The efficacy of acamprosate and naltrexone in the treatment of alcohol dependence: a relative benefits analysis of randomized controlled trials

Snyder J L, Bowers T G

CRD summary
The authors concluded that in the treatment of alcohol dependence, both acamprosate and naltrexone modestly improve outcomes compared to placebo. There was insufficient evidence to determine which drug is superior or assess long-term efficacy. In view of poor reporting of review methods, lack of information about individual studies and failure to evaluate statistical heterogeneity, these conclusions may not be reliable.

Authors' objectives
To determine the efficacy of acamprosate and naltrexone as an adjunct to psychosocial treatment of alcohol dependence.

Searching
The following databases were searched from 1985 to 2006: MEDLINE, PsycINFO, ProQuest Psychological Journals and the Cochrane Central Register of Controlled Trials. There was no language restriction.

Study selection
Randomised controlled trials (RCTs) on the efficacy of acamprosate and naltrexone compared to placebo for treatment of alcohol dependence as an adjunct to psychosocial treatment were eligible for inclusion. Outcomes of interest were abstinence and relapse rate. Relapse rate was defined as not consuming five or more standard drinks a day or not drinking on more than five days per week.

All participants in the included studies were diagnosed as alcohol dependent. Most of the naltrexone trials included only participants who had undergone detoxification therapy and who presented as medically stable; some had psychiatric co-morbidities. Naltrexone (usually 50 mgs daily) and acamprosate (various doses) were compared with placebo or with each other. The mean participant age was 43 to 45 years and the proportion of females varied (overall range nil to 38%). About 55% of participants in acamprosate RCTs and 45% in naltrexone RCTs were married. Naltrexone (usually 50 mgs daily) and acamprosate (various doses) were compared with placebo or with each other. The mean participant age was 43 to 45 years and the proportion of females varied (overall range nil to 38%). About 55% of participants in acamprosate RCTs and 45% in naltrexone RCTs were married. All placebo-controlled naltrexone studies were conducted among outpatients and included psychosocial therapy. The review reported 'cumulative abstinence duration' (CAD) as an outcome for both acamprosate and naltrexone, and relapse rate for naltrexone only. Outcomes were reported at three, six and 12 month follow-up. CAD was calculated in the acamprosate RCTs from a wide variety of measures reported in the primary studies (e.g. continued abstinence duration, glutamyl transferase, relapse rate, time to failure, drinking behaviour); detailed definitions of terms are available from the authors. CAD was calculated in the naltrexone RCTs from rates of abstinence (defined in all cases as consuming no alcohol during the trial period). Definitions of relapse varied across studies. About half the trials included post-intervention follow-up, at time points ranging from 1.5 to 12 months; assessment was often by self-report.

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

Assessment of study quality
A published scale (Chalmers 1981) was used to score studies for quality, using criteria including sample size, randomisation methods, blinding, selection and withdrawal criteria, and statistical techniques. Eligible studies were required to score at least 50 out of a possible 100 points to be included in the review. The assessment was conducted by two independent reviewers blinded to the study hypothesis.

Data extraction
The authors did not state how the data were extracted for the review or how many reviewers performed the data extraction. If data were missing because participants withdrew from treatment, they were classified as treatment failures.
Methods of synthesis
Pooled relative risks (RR) together with their 95% confidence intervals (CIs) were calculated using the DerSimonian
and Laird random-effects model. Pooled weighted mean differences together with their 95% CIs were estimated using
the non-parametric methods of Kraemer and Andrews (1982). Pooled abstinence rates were also calculated.

Results of the review
Forty-two RCTs were included in the review (n=8,428). Quality scores in the included trials (where stated) ranged from
60 to 100. Drop-out rates were high, averaging 50% (range 38% to 68% at three months).

Acamprosate versus placebo (24 RCTs, n=5765):
Acamprosate resulted in significantly higher continuous abstinence than placebo at three (RR= 1.76, 95% CI: 1.14,
2.39; nine RCTs), six (RR 1.16, 95% CI: 1.03, 1.16, eight RCTs) and 12 months (RR 1.11, 95% CI: 1.01, 1.21, six
RCTs).

Naltrexone versus placebo (18 RCTs, n=2506):
Naltrexone significantly improved relapse rates relative to placebo at three months (RR 1.20, 95% CI: 1.17, 1.47, 18
RCTs), six months (RR 4.01, one RCT) and 12 months (RR 1.19, one RCT). There was no statistically significant
difference in continuous abstinence rates between patients treated with naltrexone and placebo at three months (RR
1.23, 95% CI: 0.996, 1.78, eight RCTs). There were no relevant data for six or 12 month follow-up.

Acamprosate versus naltrexone (one RCT, n=157):
There was no statistically significant difference in mean CAD between the two groups, though other outcome measures
significantly favoured naltrexone (e.g. time to first relapse was 63 days versus 42 days, number of relapses at one year
was 41% versus 17%).

Authors’ conclusions
In the treatment of alcohol dependence, both acamprosate and naltrexone modestly improve outcomes compared to
placebo. There was insufficient evidence to determine which drug is superior or to assess long-term efficacy.

CRD commentary
The objectives and inclusion criteria of the review were not entirely clear. Some of the included trials did not appear to
conform with the inclusion criteria (e.g. they did not include a placebo arm or comply with the pre-stated definition of
relapse). It was also unclear whether all trials included a psychosocial co-intervention (or whether they were required
to). Relevant sources were searched for studies without language restriction but it was not stated whether the search was
limited by publication status. No formal assessment of publication bias was reported. Steps were taken to minimise the
risk of bias and error in the process of validity assessment by having two reviewers make decisions independently; it is
unclear whether this also applied to study selection and data extraction. Relevant criteria appear to have been used to
assess study validity, but no details of individual trial results were presented, nor were any details provided about other
characteristics of individual trials. It was difficult to assess the reliability of the statistical methods used to combine
studies, as it was unclear what types of data were extracted from the primary trials or how different data types were
pooled. CIs were not reported for all findings. In addition, no formal assessment of statistical heterogeneity was
reported. This made it difficult to assess the reliability of the reported findings, especially as there were marked clinical
and methodological differences between the trials, notably in the type of outcome measures used. In view of poor
reporting of review methods, lack of information about individual trials and failure to evaluate statistical heterogeneity,
the authors’ conclusions may not be reliable.

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

Research: The authors stated that studies are needed comparing naltrexone with acamprosate as adjuncts to
psychosocial treatment, with both abstinence and relapse to heavy drinking as outcomes, with clearly defined inclusion
criteria for participants and thorough follow-up. The optimal treatment duration for naltrexone needs to be determined.
A stepwise trial of naltrexone followed by acamprosate could also be considered.

**Funding**
Not stated.

**Bibliographic details**

**PubMedID**
18584575

**DOI**
10.1080/00952990802082198

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adolescent; Adult; Aged; Alcohol Deterrents /therapeutic use; Alcoholism /drug therapy; Female; Follow-Up Studies; Humans; Male; Middle Aged; Naltrexone /therapeutic use; Narcotic Antagonists /therapeutic use; Randomized Controlled Trials as Topic; Single-Blind Method; Taurine /analogs & derivatives /therapeutic use

**AccessionNumber**
12008107137

**Date bibliographic record published**
03/02/2009

**Date abstract record published**
20/05/2009

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.