Antidepressants for major depressive disorder and dysthymic disorder in patients with comorbid alcohol use disorders: a meta-analysis of placebo-controlled randomized trials

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CRD summary
The review found that antidepressants such as tricyclics and nefazodone appeared to have been effective for treating acute-phase unipolar depression in patients with comorbid alcohol use disorders. In view of limitations in the review, in particular the rather narrow search, possible publication bias and failure to assess study validity, these conclusions should be interpreted with some caution.

Authors’ objectives
To evaluate the effectiveness of antidepressants for acute-phase monotherapy of unipolar major depressive disorder or dysthymic disorder in patients with or without comorbid alcohol use disorders.

Searching
PubMed was searched for articles published from 1980 to March 2010. Search terms were reported. The reviewers checked the reference lists of articles retrieved and of two large meta-analyses for any additional studies.

Study selection
Eligible studies were double-blind randomised controlled trials (RCTs) of at least four weeks duration that compared acute-phase monotherapy with oral antidepressants versus placebo. Participants were adults with major depressive disorder or dysthymic disorder (diagnosed using criteria defined in the review). Studies were required to use antidepressants approved for use in North America or the European Union. The outcomes of interest were treatment and placebo response rates (using measures defined in the review), treatment discontinuation rate and heavy drinking rate. Studies limited to participants with specific types of depression or with specific comorbidities other than alcohol use disorders were excluded.

In studies of participants with comorbid alcohol use, mean participant age was 41.5 years and the mean proportion of women was 37%. Most participants had major depressive disorder and alcohol dependence, and the mean Hamilton Depression Rating Scale score at baseline was 17. Half of the studies required that participants were abstinent (for periods ranging from four to 14 days). Antidepressants included selective serotonin reuptake inhibitors (SSRIs), tricyclics and nefazodone. Most of these studies administered concurrent psychological therapies such as supportive psychotherapy. Study duration ranged from six to 24 weeks (mean 13.2). Studies that did not focus on participants with comorbid alcohol use differed significantly in several respects, including mean duration (7.1 weeks), proportion of women (61.6%) and Hamilton Depression Rating Scale score at baseline (21.6).

The authors selected the studies by consensus.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Risk ratios (RRs) were extracted or calculated for dichotomous outcomes, with 95% confidence intervals (CIs). Numbers-needed-to-treat (NNTs) were also calculated. For consistency, Hamilton Depression Rating Scale scores were preferred over other measures. If necessary, scores were imputed from graphs or from another scale, or calculated from continuous data using methods described in the review. Intention-to-treat analysis was used where possible.

The authors did not state how many reviewers performed the data extraction. Attempts were made to contact study authors for missing data.

Methods of synthesis
Studies of participants with comorbid alcohol use disorders were combined to calculate pooled risk ratios and 95%
confidence intervals, using a random-effects model. Heterogeneity was assessed with the Q statistic. Meta-regression analysis was used to explore methodological and clinical differences between participants in this group of studies (such as use of concurrent psychotherapy, severity of drinking) and also to explore differences between studies that specifically selected participants with comorbid alcohol use disorders and those that did not. Subgroup analysis was conducted by type of antidepressant (SSRI or non-SSRI).

**Results of the review**
The review included 11 studies of participants with comorbid alcohol use disorders (891 participants, range 28 to 328) plus 191 studies of participants not specifically selected for having comorbid alcohol use disorders (45,929 participants).

When studies of participants with comorbid alcohol use disorders were pooled, antidepressants were associated with a significantly higher response rate than placebo (RR 1.33, 95% CI 1.04 to 1.71; 11 RCTs; NNT nine). Subgroup analysis found no significant benefit from SSRIs compared to placebo (seven RCTs). However SSRIs were associated with a significantly higher response rate than placebo when analysis was restricted to participants without comorbid alcohol use disorder. There was no significant statistical heterogeneity.

When studies of participants with comorbid alcohol use disorders were compared (by meta-regression) with studies of participants not specifically selected for having comorbid alcohol use disorders, there was no significant difference in treatment response rates (p=0.97) or placebo response rates (p=0.342).

In other meta-regression analyses, none of the variables significantly influenced the overall findings. Other outcomes were reported in the review.

**Authors’ conclusions**
Antidepressants such as tricyclics and nefazodone appeared to have been effective for treating acute-phase unipolar depression in patients with comorbid alcohol use disorders.

**CRD commentary**
The objectives and inclusion criteria of the review were clear in most respects, but it appeared that monotherapy did not exclude the use of adjunctive psychotherapy. Only one database was searched and the review was limited to published studies, which meant that some studies may have been missed. As the authors noted, there was a potential for publication bias which was not formally assessed. It was unclear whether the search was limited by language. It did not appear that study quality was systematically assessed. It was also unclear whether appropriate steps were taken to minimise the risk of reviewer bias and error in conducting all aspects of the review process.

Appropriate statistical methods were used to combine the studies, assess heterogeneity, and explore differences between the studies. Comparisons between the studies of participants with and without alcohol use disorders were of uncertain validity, due to the indirect nature of the comparison and lack of information about the characteristics (and comparability) of the second group of studies. As the authors noted, there were relatively few studies focusing on patients with alcohol use disorders, their findings may not apply to depressed patients typically ineligible for clinical trials, and there were no studies of newer antidepressants. Many studies were very small.

In view of limitations in the review, in particular the narrow search and failure to assess study validity, the authors’ conclusions should be interpreted with some caution.

**Implications of the review for practice and research**
**Practice:** The authors stated that antidepressants such as tricyclics and nefazodone should be first-line therapy for treating unipolar depression in patients with concurrent alcohol use disorders. The severity of baseline drinking, and the presence or absence of recent sobriety did not appear to influence the potential efficacy of antidepressant treatment.

**Research:** The authors stated that power calculations for designing studies of antidepressants for unipolar depression in patients with alcohol use disorders should be in line with those for the general major depression/dysthymia population and noted that more data on recent antidepressants, including SSRIs, were required for this population. They suggested checking the effect of including unpublished studies in the current review.
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