Naltrexone, a relapse prevention maintenance treatment of alcohol dependence: a meta-analysis of randomized controlled trials

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Authors' objectives
To compare the efficacy and toxicity of naltrexone and placebo in the treatment of alcohol dependence.

Searching
MEDLINE and EMBASE (both from 1976 to January 2001), PsycLIT and the Cochrane Controlled Trials Register were searched for publications in the English language. The search terms were: 'naltrexone' (exploded); 'randomized controlled trial' or 'random allocation' or 'all random'; 'human'; and 'alcohol'. The bibliographies of relevant articles were examined for additional studies. In addition, the manufacturer of naltrexone was asked for any additional complete RCTs, and key investigators in the field were contacted. Studies reported only as conference proceedings were excluded. Where multiple reports of the same study were identified, the report providing the greatest detail was included.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) of at least 3 months' duration were eligible if the studies had complete databases. To be included in the meta-analysis, the standard deviations of the means had to be either reported in the study or be available from the authors. All included studies were double-blind RCTs of 12 weeks' duration.

Specific interventions included in the review
Comparisons of 50 mg naltrexone daily with placebo or another active drug licensed in Australia were eligible. The cointerventions included psychotherapy of various types and intensity, and standard alcohol rehabilitation programmes.

Participants included in the review
Adults (at least 18 years of age) with a diagnosis of alcohol dependence or abuse alone, as defined by the American Psychiatric Association (DSM-III-R criteria, 1987), who were treated as either in- or out-patients were eligible. The mean age of the patients ranged from 39 to 59 years. Patients who had recently been detoxified from alcohol, and who had no significant psychiatric disease or co-existing drug addiction, were included.

Outcomes assessed in the review
Studies were eligible if they assessed, at least, relapse rates, abstinence rates, and the percentage of patients discontinuing treatment due to adverse events or the percentage of patients with at least one adverse event. The definition of relapse varied between the studies. However, the definitions had in common the consumption of at least five drinks on one day for men and at least four drinks on one day for women. The patients were considered to be abstinent if they continued the study and had no alcohol over the duration of the study. The other outcomes assessed included the mean percentage of reported drinking days per patient, and the mean number of drinks per drinking day per patient.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
Eligible studies were restricted to RCTs. The quality of individual studies was assessed and scored using the following seven criteria; the maximum score possible was 12 points.
Level of security of the method of randomisation: 0 if not stated; 0.5 if controlled by the investigator; 1 if controlled by the pharmacy, central registry or blinded drug supply.

Treatment groups comparable at baseline: 0 if not stated or potentially important differences; 1 if groups comparable.

Degree of blinding: 0 if open; 0.5 if single-blind with respect to the patient; 1 if blinded observer; 2 if double-blind.

Adequacy of follow-up: 0 if significant number of drop-outs or different rates between the groups; 1 if some drop-outs and equivalent rates between the groups; 2 assessment of all patients not lost to follow-up.

Adequate description of inclusion and exclusion criteria and concomitant therapy: 0 if no description; 0.5 if partial; 1 if full.

Reliability of outcomes assessment: 0 if method not stated; 1 if sub-optimal but acceptable; 2 if highly accurate method used.

Follow-up of drop-outs sufficient to permit intention-to-treat (ITT) as well as per-protocol analysis: 0 if per-protocol only; 1 if per-protocol for key efficacy criteria with ITT for safety; 3 for ITT for efficacy and safety.

An experienced data extractor, who was not blinded to any aspect of the report or the publication, extracted the validity criteria onto a trial methodology quality rating form. The validity assessment was performed independently of the study findings on efficacy of the intervention.

Data extraction
An experienced data extractor, who was not blinded to any aspect of the report or the publication, extracted the following data onto data extraction and follow-up results forms: characteristics of the participants; study setting; intervention details; and outcomes, including adverse events. In addition, the following data were reported for studies included in the meta-analysis: type of report (journal publication or internal pharmaceutical company report); other references to the same study; location of study; subjected and diagnostic instrument; the level of blinding; the duration of treatment; and principal outcomes. In the review, the analysis included all patients randomised to treatment who received at least one dose of the assigned treatment.

Methods of synthesis
How were the studies combined?
The pooled risk difference (RD) and pooled relative risk (RR) were calculated for the main outcomes, along with 95% confidence intervals (CIs), using fixed-effect (Mantel-Haenszel) and random-effects (DerSimonian and Laird) models. The weighted mean differences (WMDs) and 95% CIs were calculated for continuous variables using both a fixed-effect and random-effects model.

How were differences between studies investigated?
Statistical heterogeneity was tested using the chi-squared test. Differences in the population characteristics and definitions of outcomes were described.

Results of the review
Seven RCTs (833 patients) were included in the meta-analysis. Four RCTs were journal publications and 4 RCTs were internal company reports (Dupont Merck).

The populations differed between the studies in terms of the age of the patients, the number of years of drinking, the percentage employed, and the percentage in a stable relationship.

The quality scores ranged from 10 to 11 (maximum 12).

Relapse rates.
Naltrexone was significantly more effective in preventing relapse into heavy drinking than placebo. Using a random-effects model, the RD was -14% (95% CI: -23, -5) and the pooled RR was 0.72 (95% CI: 0.55, 0.94). Significant heterogeneity was detected (chi-squared 11.9, d.f.=6, p=0.06).

Abstinence.

Naltrexone was associated with significantly higher abstinence rates than placebo. Using the fixed-effect model, the RD was 10% (95% CI: 3.5, 16.3) and the pooled RR was 1.28 (95% CI: 1.08, 1.52). No significant heterogeneity was detected (chi-squared 9.7, d.f.=6, p=0.14).

Alcohol consumption outcomes.

Naltrexone-treated patients reported significantly fewer drinking days than placebo-treated patients. Using a fixed-effect model, the pooled WMD was -3% (95% CI: -5.4, -0.5). No significant heterogeneity was detected (chi-squared 5.75, d.f.=4, p=0.22). Naltrexone-treated patients reported significantly fewer drinks per drinking day per patient than placebo-treated patients. Using a fixed-effect model, the pooled WMD was -1.04% (95% CI: -2.0, -0.1). No significant heterogeneity was detected (chi-squared 2.97, d.f.=3, p=0.40).

Safety.

There was no statistically-significant difference between naltrexone and placebo in the number of patients reporting at least one adverse event (RD 1%, 95% CI: -6, 8) or the number of patients who discontinued the study due to an adverse event (RD 2%, 95% CI: -1, 5). No significant heterogeneity was detected for either outcome (p=0.30 and p=0.65, respectively).

Authors' conclusions

Naltrexone was more effective than placebo at reducing relapses to heavy drinking and at improving alcohol abstinence in the short-term. However, these conclusions were drawn from data collected over a 12-week period of treatment. The optimal duration of treatment cannot be determined.

CRD commentary

The aims were stated and the inclusion criteria were defined in terms of the study design, intervention, participants and outcome. Several relevant sources of literature were searched and attempts were made to locate unpublished material. By restricting eligible studies to those published in the English language, other relevant articles might have been omitted. Duplicate articles were removed but the methods used to select the studies were not described. Eligible studies were restricted to RCTs, and a formal validity assessment was undertaken using defined criteria. Only one reviewer assessed validity and extracted the data. Relevant data and the validity scores of individual studies were tabulated.

Statistical heterogeneity was assessed and reported. The differences between the individual studies in terms of the characteristics of the populations and the definitions of the outcomes, were described. The data were combined in a meta-analysis using both a fixed-effect and random-effects model. Despite evidence of statistical heterogeneity for the primary outcome of ‘relapse rate’, the authors incorrectly supported the use of a random-effects model and did not investigate potential causes of this heterogeneity. Without an exploration of the potential causes of heterogeneity among the studies with respect to relapse rates, it is not possible to determine the circumstances in which naltrexone is of benefit.

Implications of the review for practice and research

Practice: The authors state that additional research is required before recommendations can be made.

Research: The authors state that additional follow-up studies with suitable comparison groups and longer-term outcome results are necessary to examine the long-term efficacy and tolerability of naltrexone, particularly with respect to any influence on the rates of alcohol-related complications.
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