

# Long-Term Management of Chronic Depression

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Untreated major depression tends to either wax and wane, with repeated acute episodes, or persist in a chronic unremitting state, which occurs in up to 35% of depressed patients. After acute remission, those with treated chronic major depression are at high risk of depressive relapse and recurrence. Strategies to reduce the risk of relapse and recurrence include achieving full acute remission, continuing antidepressant treatment with optimal patient adherence, and adding modified cognitive-behavioral psychotherapy. This article will review data relevant to the long-term management of chronic major depression.  
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Antidepressants work acutely for depression<sup>1,2</sup> in general and for chronic depression<sup>3,4</sup> in particular. After acute remission, long-term continuation and maintenance treatment protects patients from depressive relapses and recurrences.<sup>3-10</sup> Across studies that use a placebo-substitution paradigm, 70% to 90% of depressed patients stay well within 1 year during continued active treatment, whereas under double-blind conditions, only 20% to 50% remain well after the active antidepressant is replaced with placebo.<sup>11</sup> Those switched to placebo relapse 2 to 4 times more often compared with those who continue active treatment. (The proportion that stays well widely ranges across studies because different populations of depressed patients have different risks of relapse and recurrence, making comparisons between studies [and antidepressants] difficult.) A higher risk of relapse and recurrence is associated with a history of 3 prior episodes of depression (with more than 3 episodes conferring an even greater risk), persistence of residual symptoms and lack of full remission after acute treatment, dysthymia plus major depression (also known as *double depression*), and the presence of chronic major depression, defined as an episode lasting  $\geq 2$  years.<sup>11</sup> During long-term treatment, poor adherence has also been linked to worse outcome in some<sup>12</sup> but not all studies.<sup>13</sup> Alternatively, after antidepressants are discontinued, sequential treatment with specialized psychotherapy mitigates the risk of relapse and recurrence.<sup>14-16</sup>

As described above, evidence across multiple antidepressant classes consistently shows that long-term treatment reduces the risk of relapse and recurrence of depression. With regard to chronic major depression, however, only a few studies of long-term treatment have been published. These studies in chronic major depression have shown that maintenance treatment with either desipramine or sertraline is superior to placebo substitution.<sup>3,4</sup> This article reviews the issue of long-term treatment of chronic major depression.

## CHRONIC DEPRESSION

Chronic depression has been defined variously as dysthymia alone, major depression superimposed on dysthymia (double depression), or episodes of major depression that last  $\geq 2$  years.<sup>17</sup> It has been estimated that up to 35% of patients with major depression will have a chronic course.<sup>18</sup> While chronic depression does respond to acute pharmacologic treatment,<sup>4,10</sup> it is underrecognized and undertreated.<sup>19</sup> Patients with chronic depression tend to adapt to having the condition, consider their state to be normal, and frequently fail to seek treatment. Physicians tend to miss the diagnosis because patients with chronic depression not only fail to complain about their mood but when asked about it reply that their mood is no different than usual. It is only after patients respond to treatment that they recognize how depressed they were at baseline.

Once patients with chronic depression improve with acute treatment, they need to continue treatment in order to stay well for the long term. However, few studies have examined the long-term treatment of chronic depression, and even fewer have studied patients for more than 1 year. Nevertheless, data on the naturalistic history and long-term treatment of depression in general are relevant, and it is reasonable to extrapolate from the available data to chronic depression.

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## NATURALISTIC COURSE OF DEPRESSION

As part of the National Institute of Mental Health (NIMH) Collaborative Program on the Psychobiology of Depression, 359 patients who had recovered from their index episode of depression were followed for up to 5 years.<sup>20</sup> Of those patients who continued to take high levels of somatic treatment, more than 10% became depressed again within the first 6 months. Thereafter, patients who had continued to feel well until 6 months relapsed at the same rate regardless of treatment status, a surprising finding in light of the placebo-substitution studies of maintenance treatment that show consistent superiority of continued active antidepressants. Overall, 87% of the entire cohort had a relapse or recurrence by the end of 15 years. The clinical implications of these findings from naturalistic follow-up are profound: many patients become depressed again despite adequate long-term pharmacotherapy, and the advantages of maintenance antidepressant treatment may diminish after 6 months of wellness. Of great concern is the finding that patients who develop a recurrence and then recover from the second depressive episode are at risk of developing even more episodes. Furthermore, depressive relapse and recurrence rates may be substantially higher in clinical, as compared with research, populations.

A further analysis of these data assessed the relationship between risk factors for relapse and intensity of treatment.<sup>21</sup> For those patients with fewer than 5 prior episodes, continuation of antidepressant treatment at the level given during the acute phase protected patients from relapse for 8 months. Thereafter, the rate of relapse remained constant at 1% per week regardless of the level of treatment. For those patients who had 5 or more prior episodes, continued treatment at any level provided some protection against relapse for at least 1 year. These findings make it difficult for the clinician to decide on an optimal duration of long-term treatment for chronic depression: should it be 8 months for patients with up to 5 prior episodes, or should treatment be given indefinitely?

As for those depressed patients who fail to recover after 5 years, about a third remit in the next 5 years.<sup>18</sup> Therefore, even for those patients with chronic and resistant depression, a substantial proportion will eventually remit from their depression. The problem is that these patients continue to be at high risk of relapse and recurrence after they remit.

In another observational study, Ramana and colleagues<sup>22</sup> followed 70 patients (53 inpatients and 17 outpatients) and found that 80% remitted by 15 months. Of those who remitted, survival analysis showed that 40% experienced at least one depressive relapse within 10 months of remission. Relapsers and nonrelapsers had the same levels of long-term antidepressant treatment, a result consistent with the NIMH findings,<sup>20</sup> i.e., long-term treat-

ment provided less protection than one would expect from the results of randomized placebo-substitution studies.

## RESIDUAL SYMPTOMS AS A RISK FACTOR FOR RELAPSE: THE IMPORTANCE OF FULL REMISSION

In controlled clinical trials,<sup>23</sup> less than 50% of patients achieve full remission of their depression. Most patients instead improve but continue to have residual symptoms.<sup>14,24</sup> These symptoms include generalized and somatic anxiety, irritability, guilt and lowered self-esteem, excessive reactivity to social stress, pessimism and hopelessness, impaired work and interests, fatigue, and persistent insomnia.<sup>14</sup> As part of the large NIMH collaborative depression program, naturalistic follow-up showed that, after recovery from major depression, patients with residual subsyndromal depression had an odds ratio of 3:5 for subsequent relapse compared with those who had a full acute recovery.<sup>25</sup> This risk of relapse associated with residual symptoms is higher than the well-known risk associated with 3 or more prior episodes. If residual symptoms are associated with a higher risk of relapse, then the converse should be true: full acute remission lowers the risk of relapse. It is possible that antidepressants with more than one mechanism of action, such as venlafaxine<sup>26,27</sup> and mirtazapine,<sup>28</sup> may be associated with greater rates of remission (and lower rates of relapse) compared with single-action drugs.<sup>29</sup> With regard to chronic depression, using intent-to-treat analysis, the combination of nefazodone (another antidepressant with more than one mechanism of action) plus Cognitive Behavioral Analysis System of Psychotherapy resulted in a 48% rate of remission, compared with 29% for nefazodone alone and 33% for psychotherapy alone.<sup>30</sup> The combination treatment appeared to be superior because of synergistic rather than just additive effects. A follow-up study of these patients is underway.

## LONG-TERM TREATMENT OF DEPRESSION

Seminal studies found that continued full-dose imipramine over 3 years was associated with 80% of patients with highly recurrent depression staying well, compared with only 20% of those who were switched to placebo without psychotherapy.<sup>5</sup> For those who had stayed well for 3 years on medication treatment, continued imipramine for another 2 years (for a total of 5 years of treatment) provided further protection against depressive relapse. This extended protection with imipramine was significantly ( $p = .006$ ) superior to the protection provided for those who were switched to placebo after 3 years of taking imipramine.<sup>6</sup> These seminal studies had a profound impact on the perception and treatment of depression and ushered in the era of long-term antidepressant treatment. Since the publication of these studies, data have shown that continu-

ation and maintenance treatment with fluoxetine, sertraline, paroxetine, citalopram, bupropion, nefazodone, venlafaxine, or mirtazapine is superior for prevention of relapse and recurrence to that of placebo substitution.

### **Randomized Placebo-Substitution Maintenance Studies of Chronic Depression**

With regard to long-term treatment of chronic depression, desipramine and sertraline were superior to placebo substitution for maintenance antidepressant therapy.<sup>3,31</sup> Details of these studies are reviewed below.

In the first study<sup>3</sup> of long-term treatment of chronic depression, full and partial remitters to acute treatment with desipramine then received continuation therapy for 16 weeks. At the end of continuation treatment, patients were randomly assigned to receive maintenance treatment with either the same dose of desipramine or placebo for the next 23 months. Overall, when survival curves were compared under the assumption of proportional hazards, those who received placebo were almost 4 times more likely to have a recurrence compared with those who continued to take desipramine. The raw proportions of recurrence were 52% for the placebo group and 11% for the desipramine group, with most of the recurrences occurring within 6 months of randomization. Of note, while the study included patients with dysthymia alone, double depression, and chronic major depression, the original cohort for the acute phase contained only 14 patients with chronic major depression, and the investigators omitted the number of patients with chronic major depression in the maintenance phase. The investigators rightly point out that the distribution of chronic major depression was even between the groups but that further studies were needed to explore the long-term treatment of chronic major depression. Also, of great importance, a statistically significant difference in the recurrence rates between the placebo and desipramine groups was found in the entire cohort and in full remitters, but no difference was found between the placebo and desipramine groups among partial remitters who had residual symptoms at the end of the acute phase.

The next study<sup>31</sup> of long-term treatment of chronic depression assessed maintenance treatment with sertraline. This study included patients with either chronic or double depression. No differences were found between these 2 groups at the end of the acute phase, so these were combined for analysis. Sertraline was used to first generate a cohort of responders in a 12-week acute phase; these responders then went on to a 4-month continuation phase. Patients who remained well at the end of the continuation phase (38% of the original cohort) then went on to an 18-month, complex, double-blind, placebo-substitution maintenance phase. During the maintenance phase, patients who had an exacerbation of depression that fell short of the criteria used to define recurrence could have their doses of sertraline increased at a rate of 50 mg per week until the

maximum dose of 200 mg/day was reached. The mean dose at the end of maintenance treatment, however, was not significantly different than the mean dose used at the end of acute treatment. Only 6% of patients experienced a depressive recurrence with sertraline, compared with 23% who relapsed during placebo substitution; 26% of patients experienced depressive exacerbation with sertraline and 50% with placebo substitution. Thus, placebo-substitution patients were twice as likely to have depressive exacerbation and 4 times as likely to have recurrences compared with those taking maintenance sertraline. The presence of residual symptoms did not predict recurrence, but fewer than 15% of the cohort had residual symptoms at the start of the randomization, and this may be too small a number to detect a meaningful effect on recurrence. Remarkably, about half of the patients randomly assigned to receive placebo substitution remained well, an unexpected result given the chronicity of their depression. The investigators postulated that perhaps once patients respond to an antidepressant, the chronicity of their index episode is no longer a strong predictor of depressive relapse or recurrence.

### **THE ROLE OF ADHERENCE IN LONG-TERM TREATMENT**

While the evidence cited above clearly indicates the benefits of long-term treatment of chronic depression, the effectiveness of maintenance antidepressants is limited by problems with adherence.<sup>32</sup> Adherence with treatment across all areas of medicine is a problem; patients' reasons for not taking medications range from forgetfulness to inchoate attitudes that the medication is harmful. The power of adherence in and of itself has been underappreciated in psychopharmacology but has been studied in other areas of medicine. For example, in a trial of  $\beta$ -blockers for the prevention of death after myocardial infarction, adherence to treatment was the single most important factor in determining outcome. Those patients who adhered to treatment, whether it was active drug or placebo, had dramatically better outcomes than those who did not.<sup>33,34</sup> No one has studied, to the best of my knowledge, the differential outcome associated with good and poor adherence with placebo in any psychopharmacologic trial.

Achieving optimal adherence is a challenge with depressed patients during acute treatment because of the hopelessness associated with depression mixed with the adverse events of the drugs that precede clinical improvement. In primary care, up to a third of patients stop taking their antidepressants within 1 month, and over 40% stop within 3 months.<sup>35,36</sup> Patients especially have difficulty with adherence when they are told that they need to take medications for the long term. Ramana and colleagues<sup>13</sup> found that, after being discharged from hospitalization for depression, 20% of patients were no longer taking a selective serotonin reuptake inhibitor. The reasons that they

stopped their treatment were that they feared that the antidepressants would cause some harm, that they would get addicted to the medications, that their illness could not be treated with medications, or that the burden of side effects was not worth the possibility that the medications were keeping them well. The younger the patient, the more non-adherent they were to treatment. What is difficult to understand is that patients with good and with poor adherence to long-term treatment had the same relapse and recurrence rates. In contrast, a study<sup>12</sup> of claims-based data of more than 4000 patients found that premature discontinuation of antidepressants was associated with a 77% increased risk of relapse and recurrence.

### THE ROLE OF PSYCHOTHERAPY IN PREVENTING RELAPSE

One of the more intriguing findings in the past few years is that focused psychotherapy prevents relapse in depressed patients. In a series of reports, cognitive-behavioral therapy was modified to focus first on residual symptoms and then on cognitions that prevented episodes of well-being.<sup>14-16</sup> The premise was that the absence of negative affect (depressed mood) is not the same as the presence of positive affect (well-being). Forty patients were randomly assigned to receive clinical management or cognitive-behavioral therapy after they had responded to an antidepressant and then had that antidepressant discontinued within 3 to 5 months to mirror actual clinical practice. Compared with those who received clinical management, those who had cognitive-behavioral therapy were much less likely to have a relapse or recurrence. The routine use of this innovative technique for treating chronic depression awaits further trials.

### CONCLUSIONS

Long-term treatment of chronic depression is necessary to prevent relapse and recurrence. Strategies to lower the risk of relapse and recurrence include achieving full acute remission, continuing long-term pharmacotherapy (evidence exists for desipramine, imipramine, and sertraline), and employing focused psychotherapy. Whether or not antidepressant treatment should be maintained indefinitely remains an unanswered question. Further studies are pending on the efficacy of the newer generation of antidepressants with more than one mechanism of action (nefazodone, venlafaxine, bupropion, and mirtazapine) in the long-term treatment of chronic depression.

*Drug names:* bupropion (Wellbutrin), citalopram (Celexa), desipramine (Norpramin and others), fluoxetine (Prozac), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

*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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