Efficacy of antidepressants in substance use disorders with and without comorbid depression: a systematic review and meta-analysis

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CRD summary
This review assessed the effect of antidepressants on substance use in patients with alcohol, cocaine, nicotine or opioid dependence, with or without co-morbid depression, and on depressive symptoms in those with co-morbid depression. The authors concluded that the prescription of antidepressants appears justified in patients with nicotine dependence with or without depression. Methodological weaknesses may affect the reliability of the conclusions.

Authors' objectives
To evaluate the effectiveness of antidepressant drugs in people with drug abuse disorders, with and without a definite diagnosis of co-morbid depression.

Searching
PubMed (from 1966 to May 2004) and the Cochrane Library (Issue 2, 2004) were searched for studies in English, French and Spanish; the search terms were reported. The reference lists of retrieved articles were also screened.

Study selection
Study designs of evaluations included in the review
Double-blind, randomised controlled trials (RCTs) were eligible for inclusion. All of the included studies were placebo-controlled.

Specific interventions included in the review
Studies using any antidepressant drug as the study drug were eligible for inclusion. Selective serotonin re-uptake inhibitors (SSRIs) were the most frequently tested drugs for alcohol dependence, tricyclic antidepressants for cocaine dependence, and sustained-release bupropion and nortriptyline for nicotine dependence.

Participants included in the review
Eligible participants were people dependent on alcohol, nicotine, cocaine or opioids. All of the included studies of opioid-dependent patients were carried out under methadone maintenance treatment.

Outcomes assessed in the review
The included studies were required to report measures of the use of the drug of abuse (based on self-report or analytical determination) and of depression severity (based on scores on depression rating scales). Studies in which it was not possible to separately determine outcomes for patients with and without co-morbid depression were excluded.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The validity of the primary studies was assessed using the method of Jadad et al., which assigns a quality score ranging from 1 to 5 based on the use of randomisation, blinding and handling of withdrawals. Only studies with scores of 3 or more were included in the review. Two reviewers independently assessed the studies for validity; any disagreements were resolved by consensus.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

The numbers of patients in each group showing a reduction in consumption of the drug of abuse and an improvement in depressive symptoms were used to calculate the odds ratio (OR) and its 95% confidence interval (CI) for each outcome.

**Methods of synthesis**

**How were the studies combined?**

The studies were combined by meta-analysis using a random-effects model. The authors did not state that they assessed publication bias.

**How were differences between studies investigated?**

Differences between the studies in terms of criteria for depression and the measurement of depression were discussed in the text. In the meta-analysis, heterogeneity was investigated using a chi-squared test and by calculating the I-squared statistic.

**Results of the review**

**Alcohol dependence:** 8 RCTs (n=487) involving patients without co-morbid depression and 9 RCTs (n=359) involving patients with co-morbid depression were included. The study duration ranged from 1 to 24 weeks.

**Cocaine dependence:** 14 RCTs (n=876) involving patients without co-morbid depression and 5 RCTs (n=226) involving patients with co-morbid depression were included. The study duration ranged from 2 to 13 weeks.

**Nicotine dependence:** 18 RCTs (n=5,633) were included. In 11 of the studies, the sample included some patients with a history of major depression. The study duration ranged from 7 to 52 weeks.

**Opioid dependence:** 6 RCTs (n=396), all involving patients with co-morbid depression, were included. The study duration ranged from 4 to 12 weeks.

Five studies on alcohol dependence, eight on cocaine dependence and one on nicotine dependence were excluded during the review process because their quality score was two or less; these were not included in the numbers of studies given above (see Numbers of Studies Included).

**Alcohol dependence:** the use of antidepressants (SSRI or other) did not significantly affect any outcome except for a positive effect of non-SSRIs on depressive symptoms in patients with co-morbid depression (3 studies; OR 4.15, 95% CI: 1.35, 12.75).

**Cocaine dependence:** the use of antidepressants (SSRI or other) did not significantly affect any outcome except for a positive effect of non-SSRIs on cocaine consumption in patients without co-morbid depression (7 studies; OR 1.85, 95% CI: 1.06, 3.22).

**Nicotine dependence:** the use of bupropion (8 studies; OR 2.07, 95% CI: 1.42, 3.01) and nortriptyline (4 studies; OR 2.69, 95% CI: 1.47, 4.91) had a significant positive effect on abstinence from nicotine. The overall effect of antidepressant treatment was also positive (17 studies; OR 1.78, 95% CI: 1.36, 2.33).

**Opioid dependence:** the use of non-SSRIs in patients with co-morbid depression had a significant positive effect on reduction of opioid consumption (2 studies; OR 3.65, 95% CI: 1.10, 12.16), but the use of antidepressants did not reduce depressive symptoms.

**Authors' conclusions**

The use of antidepressants seemed to be clearly beneficial for patients with nicotine dependence with or without previous co-morbid depression. In alcohol dependence without co-morbid depression, the use of antidepressants did
not seem to be justified. SSRIs did not seem to offer significant advantages over tricyclic antidepressants.

**CRD commentary**

The inclusion criteria for the review were clear. The authors searched a relatively narrow range of sources and imposed some language restrictions, so it is possible that some relevant studies could have been missed. They did not attempt to locate unpublished studies and did not assess the risk of publication bias. The authors used a standard scale to assess validity, although this measure has some limitations. In the absence of a sensitivity analysis, it was unclear whether the exclusion of studies with a low quality score affected the conclusions of the review. It was also not clear whether measures were taken to reduce the risk of bias and errors in the study selection and data extraction processes (e.g. involvement of two reviewers working independently), although the validity assessment was performed by two independent reviewers.

Relevant details of the included studies were tabulated. The authors used standard methods of meta-analysis; heterogeneity between studies was assessed, and possible sources of heterogeneity were discussed though not investigated further. The authors' conclusion about the relative effectiveness of SSRIs and other antidepressants was based on indirect comparisons since all the studies in the review were placebo-controlled. The other conclusions reflect the evidence presented although, as the authors pointed out, most were based on relatively small numbers of studies. This, and the methodological limitations highlighted, should be kept in mind when assessing the reliability of the conclusions.

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

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

Research: The authors stated that the use of antidepressants in alcohol, cocaine or opioid dependence should be studied in well-defined patient groups with adequate doses and duration of treatment.

**Funding**

Fondo de Investigacion Sanitaria, Madrid, Spain, grant numbers G03/005 and C03/06.

**Bibliographic details**


**PubMedID**

15769553

**DOI**

10.1016/j.drugalcdep.2004.09.004

**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Antidepressive Agents /therapeutic use; Comorbidity; Depressive Disorder /drug therapy /epidemiology /psychology; Diagnosis, Dual (Psychiatry); Double-Blind Method; Humans; Randomized Controlled Trials as Topic; Substance-Related Disorders /drug therapy /epidemiology /psychology

**AccessionNumber**

12005009762

**Date bibliographic record published**

Database of Abstracts of Reviews of Effects (DARE)
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.