Evidence that patients with single versus recurrent depressive episodes are differentially sensitive to treatment discontinuation: a meta-analysis of placebo-controlled randomized trials

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CRD summary
The review found antidepressants robustly reduced relapse risk during maintenance treatment of patients with major depressive disorders. There was evidence that, with increasing numbers of episodes, patients developed resistance to antidepressant medication prophylaxis. These conclusions broadly reflected the evidence, but should be considered with some caution given the potential for clinical heterogeneity and lack of explicitly reported trial quality assessment.

Authors' objectives
The authors' objective appeared to be to evaluate whether patients with multiple episodes of depression were more sensitive to discontinuation of antidepressant treatment compared with patients with single depressive episodes.

Searching
The Cochrane Library, MEDLINE and EMBASE were searched to May 2007. Search terms were reported. References were checked for additional papers. Only published papers were considered.

Study selection
Randomised double-blind placebo controlled trials on the efficacy of continuation or maintenance treatment of major depressive disorder, using either selective serotonin reuptake inhibitors or tricyclic antidepressants, in patients who had achieved remission during acute treatment, were eligible for the review. Response was defined as a clinically significant reduction in depression symptoms (e.g. at least 50% reduction in score on a depression rating scale) and remission was defined as no or minimal symptoms remaining. Continuation treatment referred to treatment during the six months following remission to prevent relapse. Depressive episodes occurring after six months of remission were considered to be recurrence. Maintenance treatment was used to describe treatment with antidepressants to prevent recurrence.

Included trials were published between 1972 and 2006; diagnoses of depression, chronic depression or major depressive disorder were reported according to established diagnostic tools (reported in the paper). The active treatment duration ranged from six to 14 weeks (where reported), and medication was discontinued either abruptly (in two thirds of trials) or gradually (in a third of trials). Trials included patients with no prior episodes of depression, patients with at least one prior episode, or a mixture of single and recurrent episode patients. Half of the trials used an selective serotonin reuptake inhibitors, the other half used a tricyclic antidepressants. Included trials were performed in both primary and secondary care settings. All trials reported on relapse or recurrence rates as an outcome.

Study selection appeared to have been carried out by two reviewers.

Assessment of study quality
A checklist (no details provided) was used by two reviewers to assess methodological quality. The most important aspects of internal validity were considered to be method of randomisation, achievement of double-blinding, reporting of withdrawals and drop-out rates, and use of suitable survival analysis.

Data extraction
The following data were extracted from the included trials: number of previous episodes; duration of active treatment; duration of stabilisation/continuation treatment; mode of discontinuation; duration of follow-up; and duration of withdrawal of medication. Where trials included other comparator treatments not relevant to this review (e.g. psychotherapy or other combination treatments), these data were not extracted.

The numbers of individuals at risk for each follow-up interval (three, six, nine and 12 months) were extracted for each
trial or, if not reported, calculated from the presented survival curves. Risk of relapse was calculated as an odds ratio (OR) and 95% confidence interval (CI) for each trial.

Duration of continuation treatment was categorised as less than one month, one to three months, three to six months and more than six months. Discontinuation of treatment was categorised as abrupt (under one week) or gradual discontinuation (tapering for at least one week or more).

Authors were contacted for missing data where possible. The extracted data were checked by two reviewers.

**Methods of synthesis**

Random-effects meta-analysis was used to generate pooled odds ratios and 95% confidence intervals of relapse risk for selective serotonin reuptake inhibitors and tricyclic antidepressants versus placebo. Heterogeneity was checked using a $\chi^2$ test and explored where significant. Meta-regression was used to regress the log odds ratio (antidepressant effect size) onto potentially explanatory variables: time at follow-up, duration of continuation treatment, mode of discontinuation, and number of previous episodes. Publication bias was assessed using a funnel plot and Begg's test.

**Results of the review**

A total of 30 studies were included (n= 4,890 patients), 15 using selective serotonin reuptake inhibitors (n=2,984 patients) and 15 using tricyclic antidepressants (n=1,906 patients). No publication bias was reported according to the funnel plot. Although no statistically significant heterogeneity was found for the main meta-analysis, heterogeneity between included trials was noted in terms of diagnostic criteria, drop-out rates, power of the trial, drugs used and the outcome criteria reported.

Overall continuing anti-depressant therapy was shown to significantly reduce the risk of relapse (OR 0.30, 95% CI 0.25 to 0.35; 30 trials) compared to placebo. When trials were grouped and analysed according to type of medication, significant benefits were found for both selective serotonin reuptake inhibitors (OR 0.24, 95% CI 0.20 to 0.29; 15 trials) and tricyclic antidepressants (OR 0.29, 95% CI 0.23 to 0.38; 15 trials). Relapse reducing effects did not significantly differ between selective serotonin reuptake inhibitors and tricyclic antidepressants based on meta-regression.

When relapse rates were compared as a function of time at follow-up, antidepressant use significantly reduced relapse rates compared with placebo at three, six, nine and 12 months. Meta-regression confirmed this result and found no significant additive relapse-reducing effect at six, nine or 12 months compared with the first three months.

Duration of continuation phase was explored using meta-regression, but there appeared to be no significant impact of pre-randomisation period on the relapse-reducing effect of antidepressants. Meta-analysis stratified on the basis of previous depressive episodes found that the pooled odds ratio for relapse in single episode patients (OR 0.12, 95% CI: 0.06 to 0.26) was considerably lower than the odds ratio for recurrent episode patients (OR 0.37, 95% CI 0.31 to 0.44); no significant heterogeneity was found.

Meta-regression found no significant differences in relapse rates between trials that reported gradual versus abrupt discontinuation of antidepressants. A significant interaction between number of previous episodes and mode of discontinuation was found, suggesting in recurrent episode patients abrupt discontinuation was associated with a poorer relapsing prevention effect than gradual discontinuation; the confidence intervals of these odds ratios were not overlapping (suggesting a significant difference). Confidence intervals largely overlapped for single episode patients (suggesting no significant differences).

**Authors’ conclusions**

Antidepressants robustly reduced the relapse risk in the maintenance phase. There was evidence that with an increasing number of episodes, patients develop resistance to the prophylactic properties of antidepressant medication.

**CRD commentary**

This review addressed a partially defined question with relevant inclusion criteria. Relevant databases were searched, only published papers were considered, but the Begg test suggested that publication bias may not have been present.
The methodological processes of the review were not always clearly reported (i.e. who performed study selection), which made it difficult to rule out reviewer error or bias (although two reviewers did carry out data extraction and quality assessments).

The included trials appeared to have been assessed for validity, but these results were not presented. The analysis appeared to have been appropriate, although the authors did raise concerns around the clinical heterogeneity of the pooled trials.

While the conclusions broadly reflect the evidence presented, they should be considered with some caution, given the potential for clinical heterogeneity and lack of explicitly reported trial quality assessment results.

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

**Practice:** The authors stated that it was not possible to recommend the optimal duration of continuation and/or maintenance treatment with antidepressants.

**Research:** The authors did not state any implications for research.

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