Meta-analysis of relapse prevention antidepressant trials in depressive disorders
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CRD summary
This review found that continuation therapy with antidepressant medications had significant beneficial effects in patients who had already responded to initial treatment with antidepressants. The authors’ conclusions reflect the evidence presented but, given the lack of reporting of the quality assessment of included trials, the reliability of these conclusions is unclear.

Authors' objectives
To evaluate the effect of continuation treatment on the risk of relapse in patients with depressive disorders.

Searching
MEDLINE (from 1950) and EMBASE (from 1974) were searched to August 2008 for relevant studies; search terms were reported. Pharmaceutical industry trials registers, a website of clinical study results, and reference lists of retrieved articles were checked to identify additional references.

Study selection
Randomised double-blind placebo-controlled trials that assessed relapse in patients with depressive disorders who had responded to previous anti-depressant medication were eligible for inclusion. Trials had to use approved pharmacological treatments for depression at labelled doses. Trials that used a cross-over design were excluded.

Most included trials enrolled patients with a diagnosis of a primary depressive disorder; other trials enrolled patients with other depressive states including bipolar II, bipolar not otherwise specified, dysthymia, and/or double depression. Patients were typically diagnosed using Diagnostic and Statistical Manual (DSM) criteria. Mixed serotonin-norepinephrine re-uptake inhibitors (SNRIs) and selective serotonin re-uptake inhibitors (SSRIs) were the most frequently used interventions. Other trials evaluated selective norepinephrine re-uptake inhibitors (NRIs), monoamine oxidase inhibitors, and other pharmacological agents including gepirone, mianserin and bupropion. The Hamilton Depression Rating Scale was the most frequently used scale for the assessment of response; scores for defining response varied on the basis of whether the 17-item or the 24-item list was used. Other trials used the Clinical Global Impression Scale or the Montgomery-Asberg Depression Rating Scale; in a few trials, clinical judgement was used alongside other criteria to determine relapse.

Two reviewers independently selected the studies for inclusion; any disagreements were resolved by consensus.

Assessment of study quality
Two reviewers independently assessed methodological quality using the guidelines from the Cochrane Collaboration in terms of several items. Any disagreements between the reviewers were resolved by consensus.

Data extraction
Two reviewers independently extracted data to calculate odd ratios (ORs) and 95% confidence intervals (CIs) for the outcomes. In the event of missing data, the reviewers contacted the trial authors. Disagreements were resolved by consensus.

Methods of synthesis
Pooled odds ratios and 95% confidence intervals were calculated using a Mantel-Haenszel fixed-effect model. $X^2$ was used to evaluate heterogeneity between trials.

Subgroup analyses were conducted on the basis of drug class, elderly versus non-elderly adults, diagnostic classification versus depression subtype, and duration of treatment post-randomisation. Comparison analyses using the Peto and DerSimonian and Laird random-effects models were performed to assess the effects of using different statistical methods.
The Spearman's rank order correlation co-efficient was used to examine the relationship between publication year and the odds ratio.

**Results of the review**

Fifty-four trials (n=9,268 patients) were included in the review. Follow-up duration of post-randomisation treatment in the trials was classified as either short term (24 weeks, range seven to 24 weeks) and long term (range 24 to 156 weeks).

All antidepressant medications were found to significantly reduce the risk of relapse during continuation treatment compared with placebo (OR 0.38, 95% CI 0.34 to 0.41). Statistically significant heterogeneity was also observed ($I^2 = 79\%$, $\chi^2 = 19.27$) across the trials, which was found to be due to the results of monoamine oxidase inhibitors. When these data were removed, heterogeneity was not statistically significant.

Similar patterns of results showing significant benefits of continued antidepressant treatment were also observed for elderly patients (OR 0.30, 95% CI 0.22 to 0.41; eight trials; n=775 patients) and non-elderly patients (OR 0.39, 95% CI 0.35 to 0.42; 46 trials; n=8,503 patients), DSM III-IV major depressive disorder (OR 0.39, 95% CI 0.35 to 0.43; 31 trials; n=7,239 patients), major depressive disorder classified using non-DSM methods (OR 0.24, 95% CI 0.17 to 0.32; 14 trials; n=731 patients), and patients in mixed depressive states (OR 0.43 95% CI 0.33 to 0.55; n=1,298 patients). The results were similar when analysed using different statistical methods, although random-effects odds ratios were slightly lower than those calculated using fixed-effects models. Earlier trials also had lower odds ratios (Spearman's r=0.331, p=0.01).

Significant benefits of continuation treatment with antidepressants were also observed at short-term, intermediate and long-term follow-up.

Statistical heterogeneity was also substantial across the results for the analyses by age ($I^2 = 52\%$, $\chi^2 = 2.08$), diagnostic criteria ($I^2 = 79\%$, $\chi^2 = 9.70$) and treatment duration ($I^2 = 62\%$, $\chi^2 = 10.43$).

**Authors’ conclusions**

The results confirmed the importance of continuation treatment with antidepressants in patients with depressive disorders who have responded to initial antidepressant therapy. The magnitude of effects was found to be similar across all classes of treatment and in adult and elderly patients.

**CRD commentary**

The review addressed a concise question. Criteria for the inclusion of studies were clearly stipulated. Appropriate databases were searched. Attempts were made to locate unpublished studies. It was not clear if any language restrictions were applied to the searches, so there may have been some risk of language biases. Steps were taken to minimise reviewer error and bias in the review process.

Although the authors reported that they conducted a quality assessment, the results were not reported, so it was difficult to comment on the reliability of the evidence presented. The authors decision to pool the results of the trials appeared to be justified; attempts were made to explore some sources of heterogeneity for some results. The authors acknowledged some limitations of the results pertaining to optimal doses and duration of continuation therapy. The authors also stated that many trials did not permit the inclusion of patients with comorbid psychiatric disorders, which may limit the generalisability of the results to patients typically presenting in clinical practice. A supplementary table of results the authors referred to was not available.

The authors’ conclusions reflect the evidence presented but, given the lack of reporting of the quality assessment of included trials, the reliability of these conclusions is unclear.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that more research was required to determine the optimal conditions for continuation treatment with antidepressant medication dose, medication type, duration of therapy and patient characteristics.

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