Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review


CRD summary
This review compared continued antidepressant treatment with discontinued treatment in patients with depressive disorder who had responded to treatment. The authors concluded that continued treatment with antidepressants would benefit many patients with recurrent depression. Although the review has some weaknesses, the authors make reasonable conclusions and acknowledge some of the review's limitations.

Authors' objectives
To establish how long antidepressant drug treatments should be continued to prevent relapse in depressive disorders.

Searching
The Cochrane Depression, Anxiety and Neurosis Group's Controlled Trials Register and the Cochrane Controlled Trials Register were searched to April 2000; the search terms were reported. The reference lists of all selected articles and other relevant references were checked. Experts in the field and drug companies were also contacted.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) of at least one month in duration were eligible for inclusion.

Specific interventions included in the review
Studies comparing the continuation and discontinuation of treatment with antidepressants were eligible for inclusion. Most of the included studies were of a tricyclic antidepressant or a selective serotonin re-uptake inhibitor. In most of the studies the patients were randomised to continuation on the same treatment. In all studies the continuation of treatment was compared with discontinuation to placebo.

Participants included in the review
Patients with a depressive disorder who had responded to antidepressant treatment for an acute episode, or who were free from depressive illness for a period on antidepressants following initial response to treatment, were eligible. The included studies were of patients with a first episode and recurrent depressive disorder treated in primary and secondary care settings.

Outcomes assessed in the review
The primary outcome of interest was the relapse rate, defined as the return of symptoms during a period of remission or partial remission. The length of follow-up ranged from 6 to 36 months, with the greatest number of patients being followed for 12 months.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed the identified articles and resolved any disagreements by discussion with a third reviewer.

Assessment of study quality
Studies were assessed on the basis of method of randomisation, treatment allocation, blinding of the patient, investigator and outcome assessor, the reporting of withdrawals and drop-outs, and the use of intention-to-treat (ITT) analysis. Two reviewers independently assessed each study. The authors were contacted for further information where necessary.
Data extraction
One reviewer extracted the data and a second reviewer checked the extraction. The definition of relapse or recurrence in the individual primary study was used. ITT data were extracted where available, otherwise the published event rates were extracted. The proportion of patients relapsed in the treatment and control groups were calculated for individual studies, as were the odds ratio (OR) with 95% confidence interval (CI) and the percentage reduction in risk with standard error (SE).

Methods of synthesis
How were the studies combined?
The studies were stratified into six groups according to the duration of treatment prior to randomisation (1 to 2 months, 4 to 6 months, more than 12 months) and duration of randomised treatment (6, 12, or 18 to 36 months). Each of the six groups of studies was then pooled in a meta-analysis using a fixed-effect model.

How were differences between studies investigated?
In addition to the stratified analysis, the chi-squared test was used to investigate statistical heterogeneity between the studies. The relapse rate was compared across the different classes of antidepressants. In addition, where data were available, the relapse rates for the first and subsequent years were compared.

Results of the review
Thirty-one RCTs (n=4,410) were included.

When all the studies were combined (31 RCTs; 35 comparisons), the relapse rate was 18% with continuing antidepressant treatment versus 41% with treatment discontinuation. Continuing antidepressant treatment reduced the risk of relapse by 70% (SE=4) (OR 0.30, 95% CI: 0.22, 0.38, P<0.00001) compared with treatment discontinuation and this was statistically significant. There was statistically significant heterogeneity (P=0.02). The risk reduction ranged from 60 to 90% in the six separate analyses based on the length of treatment before randomisation and the duration of continuing treatment (chi-squared test for heterogeneity, P ranged from 0.03 to 0.1).

The risk reduction was similar in the first 12 months after randomisation compared with 12 to 36 months after randomisation: 81% (SE=11) versus 77% (SE=21) reduction in odds) (based on 6 trials; chi-squared test for heterogeneity, P=0.1).

The ORs for the studies grouped by type of antidepressant were not reported, though in the four groups where there was more than one trial pooled, continuing antidepressant treatment had a more favourable effect on relapse than treatment discontinuation. There was statistically significant heterogeneity (P=0.001).

There was a higher rate of trial withdrawal in patients randomised to continuing treatment (18%) compared with placebo (15%); the OR was 1.30 (95% CI: 1.07, 1.59, P=0.009). In one trial there were five suicides in 746 patients on maprotiline compared with one in 374 controls, while in another trial there was one suicide in 185 patients on sertraline compared with none in 110 controls.

Authors’ conclusions
Antidepressants reduce the risk of relapse in depressive disorder. Continued treatment with antidepressants would benefit many patients with recurrent depressive disorder.

CRD commentary
The review question was clearly stated. Several relevant electronic databases were searched and the subject headings used in the search strategy were given. Unpublished data were sought and language restrictions do not appear to have been applied. Appropriate processes were used during the study selection, data extraction and quality assessment to help reduce error and any bias. The details provided of the individual studies were also appropriate. A quality assessment of the individual studies was carried out, but the results were not reported; it is therefore not possible to assess the...
reliability of the studies included in the review.

Given the statistical heterogeneity detected and the evidence of clinical heterogeneity across the studies, it might have been inappropriate to pool all the studies in a meta-analysis. The authors’ conclusions appear reasonable. They draw attention to the possibility that the findings may overestimate the effectiveness of continued therapy, and emphasise that the results are mainly applicable to patients in secondary care settings with a high risk of relapse.

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

Practice: The authors stated that many patients with depressive disorder would benefit from continued treatment with antidepressants. The treatment benefit for an individual patient will depend on their absolute risk of relapse, with greater benefits experienced by those at higher risk of relapse.

Research: The authors stated that further RCTs are required to establish the optimum length of therapy, especially for those at low risk of relapse.

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**Other publications of related interest**

These additional published commentaries may also be of interest. Simon G. Review: continuing treatment with antidepressants reduces the rate of relapse or recurrence of depressive symptoms regardless of duration of treatment before or after randomisation. Evid Based Med 2003;8:137. Relapse prevention and antidepressants [correspondence]. Lancet 2003;361:2158-9.

**Indexing Status**

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**Record Status**
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