Efficacy of maintenance treatment with naltrexone for opioid dependence: a meta-analytical review

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CRD summary
The authors concluded that naltrexone is an effective treatment, the efficacy of which is moderated by the retention of patients. They also concluded that contingency management is a promising method for increasing retention. Overall, despite some potential limitations, the authors' conclusions appear appropriate and are likely to be reliable.

Authors' objectives
To assess the efficacy of naltrexone in the reduction of illicit opioid use, and to determine the potential moderating role of treatment retention.

Searching
MEDLINE (1966 to October 2003), EMBASE, PsycINFO, PsycLIT, and the Cochrane Library were searched without language restrictions; the search terms were reported, but not dates for the non-MEDLINE searches. References in published articles, reviews and meta-analyses were checked. No systematic attempt was made to identify unpublished studies, although one such study was identified.

Study selection
Randomised controlled trials (RCTs) with a minimum duration of 4 weeks, which compared naltrexone maintenance with control, another treatment, or with psychosocial or psychopharmacological treatment plus naltrexone maintenance, were eligible for inclusion. Most of the included studies used a psychological or behavioural treatment alone as a comparator. Concomitant treatments such as contingency management (voucher rewards) were used in some studies. The duration of interventions in the included studies ranged from 8 to 38 weeks. Eligible studies had to enrol at least 20 out-patients. The included participants were opioid dependent under the American Psychiatric Association's DSM criteria or the International Classification of Diseases system. The great majority of patients in the included studies were male, and patients were aged 18 to 49 years. Inclusion criteria for the outcomes were not stated. However, three important outcomes were identified: retention, opioid abuse and 'success' (defined as retention with opioid abstinence). The included studies also reported psychiatric symptoms, opioid-positive urines, cravings, naltrexone ingestion and rearrests. In addition, one study reported some isolated outcomes.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Two reviewers assessed the studies for validity using the criteria of the Swedish Council on Technology Assessment (SBU), which awards between 1 and 3 points for each of 11 criteria. Such criteria included randomisation, blinding, patient selection, effect size and statistical methods. Studies other than those using psychosocial treatment were also assessed using the Jadad scale, which assesses randomisation, blinding and the treatment of withdrawals and drop-outs, and has a maximum score of 5 points. Differences between the reviewers were resolved by discussion.

Data extraction
Two reviewers extracted the data and any differences were resolved through agreement. A statistician used the categorical data to calculate effect sizes (d-statistics) in consort with the reviewers. Risk differences were calculated in some instances.

Methods of synthesis
The effect sizes for effectiveness outcomes were pooled in a meta-analysis, using a random-effects model, to give a standardised mean difference (SMD). Where statistically significant heterogeneity was identified, the moderating effect of retention was assessed using a subgroup analysis, in which studies were defined as low or high retention in relation to an early (1978) reference standard study. Meta-analyses were also carried out for individual outcomes. Separate meta-
Results of the review
Fifteen RCTs (n=1,071) were included in the review.

The quality of the studies was mixed, with SBU scores ranging from 21 to 30 and Jadad scores (where applicable) ranging from 1 to 4 (most assessed studies scored 3 or 4 on the Jadad scale).

Naltrexone versus control.

Efficacy outcomes (opioid-positive urines, craving and psychiatric symptoms) (10 RCTs).

Overall, there was no statistically significant difference in retention levels between naltrexone groups and comparison groups (SMD 0.15, 95% confidence interval, CI: -0.7, 0.36). The subgroup analysis showed that retention level was significantly better in the naltrexone groups in high retention studies (SMD 0.31, 95% CI: 0.08, 0.53), while there was no difference between groups in the low retention studies. The outcome of opioid-positive urines (10 RCTs) showed a result which favoured naltrexone (SMD 0.44, 95% CI: 0.07, 0.82). This was significant only in the subgroup of 6 trials with high retention. There was significant heterogeneity (p<0.05) for both the total and the high retention group results. For opioid abuse (6 RCTs) there was no difference between the groups, either overall (SMD 0.25, 95% CI: -0.12, 0.62) or in either of the retention subgroups, but there was evidence of significant overall heterogeneity. An analysis of variance showed that naltrexone was significantly more effective in studies with high retention levels than in studies with low retention levels for all outcomes except psychiatric symptoms.

Contingency management (3 RCTs).

The contingency management groups had significantly better outcomes than the control groups during naltrexone maintenance for retention (SMD 0.46, 95% CI: 0.18, 0.73), opioid-positive urines (SMD 0.33, 95% CI: 0.06, 0.60) and naltrexone ingestion (SMD 0.55, 95% CI: 0.21, 0.89). There was no evidence of statistical heterogeneity between the studies.

Other studies.

One study compared family versus individual therapy during naltrexone maintenance and found significant differences favouring family therapy for retention, opioid-positive urines, naltrexone ingestion and percentage of days abstinent.

One study compared behaviour therapy versus no behavioural therapy during naltrexone maintenance and found no significant differences between the groups for any outcome.

One study compared naltrexone plus fluoxetine with naltrexone alone and found that the combination therapy group had significantly better retention over 6 months (risk difference 0.23, 95% CI: 0.06, 0.42).

Results were also reported for the outcomes of craving, success and rearrests (single study of each). In each case a significant result favouring naltrexone was reported.

Authors’ conclusions
Retention is an important moderator of the effectiveness of naltrexone in the treatment of opioid dependence. Naltrexone is an effective treatment for opioid dependence if the retention rate is above a certain level. Contingency management is a promising method of increasing retention.

CRD commentary
The review question and inclusion criteria for the study design, intervention and comparators, and population were clearly defined, while outcomes of interest were identified. The authors searched a number of relevant databases and took steps to reduce language bias. However, they acknowledged that systematic efforts to identify unpublished studies were not made and, as no assessment of publication bias was reported, this might have increased the possibility that some relevant studies were not included in the review. The authors reported using methods designed to reduce bias and
error in the data extraction and validity assessment, but not in the selection of studies for the review. The validity assessment used appropriate criteria. The meta-analysis for groups of studies appears appropriate and a limited investigation of heterogeneity was undertaken. The transformation of different outcome data to give an effect size which is subsequently pooled may sometimes produce results for which the meaningfulness is difficult to interpret, although in this instance individual outcomes were also pooled separately. Overall, despite some potential limitations, the authors’ conclusions appear appropriate and are likely to be reliable.

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

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