Efficacy of antidepressants and benzodiazepines in minor depression: systematic review and meta-analysis


CRD summary
The review found that there was no benefit of antidepressants over placebo in the treatment of adults with minor depression. No evidence compared benzodiazepines with placebo. Given the low quality of the included studies, the reliability of the authors’ conclusions is uncertain.

Authors’ objectives
To compare the efficacy and acceptability of antidepressant and benzodiazepine treatments for patients with minor depression.

Searching
MEDLINE, CINAHL, EMBASE, PsycINFO and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to May 2009 for published studies. The search terms were not reported in the paper. No language restriction was applied. Websites of nine pharmaceutical companies, four medical control agencies and ClinicalTrials.gov were searched.

Study selection
Randomised controlled trials (RCTs) or Phase III clinical trials were eligible for inclusion if they evaluated antidepressants or benzodiazepines versus placebo in the treatment of minor depression in patients over 18 years old. Studies of patients with serious concomitant medical illnesses were excluded. Studies of patients with major and minor depression were included if the results for minor depression were reported separately.

Included trials compared paroxetine, fluoxetine, amitriptyline or isocarboxazid with placebo. Drug dosages were not given in the review. No trial of benzodiazepines compared to placebo was identified. Four trials involved adults aged over 18; two trials involved older (60 and above) and very old (80 to 97 years) adults. The authors stated that the length of follow-up ranged from six to 12 weeks, but it was not clear whether this was the length of treatment as well as length of follow-up. Minor depression was measured on the Hamilton Rating Scale for Depression, the Montgomery-Asberg Depression Scale or the Clinical Global Impression rating scale.

Two reviewers independently selected the studies. It was not clear how disagreements were resolved.

Assessment of study quality
The Cochrane risk-of-bias tool was used to assess validity. Studies were graded according to the adequacy of: the randomisation process, sequence generation and allocation concealment; the likelihood of incomplete outcome data; selective reporting of significant results and other sources of bias, such as sponsorship bias.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
For continuous outcomes, the mean change from baseline or the mean scores at end-point, with associated standard deviation (SD) or standard error (SE), was extracted. If neither a standard deviation nor standard error were reported, the mean standard deviation of the included studies was used. When trials reported results from more than one rating scale, the reviewers used the Hamilton Rating Scale for Depression results or, if not available, the Montgomery-Asberg Depression Scale results. For dichotomous outcomes, the number of patients who responded and the number who left the study early were recorded. For crossover trials, only data from the first randomisation period was included. In the case of missing data, authors were contacted. If they did not reply, the number of patients responding to treatment was imputed.

Two reviewers independently performed the data extraction. Disagreements were resolved by discussion and consensus.
with a third reviewer.

**Methods of synthesis**

Studies were combined using a random-effects model to calculate pooled mean differences (MD) or standardised mean differences (SMD) for continuous outcomes, or relative risks (RR) for dichotomous outcomes, with 95% confidence intervals (CI). Failure to respond was calculated using an intention-to-treat analysis, either using a last observation carried forward technique (if this was done in the primary study) or defined as a drug failure (if they were excluded from analysis in the primary study).

Heterogeneity was assessed using visual inspection of the forest plot and $I^2$.

**Results of the review**

Six RCTs (395 participants) were included in the review. Three studies compared paroxetine with placebo. Fluoxetine, isocarboxazid and amitriptyline were each compared with placebo in three separate studies. Most studies were small; only one study included more than 100 patients. The overall quality of included studies was graded as low. Incomplete outcome data was not addressed in most studies. Three studies were financially supported by pharmaceutical companies.

mean change in Hamilton Rating Scale for Depression score (three RCTs): There was no significant difference between the anti-depressant and placebo groups (MD -0.93, 95% CI -2.27 to 0.41). There was no evidence of heterogeneity.

Failure to respond (four RCTs): There was no difference between the anti-depressant and placebo groups and no evidence of heterogeneity. Similar results were found when the other two studies which had only reported continuous data were included in this analysis.

Drop-out rate (two RCTs): There was no difference between the anti-depressant and placebo groups and no evidence of heterogeneity.

**Authors’ conclusions**

In patients with minor depression, there was unlikely to have been a clinical benefit of antidepressants over placebo. There was no evidence on whether benzodiazepines were of use in this context or not.

**CRD commentary**

The review question and inclusion criteria were clearly defined. The search appeared comprehensive; attempts were made to identify unpublished data, and no language restrictions were applied. Two authors performed the study selection and data extraction, which minimised the chance of reviewer error and bias. Three authors did not report on the potential effect of bias that arose from three of the included studies being funded by pharmaceutical companies.

Trial quality was assessed, but the authors noted that most of the included studies were of low quality and there was a high rate of attrition. The included studies tended to report dichotomous outcomes, despite using a continuous scale for measurement. This limited the number of studies which could be used in some analyses. Few patient characteristics and no drug regimens were reported, so the generalisability of the results was unclear. The analysis seemed appropriate and heterogeneity was assessed.

Given the low quality of the included studies, the reliability of the authors’ conclusions is uncertain.

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

**Practice**: The authors stated that antidepressants should not be considered for the initial treatment of individuals with minor depression.

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

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