Acamprosate supports abstinence, Naltrexone prevents excessive drinking: evidence from a meta-analysis with unreported outcomes

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CRD summary
The authors concluded that abstinence rates were significant increased by both naltrexone and acamprosate, but only naltrexone was associated with a significant decrease in the risk of relapse to heavy drinking in non-abstinent drinkers. Evidence appeared to support the authors' conclusions, but incomplete reporting of review methods and study quality made it difficult to assess their reliability.

Authors' objectives
To evaluate and compare the efficacy of acamprosate and naltrexone for excessive drinking.

Searching
PubMed and Cochrane Central Register of Controlled Trials were searched in November 2004 using reported search terms. Reference lists of published studies and meta-analyses were screened. Three named drug manufacturers were contacted for unpublished studies.

Study selection
Randomised controlled trials (RCTs) that compared the effects of acamprosate and/or naltrexone with placebo in patients diagnosed with alcohol dependence using a standardised system were eligible for inclusion. Interventions had to last at least four weeks and each treatment group had to contain at least 10 patients.

The primary review outcomes were: return to any drinking (defined as the first drink after a period of continuous abstinence); and return to heavy drinking (as defined in individual studies). Most of the primary studies defined heavy drinking as more than five standard drinks (10 g to 13.6 g of pure alcohol) per drinking occasion for men. Secondary review outcomes included days drinking per week, quantity consumed per day, time to first drink, time to first relapse and gamma-glutamyl transpeptidase (GGT) level.

The included studies were aimed at either abstinence or controlled drinking. Acamprosate studies usually used a drug dose of 1.332 mg/kg/day for patients under 60 kg and 1.998 mg/kg per day for heavier patients. All studies were set in outpatient departments that used psychosocial interventions. Studies were conducted mainly in Europe. Treatment duration ranged from 56 days to one year. The mean age of patients was between 40 and 50 years. Treatment generally started from five to 14 days after alcohol detoxification.

Naltrexone studies used a drug dose of 50 mg/day. All studies used psychosocial co-interventions. Studies were conducted mainly in the United States. Treatment duration ranged from 51 days to one year. The mean age of patients was between 36 and 58 years.

The authors stated neither how papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
Study quality was assessed using drop-out and compliance rates, validity of methods used to measure outcomes and operationalisation. The authors did not state how the validity assessment was performed.

Data extraction
Two reviewers independently extracted data from 25 per cent of the studies that were randomly selected; agreement was 100 per cent. One reviewer extracted data from the remaining studies on to a data extraction form. Researchers and the drug manufacturer Merck Lipha Santé were contacted for missing data. Data that were provided, but not explicitly sought were excluded. In the review, relapse rates were calculated for all patients and for the subgroup of non-abstinent patients. Numerical results were extracted from graphs if required. For each study, relative risks of dichotomous
outcomes were calculated with 95% confidence intervals (CI) on an intention-to-treat (ITT) basis; drop-outs were classified as treatment failures. Standardised mean differences (SMD) were calculated for continuous data.

Methods of synthesis
The studies were grouped by outcome and specific drug. Pooled RRs and SMD with 95% CI were calculated using the fixed-effect Mantel-Haenszel method for homogeneous studies and the DerSimonian and Laird random-effects model for heterogeneous. The number needed to treat (NNT) to prevent one additional incidence of relapse was calculated with its 95% CI. The weighted proportions of unpublished results were reported for each outcome. Statistical heterogeneity was assessed using the Q-statistic and the I² statistic. Publication bias was assessed using a funnel plot and Begg's test. Subgroup analyses were conducted to examine the effect of the drugs on non-abstinent drinkers.

Results of the review
Twenty-one RCTs evaluated acamprosate (n=5,280). Twenty RCTs evaluated naltrexone (n=2,182).

The risk of having a first drink after abstinence was reduced significantly with acamprosate compared to placebo (RR 0.84, 95% CI: 0.78, 0.91; NNT 7.7, 95% CI: 5.6, 13.0) and with naltrexone compared to placebo (RR 0.93, 95% CI: 0.88, 0.99; NNT 17.4, 95% CI: 9.7, 111.0). The sample weighted proportions of unpublished data were 10.8 per cent for acamprosate and 33.8 per cent for naltrexone. Significant heterogeneity was found for both analyses: p<0.00001, I² 83.6% for acamprosate; and p=0.08, I² 33.8% for naltrexone.

The risk of relapse to heavy drinking was significantly reduced with acamprosate compared to placebo (RR 0.82, 95% CI: 0.73, 0.92; NNT 8.6, 95% CI: 5.7, 18.7) and for naltrexone compared to placebo (RR 0.80, 95% CI: 0.71, 0.91; NNT 8.1, 95% CI: 5.5, 16.5). The sample weighted proportion of unpublished data was 79.2 per cent for acamprosate and 0 for naltrexone. Significant heterogeneity was found for both analyses (p<0.0001, I² 75.5% for acamprosate and p< 0.0001, I² 64.6% for naltrexone).

For non-abstinent drinkers there was no significant difference in the risk of heavy drinking between acamprosate and placebo (RR 0.98, 95% CI: 0.94, 1.02), but the risk of heavy drinking was significantly reduced with naltrexone compared to placebo (RR 0.88, 95% CI: 0.80, 0.96; NNT to prevent one additional relapse to heavy drinking was nine).

The funnel plot was asymmetrical suggesting the potential for publication bias, but Begg's test showed no significant evidence (p=0.09 and 0.31 for the two main analyses).

Authors’ conclusions
Abstinence rates were significant increased by both naltrexone and acamprosate, but only naltrexone was associated with a significant decrease in the risk of relapse to heavy drinking in non-abstinent drinkers.

CRD commentary
The review question was clearly stated. Two relevant databases were searched to the end of 2004 and attempts were made to locate unpublished studies, minimising publication bias. The potential for publication bias was assessed and limited evidence was found. It was not clear whether any language limitations had been applied, so the potential for language bias could not be assessed. Only RCTs were included. Study validity was apparently assessed, but results were not reported. Data were extracted on an ITT basis. The lack of duplication of all of the data extraction process and incomplete reporting of methods used for study selection and validity assessment meant that there was potential for reviewer error and bias. Appropriate methods were used for the meta-analyses and heterogeneity was assessed. Although differences between studies were acknowledged in the discussion, there was no mention in the results section of the significant heterogeneity presented in several of the meta-analyses; forest plots did, however, indicate a generally consistent direction of treatment effect. The authors pointed out that all studies used psychological co-interventions and these may have influenced results. Evidence appeared to support the authors’ conclusions, but incomplete reporting of review methods and study quality made it difficult to assess their reliability.

Implications of the review for practice and research
Practice: The authors stated that to maximise benefits from treatment, the motivational status of alcohol-dependent patients could be matched to the effects of individual drugs.

Research: The authors stated that there was need for additional studies to evaluate the effects of acamprosate in controlled drinking and a need to examine the influence of treatment goals (abstinence or controlled drinking) on the effects of drug treatments. RCTs would be needed to directly compare the effects of acamprosate and naltrexone on different outcome measures.

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