Retention rate and illicit opioid use during methadone maintenance interventions: a meta-analysis
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Authors' objectives
To examine the efficacy of methadone maintenance strategies in opioid addiction, in terms of the retention rate and reduction in illicit opioid use.

Searching
PubMed (1966 to December 1999) was searched using the MeSH terms 'Methadone' and 'Randomised controlled trials'; the Cochrane Library (Issue 4, 1999) was searched using the word 'methadone'. No language restrictions were used. The references lists of the retrieved articles were checked, while journals of drug abuse listed in the psychiatry and substance abuse category of the 1997 Journal Citation Reports were handsearched by scanning the table of contents. Conference abstracts were excluded.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs) were eligible for inclusion. Crossover trials were excluded. The duration of the included studies ranged from 13 to 40 weeks.

Specific interventions included in the review
Studies of methadone treatment (where the dose was clearly stated), maintained for 12 weeks or more, were eligible for inclusion. Trials in which opioid detoxification was the main objective were excluded. Some included studies used methadone administered in a fixed dose (20 to 100 mg/day), while others used an adjusted dose (mean dose at final end point: 54 to 97 mg/day). The comparators used by the included studies were buprenorphine (2 to 12 mg/day), levomethadone (LAAM; given 3 times per week at doses of 65 or 80 mg/day) and placebo. Most of the studies also had more than one methadone treatment group.

Participants included in the review
Details of the participants eligible for inclusion were not explicitly stated. Most of the included participants were male, 43% were Caucasian and the mean age was 34.4 years.

Outcomes assessed in the review
Studies reporting on the programme retention rate and/or illicit opioid use (based on urine sample tests) were eligible for inclusion.

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 studies were assessed using the checklist developed by Jadad et al., which evaluates the randomisation, blinding process and description of withdrawals. Each study was given a quality score on a scale of 1 (low quality) to 5 (high quality). Two reviewers, working together, assessed the studies.

Data extraction
Two independent reviewers extracted the data. The methadone dose was categorised into two groups: less than 50 mg/day (low dose), and greater than or equal to 50 mg/day (high dose). For studies that used a flexible dose titration, the dose included in the analysis was the mean dose administered at the time of the end point evaluation. The
buprenorphine dose was also categorised into two groups: less than 8 mg/day (low dose), and greater than or equal to 8 mg/day (high dose).

Methods of synthesis
How were the studies combined?
Summary odds ratios (ORs) were calculated using logistic regression within a multilevel model framework. The model parameters were estimated using restricted maximum likelihood for final estimates and 95% confidence intervals (CIs). High-dose methadone was used as the reference category. The programme retention rates were analysed in terms of 'failures in retention'.

How were differences between studies investigated?
The homogeneity of effects was explored, including additional random effects for drug groups. When significant, these were retained in the model to account for heterogeneity among the studies.

Results of the review
Thirteen trials with 1,944 patients were included. Of these, 1,282 patients received methadone.

Two studies had a quality score of five while the remainder had a quality score of four.

Methadone versus placebo.
High doses of methadone were more effective than placebo in reducing illicit opioid use (OR 2.44, 95% CI: 1.35, 4.43, P=0.0033) and programme retention failure (OR 8.76, 95% CI: 3.82, 20.07, P<0.0001). Low doses of methadone were better than placebo in terms of retention rates, but not for illicit opioid use (the actual results were not presented). Only one included study included both a low-dose methadone and placebo intervention group.

High- versus low-dose methadone.
High doses of methadone were more effective than low doses in reducing opioid use (OR 1.72, 95% CI: 1.26, 2.36, P=0.0007). There was no statistically significant difference between the groups in terms of retention rates (OR 1.25, 95% CI: 0.94, 1.67, P=0.13).

Methadone versus buprenorphine.
High doses of methadone were more effective than low doses of buprenorphine for reducing retention failures (OR 2.72, 95% CI: 1.12, 6.58, P=0.027) and illicit opioid use (OR 3.39, 95% CI: 1.87, 6.16, P=0.0001). There was no statistically significant difference between high doses of methadone and high doses of buprenorphine for either retention rates (OR 1.14, 95% CI: 0.83, 1.59, P=0.042) or illicit opioid use (OR 1.08, 95% CI: 0.75, 1.57, P=0.68).

Methadone versus LAAM.
High doses of methadone were more effective than LAAM in reducing retention failure (OR 1.92, 95% CI: 1.31, 2.81, P=0.0008). There was no statistically significant difference between the groups for illicit opioid use (OR 0.72, 95% CI: 0.46, 1.11, P=0.14). Methadone at low doses was worse than LAAM in terms of illicit opioid use, but there were no significant difference between the two treatments for retention failure (the actual results were not presented).

Authors' conclusions
The authors proposed that the drug of choice for opioid dependence in agonist-maintenance programmes is oral methadone at doses of at least 50 mg/day.

CRD commentary
The review question was clear in terms of the intervention, outcomes and study design, but the authors did not state
any pre-specified inclusion criteria with regards to the study population. Only two electronic databases were searched and the search strategy used was limited; this means that some important information may have been missed. No attempt to search for unpublished studies or grey literature was made. The authors did not state how they selected the studies, but two reviewers were involved in the data extraction and quality assessment processes, which will have helped to reduce errors and reviewer bias. However, the two reviewers assessed the study quality together rather than independently. Only minimal data on the included studies were presented, with very little information on the study population, which minimises the reader's ability to assess the possibility of clinical heterogeneity. There was no information on between-study differences (or statistical heterogeneity). The results of the meta-analysis were based on indirect comparisons, and the authors did not discuss the implications of this. The results of LAAM were based on three included studies, none of which compared the use of low-dose methadone with LAAM.

High-dose methadone was used as the reference category in the meta-regression, yet the results were given in terms of low-dose methadone versus placebo and LAAM (but not buprenorphine), although the actual data were not presented. It was unclear what these results were based on, and whether separate meta-regression calculations were performed using low-dose methadone as the reference standard. The number of studies contributing to each comparison was unclear and the authors use of meta-regression means that the results were based on indirect comparisons, i.e. the summary ORs were based on pooled high-dose methadone data versus placebo (or any other comparator) data, rather than pooled individual study comparisons of placebo versus high-dose methadone.

The authors based their conclusion about the use of high-dose methadone on the fact that the new drugs, buprenorphine and LAAM, were not shown to be superior to methadone. However, high-dose methadone was not found to be superior to high-dose buprenorphine either.

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

**Practice:** The authors proposed that the drug of choice for opioid dependence in agonist-maintenance programmes is oral methadone at doses of 50 mg/day or higher.

**Research:** The authors did not state any implications for further research.

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