Pharmacological treatment of cocaine dependence: a systematic review
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Authors' objectives
To assess the efficacy of pharmacotherapy for treating cocaine dependence.

Searching
The Cochrane Library (Issue 4, 2001), EMBASE (from 1980 to October 2000), MEDLINE (from 1966 to October 2000), PsycLIT (from 1974 to July 2000), Biological Abstracts, and LILACS (from 1982 to 2000) were searched and the reference lists of retrieved articles were checked. Conference abstracts and book chapters were also scanned. Trial authors and drug manufacturers were contacted.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Trials of drugs used for the treatment of cocaine dependence were eligible for inclusion in the review. The drug treatments in the included trials were grouped into the following categories: antidepressants, carbamazepine, dopamine agonists, and miscellaneous. The antidepressants included desipramine, fluoxetine, ritanserin, gepirona, bupropion and imipramine. The dopamine agonists included amantadine and bromocriptine. The miscellaneous treatments included naltrexone, mazindol, lithium, disulfiram, phenytoin, nimodipine, lithium carbonate, NeuRecover-SA and risperidone. The drugs were compared with each other or to placebo.

Participants included in the review
Studies of patients with cocaine dependence, however diagnosed, were eligible for inclusion in the review. Patients with an additional diagnosis, such as opiate dependence, were also eligible for inclusion. Most of the included studies were carried out in out-patients. The mean age, where reported, varied from 27.7 to 40.5 years. Some of the included participants had various co-morbidities, such as alcohol, marijuana, tobacco or heroin dependence, major depression, antisocial personality disorder, anxiety disorder, attention deficit disorder, dysthymia.

Outcomes assessed in the review
The following outcomes were reported to be of interest: retention in treatment, the number of people reporting adverse events, positive urine samples (for cocaine metabolites), craving, severity of dependence, amount of cocaine consumed and quality of life measures.

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

Assessment of study quality
The validity assessment was based on the adequacy of allocation concealment: adequate allocation concealment was taken to indicate a low risk of bias and inadequate allocation concealment a high risk of bias. Trials which described adequate allocation concealment were rated as 'A'; trials which did not describe the concealment of allocation were rated as 'B'. Blinding was also discussed in the 'Results' section. The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

Data extraction
The reviewers extracted the data independently. The trial authors were contacted for missing outcome data.
continuous data, the mean and standard deviations had to be reported and the standard deviation, when multiplied by two, had to be less than the mean, otherwise the data were not included in the meta-analysis. Where possible, an intention-to-treat analysis was performed.

**Methods of synthesis**

**How were the studies combined?**
A random-effects model (DerSimonian and Laird) was used to calculate the pooled relative risk (RR) and 95% confidence interval (CI) for each dichotomous outcome. Continuous outcomes were not pooled due to limited data.

**How were differences between studies investigated?**
Heterogeneity was assessed visually from graphs and using the chi-squared test. A P-value of less than 0.10 was interpreted as evidence of statistical heterogeneity.

**Results of the review**

Forty-four RCTs (n=2,723) were included in the review: 20 (n=1,383) on antidepressants, 5 (n=451) on carbamazepine, 12 (n=520) on dopamine agonists and 7 (n=369) on miscellaneous drugs.

Nine trials received the validity rating 'A' on the basis of adequate allocation concealment; allocation concealment was not described in the remaining trials and these were rated 'B'. Ninety per cent of the included trials were double-blind.

The main efficacy outcome reported was the presence of cocaine metabolites in the urine. The pooled results for each drug showed no significant differences between the active drug and placebo. Significant heterogeneity was present within 14 trials of desipramine (chi-squared 12.7, d.f.=6, P=0.048). Heterogeneity was still present when data for patients with opioid dependence were analysed separately. Data for the other efficacy outcomes were skewed or missing and could not be entered into the meta-analysis.

Ten trials did not report the drop-out rates. The drop-out rates in the remaining studies ranged from 0 to 84%. No statistically-significant differences were found between the active drugs and placebo, except in one small trial of fluoxetine, where significantly more people on fluoxetine completed the study (RR 0.53, 95% CI: 0.32, 0.88, n=32).

No statistically-significant differences were found between the drug and placebo groups in terms of the risk of side-effects.

Direct comparisons of drugs found no statistically-significant differences between amantadine and bromocriptine, or amantadine and desipramine.

Similar results were obtained when trials where patients had a primary diagnosis of cocaine dependence were compared to trials of patients with cocaine and opioid dependence or patients on methadone maintenance treatment.

**Authors’ conclusions**
The authors concluded that there is no current evidence to support the clinical use of carbamazepine, antidepressants, dopamine agonists, disulfiram, mazindol, phenytoin, nimodipine, lithium and NeuRecover-SA in the treatment of cocaine dependence. Larger RCTs should be conducted for the most promising medications. The high drop-out rate in the RCTs suggested that psychotherapeutic supportive measures may be useful in keeping patients in treatment programmes.

**CRD commentary**

This systematic review used a focused research question to generate appropriate study inclusion criteria. The literature search was comprehensive. It was not stated whether studies published in all languages were eligible for inclusion; if not, this may have led to some relevant studies being missed. Few details of the review process were given, but it was stated that the data were extracted independently, which reduces the potential for human error. The validity assessment focused on the adequacy of allocation concealment, which, since strongly related to the potential for bias in the results,
was appropriate for the RCTs included in the review. Blinding and drop-out rates were also discussed, but other aspects of validity could also have been assessed to provide a more detailed assessment of the included studies. Essential details of the included studies were tabulated.

The data were pooled appropriately with an assessment of statistical heterogeneity; skewed continuous data were not pooled. Publication bias does not appear to have been assessed. The authors’ conclusions were based upon results that are likely to have been reliable. Some of the results have also been published as Cochrane Reviews (see Other Publications of Related Interest nos.1-3).

Implications of the review for practice and research
Practice: The authors state that clinicians may consider prescribing antidepressants for which the highest number of patients and studies are available. They also state that, in the absence of motivation for behaviour change, pharmacological agents (with the possible exception of cocaine-specific blocking or maintenance agents) are unlikely to promote behaviour change. The authors further suggest that clinicians may consider adding psychosocial and psychotherapeutic supportive measures to medication.

Reviewer’s comment: The results of the review did not present evidence that antidepressants are effective.

Research: The authors state that it may be necessary to conduct a new set of studies testing hypotheses concerning possible interactions between treatment and patient characteristics. They state that there is a need for a systematic review of psychosocial interventions, but that larger RCTs should be reserved for medications showing the most promising and relevant evidence.

Bibliographic details

PubMedID
12144591

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Antidepressive Agents /therapeutic use; Carbamazepine /therapeutic use; Cocaine-Related Disorders /drug therapy; Data Collection; Dopamine Agonists /therapeutic use; Humans; Patient Dropouts; Randomized Controlled Trials as Topic /standards; Treatment Outcome

AccessionNumber
12002006587

Date bibliographic record published
29/02/2004

Date abstract record published
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.