A meta-analysis of retention in methadone maintenance by dose and dosing strategy

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CRD summary
The authors concluded that retention rates for methadone maintenance treatment were greater with higher doses of methadone and with flexible dosing strategies. Given the potential for publication bias and bias in the review process, the unclear quality of the included trials and uncertainty regarding the analyses, the authors' conclusions are unlikely to be reliable.

Authors' objectives
To assess the impact of methadone dosage and dosing strategy on retention in methadone maintenance treatment.

Searching
MEDLINE, EMBASE and the Chinese National Knowledge Infrastructure (CNKI) databases were searches up to August 2007 for articles in any language. Search terms were reported. Bibliographies of retrieved articles were handsearched.

Study selection
Double-blind, randomised controlled trials (RCTs) of methadone maintenance treatment, that reported in detail the doses and dosing strategy and reported on retention rates, were eligible for inclusion. Trials had to report the sample size and follow-up period for each group of participants. Trials were excluded if they were crossover design or if they had opioid detoxification as the primary objective. Trials with specialised adjuvant behavioural interventions were excluded, unless there was a control group without these interventions, in which case this group was included.

Included trials compared different doses of methadone, or methadone to levo-acetylmethadol, buprenorphine or placebo over a period ranging from 13 to 52 weeks. Methadone doses ranged from 20mg/day to 160mg/day. Sixty five percent of patients received a fixed dosing strategy. The remainder received a flexible dosing strategy. Included trials were conducted in the USA, Australia and Europe. Trial dates ranged from 1972 to 2003.

The authors did not state how the studies were selected for the review.

Assessment of study quality
The authors did not state that they assessed study validity.

Data extraction
The number of patients in the methadone group at the start and the end of the trial was extracted and used to calculate a percentage retention rate. Where trials had more than one follow-up period, data were extracted from the longest follow-up period.

The authors did not state how the data were extracted for the review.

Methods of synthesis
Trials were grouped according to three predictor variables of methadone retention: dose (under 60mg/day versus over 60mg/day), duration of follow-up (short-term of three to six months versus long-term of six to 12 months), and dosing strategy (flexible versus fixed). It appeared that simple addition across trials was used to estimate retention rates for each predictor variable category. Pearson's $\chi^2$ was used to compare retention rates across predictor variable groupings. A multilevel logistic regression was used to calculate summary odds ratios comparing retention in each of the predictor variables controlling for the other two.

Results of the review
Eighteen RCTs were included for review (n=2,831 patients).
Univariate analyses showed that doses of more than 60mg/day of methadone were associated with greater retention in both the short-term (62.5% versus 50.6%; p=0.0005) and the long-term (57.0% versus 42.5%; p<0.0001) compared with methadone doses of less than 60mg/day. Flexible dosing regimes were associated with significantly greater retention rates both in the short-term (61.0% versus 49.9%, p=0.0007) and the long-term (61.7% versus 45.9%, p<0.0001) compared with fixed dosing regimes.

Multivariate analyses showed that doses of more than 60mg/day significantly increased the likelihood of treatment retention compared to doses of less than 60mg/day (OR 1.74, 95% CI 1.43 to 2.11). Flexible dosing strategies significantly increased the likelihood of treatment retention (OR 1.72, 95% CI 1.41 to 2.11). Retention significantly decreased at six to 12 months (long-term) compared with three to six months (OR 0.80, 95% CI 0.65 to 0.87).

**Authors' conclusions**
Retention rates for methadone maintenance treatment were greater with higher doses of methadone and with flexible dosing strategies.

**CRD commentary**
The review addressed a clear question with well-defined inclusion criteria for study design, intervention and outcomes. Inclusion criteria for participants were not stated. Limited details were available for participants, making it difficult to assess the homogeneity of the studies and generalisability of the findings. Several relevant databases were searched for articles in any language, minimising the risk of language bias. There did not appear to have been any attempts to identify unpublished data. Publication bias was not assessed, so it could not be ruled out. It was unclear whether appropriate steps were taken in the review process to minimise the risk of reviewer error and bias.

A validity assessment did not appear to have been conducted, so it was not possible to ascertain the quality of the included trials. Despite the fact that only RCTs were eligible for inclusion, data only appear to have been extracted from the treatment arms. Therefore the trials were treated as uncontrolled trials, losing the benefits of RCTs. Also, the results appeared to have been summed across trials, rather than using appropriate methods for pooling data.

Given the potential for publication bias and bias in the review process, the unclear quality of the included trials and uncertainty regarding the analyses, the authors' conclusions are unlikely to be reliable.

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

**Research:** Further RCTs are needed to investigate the impact of high methadone doses (over 120mg/day) on retention rates, other outcomes and the risk/benefit ratio, especially in high risk patients. Further RCTs are needed in developing countries.

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