A systematic review of the effectiveness of naltrexone in the maintenance treatment of opioid and alcohol dependence


CRD summary
The authors concluded that there is insufficient evidence to confirm or refute the effectiveness of naltrexone for treating opioid dependence, but there is evidence for its effectiveness in managing alcohol dependence. The effect of combining naltrexone with psychosocial interventions is unclear. Despite methodological limitations and inadequate reporting in the review, the data presented appear to support these conclusions.

Authors' objectives
To assess the effectiveness of naltrexone (NTX), with or without psychosocial therapy, in the maintenance treatment of opioid and alcohol dependence.

Searching
The following databases were searched in March 2004, from inception: PubMed, EMBASE, PsycINFO and the Cochrane Central Register of Controlled Trials. Search terms were reported. The reference lists of studies and reviews retrieved were checked. Only studies published in English were included.

Study selection
Inclusion was apparently restricted to randomised controlled trials (RCTs) of NTX maintenance treatment for outpatients, aged 18 to 75 years, with alcohol or opiate abuse/dependence. Comparisons of interest were NTX versus placebo and NTX plus psychosocial treatment versus NTX alone. Studies were required to report at least one of the following outcomes: relapse rate (four/five or more alcoholic drinks per occasion/day for women/men respectively); continuous abstinence (confirmed by urine or blood sampling or by self-report); frequency of substance abuse; time to first relapse; and time to first drink. Studies of specific populations were excluded.

Many of the included studies (especially the alcohol studies), used psychosocial co-interventions, often with a cognitive behavioural orientation. The opioid studies included a wide variety of participants, interventions and outcome measures. Most studies focused on outcomes at 12-13 weeks and few reported long term data. Abstinence was verified by urinalysis, where stated.

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

Assessment of study quality
An overall validity score was calculated for each study by allocating points for compliance with the following quality criteria: randomisation, allocation concealment, blinding, inclusion of all participants in analysis, similarity of participants at baseline and equal treatment of groups.

Two reviewers independently assessed study validity.

Data extraction
The risk difference (RD) between study groups was calculated for dichotomous outcomes and the weighted mean difference (WMD) for continuous data, with 95% confidence intervals (CIs). Where results were not reported for all randomised participants, the analysis was based on the data available.

Two reviewers independently extracted the data.

Methods of synthesis
Where studies were clinically homogenous, they were combined using a random-effects model to calculate pooled RDs and WMDs. For dichotomous outcomes, numbers needed to treat (NNTs) were also calculated. Statistical heterogeneity was assessed using visual inspection of forest plots and the $\chi^2$ test (with $p \leq 0.05$ denoting statistical significance).
Results were grouped by the duration of follow-up (medium term was 4 to 16 weeks, long term was 16 to 32 weeks). Subgroup analyses were conducted to investigate the impact of individual versus group psychotherapy. The effect of treatment compliance on outcome was calculated using Spearman's non-parametric correlation. The results were grouped by disorder, outcome measure and duration of follow up. A narrative synthesis was conducted where heterogeneity precluded pooling of the data or where measures of variance were not reported. A qualitative analysis was also performed, allocating grades to the evidence (strong, moderate, limited/conflicting, none) according to the quality, quantity and consistency of the relevant studies.

**Results of the review**

Twenty-four trials were included in the review: 21 were rated high quality (scored at least 9 of a possible 16 points). The mean quality score was 10 points (range 7 to 13 points).

**Opioid studies**

NTX versus placebo (seven trials): For abstinence rate, one trial reported a statistically significant medium term and long term effect, favouring NTX; three others reported no statistically significant differences between the groups. Findings were inconclusive due to heterogeneity for psychosocial co-interventions.

**Alcohol studies**

NTX versus placebo (17 trials):  

**Medium-term effectiveness:** For relapse rate, pooling of 14 trials (n=2,105) found a statistically significant risk-difference favouring NTX, 13% (95% CI: 7%, 18%; NNT=8, p <0.00001). There was heterogeneity of borderline statistical significance for this analysis (p=0.05), but the forest plot did not show marked variation between the studies. For continuous abstinence, pooling of seven trials (n=779) found no statistically significant difference between the groups, with no statistically significant heterogeneity. For percentage of drinking days, three of four trials found a statistically significant benefit (2.7 to 6.7 days) for NTX. For the time to first relapse five of nine relevant trials significantly favoured NTX, as did one of six relevant trials for time to first drink. Other trials reported no significant difference between the groups.

**Long-term effectiveness (four trials):** For relapse rate, two of four trials found a statistically significant difference in favour of NTX. Pooling of two trials found no significant difference between the groups in percentage of drinking days. For psychosocial co-interventions, four trials reported improved outcomes associated with a combination of CBT and NTX and three found CBT superior to supportive therapy for reducing relapse rates. Results of subgroup analyses and of the qualitative analysis were also reported.

**Authors' conclusions**

There is insufficient evidence to confirm or refute the effectiveness of naltrexone for treating opioid dependence, but there is evidence for its effectiveness in managing alcohol dependence. The effect of combining naltrexone with psychosocial interventions is unclear.

**CRD commentary**

The review objectives and inclusion criteria were clear in most respects, although the criteria for study design were vague and 'psychosocial treatment' was not defined. Relevant sources were searched for studies, but the limitation to studies published in English means that some may have been missed. Moreover publication bias was not formally assessed. Relevant quality criteria were considered, and steps were taken to reduce error and bias in quality assessment and data extraction by having two reviewers make decisions independently. It is unclear whether this also applied to study selection. The authors noted that more data may have been available if attempts had been made to contact authors for missing information. Insufficient details were available about the primary studies, with no information about baseline sample numbers, participant characteristics or disease severity. Nor were any quantitative findings reported for most studies. These factors made it difficult to interpret the strength and applicability of reported findings. The statistical methods used to pool studies appear suitable. Also, the authors appropriately used narrative synthesis where there was marked heterogeneity between studies. Despite methodological limitations and rather poor reporting in the review, the data presented appear to support the authors' main conclusions.
Implications of the review for practice and research

Practice: The authors stated that it is crucial that patients take NTX as prescribed in general practice, to control safety issues and evaluate treatment effectiveness.

Research: The authors stated that more RCTs are needed in this field, with longer treatment and longer post-treatment follow-up. Research is needed on strategies for preventing withdrawal from treatment and improving compliance with therapy.

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