Antidepressants in long-term therapy: 
a review of tricyclic antidepressants and 
selective serotonin reuptake inhibitors

Hirschfeld RMA. Antidepressants in long-term therapy: a review of 
tricyclic antidepressants and selective serotonin reuptake inhibitors. 

Objective: Although depression has been shown to be a long-term 
disorder, most research studies have concentrated on its acute treatment. 
Method: A literature review of the use of tricyclic antidepressants (TCAs) 
and selective serotonin reuptake inhibitors (SSRIs) in long-term 
treatment of depression was performed and recommendations regarding 
long-term treatment were summarized.
Results: Studies conclusively document the need for continuation 
treatment after initial remission of symptoms to prevent relapse. Studies 
also suggest that continuation treatment should last a minimum of 3–6 
months following acute response. Conclusions from a few maintenance 
studies clearly show that recurrence rates are lower when patients at risk 
for recurrence continue their active treatment at its original dose than 
when they are switched to placebo.
Conclusion: Overall, studies conclude that depression is a recurrent, often 
chronic, lifetime illness requiring long-term treatment. Continuation 
therapy of 3 to 6 months after acute stabilization should be considered 
standard for all depressed patients, and maintenance therapy should be 
considered for many depressed patients. Newer agents, such as the 
SSRIs, are preferable to the TCAs for long-term treatment based on their 
superior tolerability and safety. However, because of the limited number 
of maintenance studies, further studies using a prospective, randomized 
design are needed to address this issue.

Introduction
Approaches to the diagnosis and treatment of depression have changed markedly over the years. 
At the turn of the century (Kraepelin, 1899), depression was considered to be a long-term 
problem requiring long-term treatment. As part of 
the psychopharmacological revolution of the 1960s 
and 1970s, depression was reconceptualized as a 
short-term illness requiring only short-term treat-
ment. Studies in the 1980s changed this notion. For 
example, Fig. 1 shows results from an NIMH study 
of 431 patients treated within a community (1). After 
5 years, 55% of patients had suffered at least one 
recurrence of the illness, 12% had been chronically 
deressed all the time and only 33% had recovered 
and were in continued good health. After 15 years, 
the overwhelming majority of patients had suffered 
at least one recurrence (82%), 6% had been 
deressed the entire time and only 12% had 
recovered and stayed well. This study, and others, 
showed clearly that depression is a long-term, often 
life-long disorder.

None the less, most research on the treatment of 
depression has involved only short-term therapy. In a 
comprehensive review, Janicak et al. (2) discovered 
95 acute treatment studies (1–3 months) with 
tricyclic antidepressants (TCAs) and monoamine 
oxidase inhibitors involving nearly 7000 patients. In 
contrast, the number of long-term treatment studies 
(continuation and maintenance) is very small. This 
paper will review these long-term studies.

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Results

The goal of short-term treatment (1–3 months) is to stabilize acute symptoms and achieve remission. Continuation treatment, which begins after acute remission is achieved, is intended to prevent relapse back into the depressive episode. Maintenance treatment attempts to prevent a recurrence of depression following completion of continuation therapy.

In both continuation and maintenance therapy, a key question is the minimum duration of treatment required to achieve sustained remission. Some studies have addressed this question. For example, Doogan et al. (3) conducted a study in which 467 depressed patients were treated with open-label sertraline for 8 weeks. The responders (300 patients) were then randomized to continue with sertraline or switch to placebo. After 44 weeks only 13% of sertraline patients had relapsed compared with 46% of those who had switched to placebo. A number of other studies employing short-term treatment with TCAs (4–7), selective serotonin reuptake inhibitors (SSRIs) (3, 8, 9), and other new antidepressants (10) show the same trend with a greater percentage of placebo patients relapsing over time compared with active treatment.

These studies conclusively document the need for continuation treatment, but they are not informative regarding the length of treatment. A recent fluoxetine study by Reimherr (11) addresses this important issue. Outpatients whose depressive symptoms remitted after 12 weeks treatment with open label fluoxetine 20 mg/day were included in the study. At this stage the patients were split into four equal groups. One group continued with fluoxetine, and the remaining groups were randomized to placebo at 12 weeks, at 26 weeks or at 50 weeks after the start of the study. Patients were then followed for 12 weeks to compare relapse rates. Results are shown in Table 1.

Of those randomized to placebo at 12 weeks, 49% relapsed during the following 12 weeks compared with 26% of fluoxetine patients. Of those randomized at 26 weeks, the figures were 23% vs. 9%, and after the 50 weeks the figures were 16% and 11%. The first two comparisons were statistically significant in favour of fluoxetine. The three randomization points represented total treatment times with fluoxetine of 3 months, 6 months and almost 12 months, or continuation treatment (after remission) of 0, 3 and 9 months. The conclusion from these data is that patients should be continued on treatment for about 3–6 months after initial remission of symptoms to prevent relapse, but that by 1 year the value of continued treatment diminishes. It should be noted, however, that these patients were not at high risk for recurrence and that because there were so few patients in the study by the end of week 62, the study lost power to detect treatment differences. Because patients with a history of recurrences would be more likely to exhibit new symptoms by 1 year, analysis for first-time depressives versus recurrent depressives would have been helpful.

While some studies have examined continuation therapy, very few have attempted to answer the question of whether maintenance therapy prevents recurrence. Montgomery et al. (12) studied 456 patients with DSM-III-defined major depression who had experienced recurrence of depression. The patients were treated with open-label fluoxetine for 6 weeks, and responders continued on fluoxetine for a further 18 weeks, making a total of 6 months of treatment. The 220 patients with sustained remission were randomized to continue on fluoxetine or switch to placebo. After 1 year, 74% of fluoxetine patients remained well compared to 43% of placebo patients.

<table>
<thead>
<tr>
<th>Interval</th>
<th>Fluoxetine</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>weeks</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>12–24</td>
<td>299</td>
<td>26</td>
</tr>
<tr>
<td>26–39</td>
<td>105</td>
<td>9</td>
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<td>50–52</td>
<td>28</td>
<td>11</td>
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* Fluoxetine vs. placebo.
Long-term therapy

Depression is a recurrent, often chronic, lifetime illness requiring long-term treatment. Continuation therapy of 3-6 months after acute stabilization should be considered for all depressed patients, and maintenance therapy should be considered for many depressed patients. The long-term treatment of depression must include the management of side-effects. Although the effectiveness of TCAs is equivalent to that of the newer agents, the superior tolerability and safety profile of the SSRIs makes them more desirable for long-term treatment. However, because of the limited number of maintenance studies, especially studies which directly compare two or more agents, further studies using a prospective, randomized design are needed to address this issue.

Acknowledgement
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References

Some older maintenance studies employing TCAs and MAOIs (13, 14) report similar results. In one of these studies (13), a group of patients who had been treated with imipramine and achieved remission were randomized into one of five groups, either imipramine, imipramine with psychotherapy, placebo, placebo with psychotherapy or psychotherapy alone for 3 years. After this time about 22% of imipramine patients (+ psychotherapy) had relapsed compared with 65-70% of psychotherapy (+ placebo) and about 90% of placebo patients. In a follow-up study (15), some of the imipramine patients who had not suffered a recurrence were re-randomized to a further 2 years of treatment with imipramine or placebo, and although numbers were small 67% of patients (6/9) randomized to placebo had a recurrence compared with 9% (1/11) receiving imipramine. In addition, some of the patients in the original study who had suffered recurrences were treated again, and if they responded they were put into maintenance on full or half dose imipramine and followed for 3 years (16). Of those on full dose, 30% had a recurrence within that period, compared to 70% receiving half dose.

The conclusions from this limited number of maintenance studies are clear: recurrence rates are much lower on active treatment (10-30%) compared to placebo (60-90%), and full dose (that which was sufficient for original remission) would be recommended over any reduced dose of active drug during a maintenance period. Table 2 lists risk factors for recurrence. It should be noted that most of the studies reported above include only acutely depressed patients and specifically exclude chronically depressed patients. Presumably such patients are harder to treat and, at best, respond more slowly to treatment. These patients are the focus of several ongoing maintenance studies.

Table 2. Risk factors for recurrence
- History of frequent or multiple episodes
- Double depression (major depression plus dysthymia)
- Onset after the age of 60 years
- Long duration for episodes
- Severe index episode
- Seasonal pattern
- Family history of depression
- Poor symptom control during continuation therapy
- Comorbid anxiety disorder or substance abuse

Conclusion
Depression is a recurrent, often chronic, lifetime illness requiring long-term treatment. Continuation therapy of 3-6 months after acute stabilization should be considered for all depressed patients, and maintenance therapy should be considered for many depressed patients. The long-term treatment of depression must include the management of side-effects. Although the effectiveness of TCAs is equivalent to that of the newer agents, the superior tolerability and safety profile of the SSRIs makes them more desirable for long-term treatment. However, because of the limited number of maintenance studies, especially studies which directly compare two or more agents, further studies using a prospective, randomized design are needed to address this issue.
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