Discontinuing antidepressant treatment in major depression

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Authors' objectives
To examine the benefits of long-term antidepressant treatment in major depression, and the risks of discontinuing medication at various times after clinical recovery from acute depression.

Searching
MEDLINE was searched from January 1970 to January 1997) using the search terms 'depression', 'antidepressants' and 'long-term'. The references cited in retrieved reports were also examined.

Study selection
Study designs of evaluations included in the review
The included studies were blind, placebo-controlled with randomised discontinuation or data suitable for survival analysis. Of the 27 studies in the review, 23 were double-blind with placebo control, 2 were single-blind with placebo control, 1 was double-blind and 1 was open. To be included in the review, trials had to be of at least 6 months in duration and compare 10 or more treated versus untreated patients. The follow-up ranged from 6 to 60 months (mean 16.6 months, SE=12.8).

Specific interventions included in the review
The antidepressants were: amitriptyline, clomipramine, desipramine, nortriptyline, imipramine, tricyclic antidepressants, zimeldine, phenelzine, fluoxetine, paroxetine, mianserin, maprotiline, sertraline, and dothiepin. Some of the agents were combined with lithium. The doses ranged from 20 to 250 mg/day.

Participants included in the review
The patients had nonbipolar major depression, including major depressive disorder, depression, unipolar disorder and mixed. The diagnostic criteria varied, and some investigators included an unspecified minority of patients with bipolar II disorder, dysthymia, atypical depression, or major depressive episodes associated with another syndrome. The average age of the participants was 50.0 (standard error, SE=11.4) years, and 63.8% (SE=21.3) were female. Patients were treated and were stable for an average of 5.78 (SE=11) months after recovery from a depressive episode, prior to the discontinuation of treatment.

Outcomes assessed in the review
The outcome measures were: relapse rates (percentage of patients becoming depressed per month), survival analysis, stability over time, treatment length, effect of drug discontinuation rate, and effect of past history of depression.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
Validity was not formally assessed, but the inclusion criteria stipulated that the studies had to be blind, placebo-controlled and randomised.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.
Methods of synthesis
How were the studies combined?
The crude relapse rates (percentage of patients becoming depressed per month) were evaluated in several ways. Within-study paired t-tests were used to provide an overall comparison of monthly relapse rates with and without continued antidepressant treatment. Relationships between treatment duration and subsequent relapse risk after stopping treatment were tested by linear regression or Spearman non-parametric rank correlation. In addition, analysis of variance (ANOVA) was used to compare the risks after discontinuing treatment at different times, and to test the prediction that relapse risk would be reduced by the slow discontinuation of medication after long-term treatment of depression. Survival times were computed by a Kaplan-Meier analysis (time to 50% relapse plus or minus SE). Differences in survival functions were evaluated using the Mantel-Cox or Wilcoxon chi-squared statistics. All statistical tests were two-tailed and used a p-value of less than 0.05 to indicate significance. Computations were performed using StatView software (version 4.5) for the Macintosh computer.

How were differences between studies investigated?
The authors did not perform a direct test for heterogeneity. However, they examined the characteristics of the individual studies, e.g. the different diagnostic criteria that were employed and the type of depression investigated. They concluded that the studies were heterogeneous.

Results of the review
Twenty-seven studies involving a total of 3,037 participants were included; 17 involved a tricyclic antidepressant or similar agent, 5 a monoamine oxidase inhibitor, and 5 a selective serotonin re-uptake inhibitor.

Patients whose antidepressants were discontinued showed much higher relapse rates than those whose treatments were continued: 6.24% (SE=5.34) versus 1.85% (SE=1.51), (P<0.001); a 3.37-fold difference). They also showed a shorter time to 50% relapse, 14.2 (SE=0.5) months versus 48.0 (SE=4.7) months (P<0.001), and a higher 12-month relapse rate, 44.8% versus 19.4% (P<0.001). Longer prior treatment did not yield lower post-discontinuation relapse risk. The differences between 'on' versus 'off' antidepressants fell markedly with longer follow-up. The relapse ratio (off/on antidepressants) fell continuously, in apparent logarithmic fashion, from a high of 3.69 at 2 months, to only 1.34 at the 5-year follow-up. The relapse ratio averaged 1.92 (SE=0.55) across the follow-up times; a ratio of 1.0 indicated no difference in risk with versus without the drug. Contrary to expectation, the relapse risk did not fall with longer stabilisation prior to discontinuation of an antidepressant. The relapse risk was not associated with diagnostic criteria. More previous illness was strongly associated with higher relapse after discontinuation of antidepressants. In patients with at least 3 past episodes or a chronic course, the 2-year survival rate was 71.7% (95% confidence interval, CI: 64.6, 78.9) with antidepressant versus 14.7% (95% CI: 7.10, 22.2) without; this was a highly significant 4.88-fold difference. However, among patients with only 1 or more past episodes, the corresponding 2-year survival rates differed little: 64.1% with treatment (95% CI: 58.7, 69.4) versus 52.7% without (95% CI: 42.9, 62.6), a non significant 1.22-fold difference. More previous illness had no effect on response to continued treatment; patients with infrequent prior illness showed only minor differences between the drug and placebo treatments.

Authors' conclusions
Compared with patients whose antidepressants were discontinued, those with continued treatment showed lower relapse rates, a longer time to 50% relapse, and a lower 12-month relapse risk. However, lower prior treatment did not yield a lower post-discontinuation relapse risk, and differences in relapses 'off' versus 'on' antidepressants fell markedly with longer follow-up. Contrary to prediction, gradual discontinuation did not yield lower relapse rates. The relapse rates were not associated with diagnostic criteria. More previous illness was strongly associated with higher relapse risk after discontinuation of antidepressant treatment, but had no effect on the response to continued treatment.

CRD commentary
The authors presented a clear review question. Sufficient details of the primary data were tabulated. The search was fairly narrow, and could have been extended to include other databases such as EMBASE, and an attempt to identify unpublished literature. The inclusion and exclusion criteria were not stated clearly. No formal validity assessment was
undertaken. The primary studies were combined appropriately, but the authors did not state how those participants who dropped out of therapy were dealt with in the data analysis. It was also unclear at what point randomisation took place. The authors stated that the studies involved substantial heterogeneity, e.g. different diagnostic criteria were employed and different types of depressive illnesses were included. In addition, the types of antidepressants used varied considerably. The authors pointed out the following limitations of their review: none of the studies systematically varied clinical features such as past history, the period of stabilisation after recovery from an index of depressive episode, or the rate of antidepressant discontinuation. The authors believe that these limitations constrain the conclusions that can be derived from the present analyses.

This was a reasonably thorough review and the authors’ conclusions follow logically from the results.

**Implications of the review for practice and research**

The authors state that continuing treatment for several months after recovery from an acute depressive episode - at least until apparently secure remission of acute illness is achieved - is recommended as a prudent practice and a hedge against subtle continued morbidity.

The authors also suggest that it would be informative to subject long-term antidepressant therapy to cost-benefit analyses. Future research involving planned discontinuation of antidepressant treatment should vary the duration of stabilisation before discontinuation and discontinue medication at defined rates over weeks or months, or compare short- versus long-acting agents within the same study; these should be stratified by the number of previous episodes. Specific assessments are also needed to determine the efficacy of retreatment and to compare newer agents with the tricyclic antidepressants most often represented in reported trials.

The clinical effectiveness, safety and costs of sustained versus intermittent treatment of major depressive episodes remain to be determined.

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