Efficacy of opiate maintenance therapy and adjunctive interventions for opioid dependence with comorbid cocaine use disorders: a systematic review and meta-analysis of controlled clinical trials

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CRD summary
This review concluded that dual opioid and cocaine dependence could be effectively treated with opiate maintenance therapy combined with other interventions. Higher opiate therapy doses were better than lower doses and methadone was better than buprenorphine. There was potential for bias in the review and small samples in the included trials, which limit the reliability of the authors’ conclusions.

Authors' objectives
To determine the efficacy of opiate maintenance therapy and additional interventions for dual heroin and cocaine dependence.

Searching
PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and PsycINFO were searched to September 2007, for articles published in any language. The search terms were reported. The authors also handsearched the reference lists of retrieved articles.

Study selection
Parallel-group randomised controlled trials (RCTs) of opiate maintenance therapy compared with placebo or an alternative opiate maintenance therapy, or plus other interventions compared with an inactive control group, were eligible for inclusion if they were of patients who were opiate dependent and cocaine users. Abstracts without a full report were excluded, as were laboratory studies.

The included trials compared low-dose versus high-dose opiate maintenance therapy, buprenorphine versus methadone, and various adjuvant interventions versus control. All of the trials were conducted in the USA. The doses and treatment regimens varied across trials. All of the participants were heroin dependent and most had comorbid cocaine dependence. Their mean age ranged from 32 to 43 years, and half of them were Caucasian. The primary outcomes were the proportion of patients achieving sustained heroin abstinence and the proportion of patients achieving sustained cocaine abstinence. Secondary outcomes included heroin and cocaine use (defined as the number of drug-free urine analyses during the intervention) and the retention of patients in the trial.

The authors did not state how many reviewers selected the trials.

Assessment of study quality
Quality assessment was undertaken using modified Jadad criteria to assess the description and appropriateness of the randomisation and blinding, and the description of withdrawals or drop-outs. The authors did not state how many reviewers assessed quality.

Data extraction
Data were extracted on heroin and cocaine abstinence and used to calculate relative risks and 95% confidence intervals. Trial authors were contacted for missing data. The drug-free urine sample data were extracted and used to calculate standardised mean differences. The authors did not state how many reviewers extracted the data.

Methods of synthesis
A random-effects meta-analysis was undertaken to calculate the pooled relative risks and standardised mean differences. Statistical heterogeneity was assessed using the $I^2$ and $X^2$ tests. Publication bias was assessed using the Egger test. Subgroups were analysed for cocaine dependence versus abuse and opiate maintenance therapy versus none before the trial. Sensitivity analysis was conducted by removing low-quality trials.
Results of the review
A total of 37 RCTs were included, with 3,029 patients.

**Opiate maintenance therapy:** Compared with low-dose therapy, high-dose therapy achieved a statistically significant greater sustained heroin abstinence (RR 2.24, 95% CI 1.54 to 3.24; I²=0%; five RCTs), but there was no statistically significant difference in cocaine abstinence. Compared with buprenorphine, methadone achieved a borderline statistically significant greater sustained heroine abstinence (RR 1.39, 95% CI 1.00 to 1.93; I²=37%; five RCTs) and a statistically significant greater sustained cocaine abstinence (RR 1.63, 95% CI 1.20 to 2.22; I²=0%; five RCTs).

**Therapy plus other interventions:** Compared with control, indirect dopamine agonists achieved a statistically significant greater sustained cocaine abstinence (RR 1.44, 95% CI 1.05 to 1.98; I²=6%; five RCTs), as did indirect noradrenaline agonists (RR 2.73, 95% CI 1.20 to 6.21; I²=0%; two RCTs), contingency management for cocaine alone (RR 3.11, 95% CI 1.80 to 5.35; I²=37%; six RCTs), and contingency management plus cognitive behavioural therapy (RR 2.96, 95% CI 1.25 to 7.03; I²=44%; two RCTs). Compared with control, there was no statistically significant difference in cocaine abstinence with direct dopamine agonists, gamma-aminobutyric acid (GABA) agonists, contingency management for cocaine and heroin, nor cognitive behavioural therapy alone.

**Other analyses:** Cocaine dependence versus abuse had no effect on the results, but opiate maintenance therapy before the start of the trial had a non-significant lower effect for two additional therapies. Sensitivity analysis indicated that trial quality did not affect the results, nor did any one trial. There was no evidence of publication bias.

Authors’ conclusions
Dual opioid and cocaine dependence could be effectively treated with opiate maintenance therapy combined with other interventions. Higher doses of opiate therapy were better than lower doses and methadone was better than buprenorphine.

CRD commentary
The inclusion criteria were clearly defined and three relevant databases were searched for articles in any language. Publication bias was assessed and was not detected. The authors did not state how many reviewers selected the trials, assessed their quality, and extracted the data, which may have introduced error and bias into the review. The quality assessment was based on a standard checklist; the results were available online, but were not free and could not be verified. A large number of trials were included, but few of them compared the same interventions and many had small samples. The trial data were pooled using a random-effects meta-analysis, and statistical heterogeneity was explored, which appears to have been appropriate.

The potential for bias in the review and the small samples in many of the trials, limit the reliability of the authors’ conclusions.

Implications of the review for practice and research
**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that future research should be carried out in countries other than the USA, and additional interventions should be assessed for buprenorphine-maintained patients. Research should investigate the combination of indirect dopamine agonists with contingency management to reinforce cocaine abstinence.

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Not stated.

Bibliographic details
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.