Treatment of depression in patients with alcohol or other drug dependence: a meta-analysis
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CRD summary
This review assessed the treatment of depression in patients with alcohol or other drug dependence. The authors concluded that antidepressant medication has a modest beneficial effect for patients with combined depressive and substance use disorders. The conclusions are based on a well-conducted review with good-quality studies, but it should be noted that not all of the studies showed a beneficial effect.

Authors’ objectives
To assess the efficacy of antidepressant medications for the treatment of combined depression and substance use disorders.

Searching
PubMed, MEDLINE and the Cochrane library were searched from 1970 to December 2003 for publications in any language; the keywords were reported. In addition, the reference lists of key publications and reviews were screened and experts in the field were contacted.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs; parallel groups only) were eligible for inclusion.

Specific interventions included in the review
Studies that compared antidepressants with placebo were eligible for inclusion. The included studies used viloxazine, sertraline, desipramine, imipramine, fluoxetine and nefazodone.

Participants included in the review
Studies of patients who met diagnostic criteria for a current drug or alcohol-use disorder and a current unipolar depressive disorder, according to American Psychiatric Association criteria (DSM-III, DSM-III-R or DSM-IV) with diagnoses made by clinical or structured diagnostic interview, were eligible for inclusion. More than half of the studies had recruited alcohol-dependent patients; other studies were in methadone-maintained opiate-dependent and cocaine-dependent patients.

Outcomes assessed in the review
Trials had to report depressive symptoms to be eligible. The primary outcome in the review was depression using the Hamilton Depression Scale (HDS). This was reported in all of the included studies. The review also assessed self-reported substance abuse (sustained abstinence or substance remission).

How were decisions on the relevance of primary studies made?
Two reviewers independently screened potentially relevant publications. Studies were included when consensus was reached.

Assessment of study quality
The reviewers used two published scales to assess the validity of the studies: a 15-item quality scale addressing methodology and reporting of the trials with regard to randomisation, blinding, sample selection, therapeutic regimen, outcome measures, statistical analysis; and one guideline rating the adequacy of the allocation concealment, the method of generating the sequence of allocation and blinding. Two reviewers independently rated the quality of the studies.
Data extraction
One reviewer extracted the data and a second reviewer checked them, with any discrepancies being resolved by consensus. With regard to depression, the standardised difference between mean HDS scores was extracted or computed from the F-test in covariance analyses, or from means and standard deviations (SDs) or the significance level. Intention-to-treat data or the most complete sample were used for analysis. With regard to substance use, the standardised difference between means was calculated from raw means and SDs, or estimated from graphs. Where several measures were available, average effect sizes were used. Categorical measures of depression and substance abuse were also extracted.

Methods of synthesis
How were the studies combined?
Pooled effect sizes weighted by the inverse of the variance were calculated, along with 95% confidence intervals (CIs), applying a random-effects model. For the primary outcome, the results from a fixed-effect model were also reported. Publication bias was investigated by inspecting the funnel plot and specific sensitivity analyses (details of these analyses were reported).

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Q and I² statistics. Heterogeneity was explored in an extensive moderator analysis and subgroup analyses were undertaken according to significant factors.

Results of the review
Fourteen trials (n=848) were included in the review.

The included trials were of moderately high quality: all studies were rated adequate for allocation concealment, method of randomisation and blinding.

The pooled effect size for improvement in depression was 0.38 (95% CI: 0.18, 0.58), showing a small to medium effect of the antidepressant treatment compared with placebo (14 studies). However, the results of the individual studies were statistically heterogeneous (P<0.02), with 6 studies showing no benefit of the treatment (effects ranged from -0.21 to 1.07).

The pooled effect size for improvement in substance use was 0.25 (95% CI: 0.08, 0.42), based on 13 studies. The results in the individual studies ranged from -0.27 to 0.81 and significant statistical heterogeneity was found (P<0.15).

Studies with larger effect sizes for depression showed more improvement with regard to the quantity of substance use, but sustained abstinence rates were low. Studies with low placebo response showed larger effects, and diagnostic methods and concurrent psychosocial interventions seemed to influence the results.

There was little indication of publication bias.

Authors' conclusions
Antidepressant medication exerted a modest beneficial effect for patients with combined depressive and substance use disorders. The authors also stressed that concurrent therapy targeting the addiction was also indicated.

CRD commentary
This was a review with a clear question and strict inclusion criteria. The search showed efforts to identify relevant published and unpublished data and the potential for publication bias was investigated. Measures were taken to reduce errors and bias in the selection and quality rating of the studies. The studied outcomes were not objective measures, but the fact that only double-blinded RCTs were included in the review will have reduced bias in favour of the treatment.

The review provided a pooled effect size across all of the included studies, which proved to be heterogeneous with regard to depression. Factors influencing the treatment effects were also investigated and significant moderators were
detected. The sample sizes of the identified studies were small, but they seemed to be of good or sufficient quality. The authors' conclusions that antidepressant medication exerted a modest beneficial effect are likely to be reliable, but it should be noted that not all of the studies showed a beneficial effect.

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

Practice: The authors stated that specific interventions targeting addiction are necessary, but these should not detract from the importance of treating the depression in patients with concurrent depression and alcohol or other drug dependency. Efforts to differentiate depression and substance-related depressive symptoms should be made.

Research: More research is needed to analyse variations in the strengths of the effect of treating depression when differentiating depression and substance-related depressive symptoms.

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