phase, it is necessary to extend the time that the full acute dose of antidepressants is prescribed (and hopefully taken) for 4 to 9 months after acute response/remission. Once this time of high risk passes, a slow taper of the antidepressant (for those who are not at high risk of recurrence) may be considered, with the speed of taper dependent on the dose taken. In general, the shorter the half-life of the antidepressant, the more gradual the taper necessary to prevent any discontinuation syndrome.

PREVENTION OF DEPRESSIVE RELAPSE AND RECURRENCE

For patients at high risk of recurrence, maintenance treatment is necessary. Full doses of antidepressants are required for full prophylaxis, and the duration of the maintenance phase should be at least a year, although the upper limit is less well defined. For some patients, maintenance treatment can be indefinite; for others, the risk of side effects compared with the risk of recurrence may compel them to choose discontinuation of their antidepressant and instead go into a phase of watchful waiting, with the option of restarting their antidepressant at the first sign of a depressive recurrence. As reviewed below, convincing and consistent evidence shows that patients who are maintained on treatment with their antidepressants have a substantially reduced risk of recurrence compared with those who are switched to placebo under double-blind conditions. Nevertheless, some patients treated with maintenance antidepressants will become depressed anyway since, as with all medications used for chronic disease, the prophylactic effects fall short of complete protection.¹²

Because maintenance antidepressant treatment should not be recommended lightly, it is essential that only those patients who are at high risk of depressive recurrence be considered for long-term, perhaps indefinite, treatment. The risk factors for depressive recurrence are listed in Table 1. Patients who have any one of these factors should be candidates for maintenance treatment. Those with more than 1 risk factor should receive careful long-term treatment coupled with psychoeducation about the possible necessity of indefinite treatment.

Once it has been established that maintenance treatment is necessary, then several broad options exist: either psychotherapy or maintenance antidepressant treatment alone may be recommended, or antidepressants may be combined with psychotherapy.

Table 1. Risk Factors for Depressive Recurrence^a

Residual symptoms
More than 3 prior depressive episodes
Chronic depression (episode > 2 y)
Family history of mood disorders
Comorbidities (e.g., anxiety disorder, substance abuse)
Late onset (age > 60 y)

^aBased on references 3, 7, and 13–18.

PSYCHOTHERAPY WITH OR AFTER PHARMACOTHERAPY

The modern era of relapse and recurrence prevention can be traced to the seminal reports from the University of Pittsburgh group.^{13,19} They studied a group of highly recurrent depressed outpatients, treating them with a combination of full-dose imipramine plus interpersonal psychotherapy (IPT). Responders then continued the combined treatment for another 17 weeks. Those patients who were still responders were then randomly assigned to (1) continue on treatment with imipramine plus IPT, (2) continue on treatment with imipramine plus medication management, (3) receive placebo substitution plus IPT, (4) receive IPT alone, or (5) receive placebo substitution plus medication management. The randomized phase continued for 3 years. Survival analysis demonstrated a highly significant prophylactic effect for active imipramine treatment maintained at a mean daily dose of 200 mg and a modest prophylactic effect for monthly IPT. The imipramine groups had a 3-year recurrence rate of 20%, with essentially no difference between the imipramine plus medication management group (21.5%) and the imipramine plus IPT group (24.0%). The IPT groups without active medication had a recurrence rate of 61.5%. The group with placebo and medication management experienced a 78.2% recurrence rate. The study concluded that full-dose imipramine prevented recurrence (imipramine vs. placebo, $p > .0001$) and that monthly IPT increased the duration of wellness compared with that of patients who received no treatment (IPT vs. placebo, $p < .052$).

Fava and colleagues^{20–22} used cognitive-behavioral therapy (CBT) to reduce residual symptoms in patients who had responded but not remitted to antidepressants. Relapse rates were consistently lower in the psychotherapy group over the next 6 years, although the differences reached statistical significance only in year 4: the respective relapse rates for the CBT group compared with those of the clinical management group after 2 years were 15% and 35% ($p \geq .27$); after 4 years, 35% and 70% ($p < .05$); and after 6 years, 50% and 75% ($p = .06$).

Paykel and colleagues²³ similarly found that cognitive therapy reduced relapse rates for patients who had residual symptoms. They randomized 158 patients who were treated with adequate antidepressant therapy but who continued to be symptomatic. Patients received either 16

sessions of cognitive therapy (plus 2 booster sessions) or clinical management over 20 weeks, then had 1 year of follow-up. Of note, patients were allowed to have an increase of up to 30% in their dose of antidepressants. In one sense, one could consider this research a study both of the effect of cognitive therapy on drug-resistant symptoms and of the addition of cognitive therapy to ongoing pharmacotherapy to prevent depressive relapse.

Overall, patients who received cognitive therapy had a lower cumulative relapse rate compared with those receiving only clinical management; the rates were 29% and 47%, respectively ($p = .02$). Cognitive therapy also increased full remission rates at 20 weeks, but did not reduce the level of residual symptoms compared with clinical management alone. Cognitive therapy appeared to improve social functioning by week 20, but this advantage was lost by the end of the study. It is possible, but by no means proven, that cognitive therapy reduced the rate of relapse without reducing symptoms because the therapy taught patients skills needed to compensate for their symptoms and problems.²⁴

Within the last few years, modifications to Beck's CBT have been tested for the prevention of depressive recurrence after the discontinuation of antidepressants in those patients who are at high risk of recurrence. One modification of CBT is well-being therapy (WBT).²⁵⁻²⁷ WBT differs from CBT in that WBT focuses on residual depressive symptoms (such as irritability, fatigue, hopelessness, diminished motivation, and excessive reactivity to stress), modifies problematic lifestyles, and enhances a sense of well-being by preventing premature interruption of pleasurable experiences. In effect, WBT changes the focus of therapy from correcting dysphoria-inducing automatic dysfunctional thoughts to increasing hedonic experiences by removing cognitive barriers to pleasure.^{26,27}

This modified approach was tested in a study that suggested that WBT might well prevent recurrence in depression.²⁵ In that trial, 40 patients with a history of recurrence were treated to remission with medications, then randomly assigned to either clinical management or WBT during the continuation phase; of note, WBT was given for only 10 sessions, once every other week, then discontinued. All patients were tapered off their antidepressants after about 3 months during the continuation phase. The rationale for this approach was that most patients stop taking their medication within this time in actual clinical practice. Relapse rates were strikingly different: 80% of patients treated with medication only had recurrences over the next 2 years compared with 25% of patients who also received WBT ($p < .001$).

Note that this study was designed for those patients who continue to experience residual symptoms and that all patients discontinued medication. None of the patients in the WBT or clinical management groups received antidepressant medication following recovery. As noted by

Rush and Thase,²⁸ the cause of the prophylactic effect of the WBT is unclear; either the removal of residual symptoms resulted in a better long-term outcome or the WBT itself was the cause. While preliminary studies of WBT are promising, more definitive studies are needed before this interesting CBT modification can be recommended for routine practice.

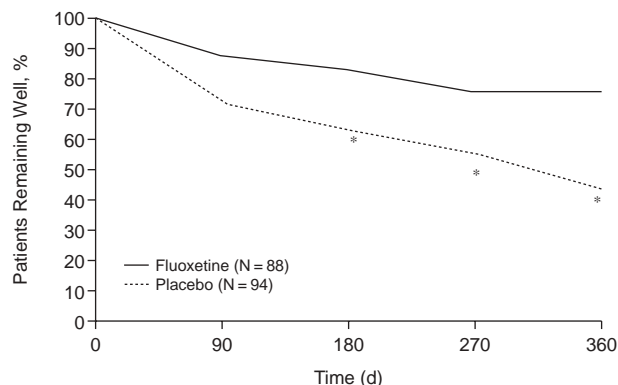
Another modification of CBT, mindfulness-based cognitive therapy (MBCT), has been developed by Teasdale and colleagues.^{29,30} In contrast to WBT, MBCT uses a group format that blends mindfulness meditation with cognitive therapy. Within an Interacting Cognitive Subsystems framework, processing of emotional information can be done by "mindlessly emoting," "conceptualizing/doing," and "mindful experiencing/being." According to this model, it is only the mode of "mindful experiencing/being" that facilitates emotional processing; MBCT teaches recovered depressed patients to switch to the most effective mode, thereby reducing depressive relapse. MBCT is given in 8 weekly, 2-hour group sessions.

Teasdale and colleagues³¹ assessed the effectiveness of MBCT in the prevention of relapse/recurrence by randomly assigning 145 recovered depressed patients to receive either MBCT or treatment as usual. During 60 weeks of follow-up, patients who were at high risk of relapse (i.e., those who had experienced 3 or more prior depressive episodes) and had received MBCT had a cumulative probability of becoming depressed again of 40%. Similar patients in the treatment-as-usual group had a probability of relapse of 66% ($p < .01$). Patients with a history of 2 or fewer depressive episodes showed no significant difference in the probability of relapse whether they were given MBCT or treatment as usual.

ANTIDEPRESSANTS

The accepted method for assessing the long-term prophylactic efficacy of antidepressant treatment is the double-blind, placebo-switch paradigm. In this paradigm, patients who respond or remit to an acute trial of an antidepressant are randomly assigned to continue taking their antidepressant or to switch to placebo at some point. Some studies immediately randomize patients, while others require that patients remain well for a predetermined length of time before randomization. To minimize possible discontinuation reactions from the sudden cessation of antidepressants, most studies include some reasonable period of tapering; otherwise, what may appear to be either a depressive relapse or a recurrence could actually be a discontinuation syndrome.

Fluoxetine was the first of the modern antidepressants to be tested for the long-term prevention of recurrence.¹⁴ In this study, patients with at least moderate depression were treated openly with fluoxetine at doses ranging from 40 to 80 mg daily for 6 weeks. Response was defined as a

Figure 1. Prevention of Recurrence: Fluoxetine^a

^aData from Montgomery et al.¹⁴ Observed cases; recurrence was defined as HAM-D score > 18. Fluoxetine dose was 40 mg/day.

* $p < .001$.

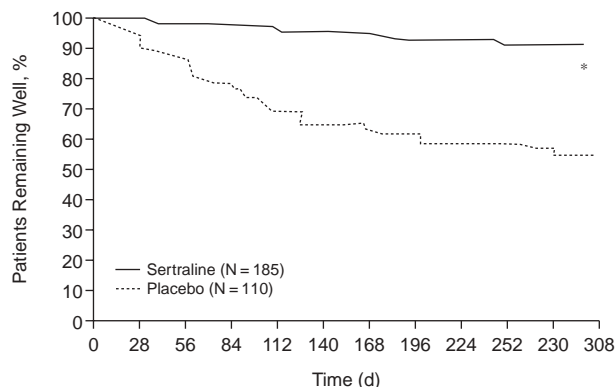
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

Hamilton Rating Scale for Depression (HAM-D) score below 12. Patients who responded were continued on fluoxetine treatment for another 18 weeks, with all patients receiving 40 mg/day by 6 months; therefore, some patients had their doses decreased. Those patients who had HAM-D scores of 8 or less after a total of 26 weeks were randomly assigned to continue taking fluoxetine, 40 mg/day, or to switch to placebo for an additional year. Using survival analysis, the probability of remaining well with fluoxetine or with placebo was 74% and 43%, respectively ($p < .001$) (Figure 1).

Sertraline has also been assessed for prophylactic efficacy in the prevention of relapse. Patients with mild-to-moderate depression were treated openly with sertraline for 8 weeks, followed immediately by randomization to a 44-week double-blind, placebo-substitution phase. By the end of the double-blind phase, 13% of the sertraline group had experienced another episode of depression, compared with 45.7% of those patients randomly assigned to placebo ($p < .001$)¹⁵ (Figure 2).

Montgomery and Dunbar³² similarly assessed paroxetine for long-term treatment. Patients at high risk of relapse or recurrence (i.e., those who experienced 2 or more episodes in the preceding 4 years) were treated openly with paroxetine, 20 to 30 mg/day, for 8 weeks. Responders were then randomly assigned to continue taking paroxetine or to switch to placebo for 12 months. Within the first 16 weeks, 19% of the placebo group relapsed, compared with only 3% of the paroxetine group ($p < .01$). During weeks 17 to 52, 30% of the placebo group relapsed, compared with 14% of the treatment group ($p < .05$).

Two open-label studies of citalopram treatment have been reported. In the first, citalopram was given for 8 weeks, then responders were randomly assigned to a

Figure 2. Prevention of Relapse and Recurrence: Sertraline^a

^aReprinted with permission from Doogan and Caillard.¹⁵ Last observation carried forward; intention-to-treat population. Relapse and recurrence were defined as CGI-S score greater than or equal to 4. Mean sertraline dose was 69 to 82 mg/day.

* $p < .001$.

Abbreviation: CGI-S = Clinical Global Impressions-Severity of Illness scale.

24-week placebo-substitution phase. The probability of relapse was 13.8% for the citalopram group and 24.3% for the placebo group ($p = .04$).³³ In the second study, patients at high risk of recurrence received 20, 40, or 60 mg of citalopram daily for 6 to 9 weeks. Responders received 16 weeks of continuation treatment, then 48 to 77 weeks of randomized, double-blind placebo substitution.³⁴ During the double-blind phase, about 20% of the citalopram group experienced a recurrence compared with 50% of the placebo group. When patients were divided into dosing groups of 20, 40, or 60 mg/day, p values for differences in the time to recurrence between the active medication and placebo groups were .004, .001, and .0157, respectively.

Finally, venlafaxine HCl was shown to prevent relapse and recurrence after an 8-week open-label phase followed by a 6-month randomized, placebo-substitution phase, with doses ranging from 75 to 225 mg/day. The probability of relapse for the venlafaxine group was 28.2%; for the placebo group, the probability was 52.4% ($p < .001$).³⁵ Those patients who responded to acute treatment and who remained in remission for the 6 months were then rerandomized to receive maintenance treatment with venlafaxine HCl or to switch to placebo. Cumulative recurrence rates after 12 months were 22% for the venlafaxine group compared with 55% for the placebo group ($p < .001$).³⁶

CONCLUSION

A consistent body of data supports continuation pharmacotherapy for the prevention of depressive relapse and recurrence. Those depressed patients at high risk of

recurrence need longer maintenance treatment, perhaps indefinitely. CBT and some modifications of CBT appear promising in the prevention of relapse and recurrence, even after the discontinuation of antidepressants.

Drug names: citalopram (Celexa), fluoxetine (Prozac and others), sertraline (Zoloft), venlafaxine (Effexor).

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