The efficacy of acamprosate in the maintenance of abstinence in alcohol-dependent individuals: results of a meta-analysis

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CRD summary
This review assessed the effect of acamprosate in the maintenance of abstinence in alcohol-dependent (and abusing) individuals. The authors concluded that acamprosate has a significant beneficial effect in enhancing abstinence. The authors' conclusions seem reasonable but, owing to the high drop-out rate in the included studies, assumptions regarding the outcome were made for many participants.

Authors' objectives
To assess the effects of acamprosate on abstinence in alcohol-dependent individuals.

Searching
Ten named databases were searched from January 1985 to April 2003; the search terms were given. No language restrictions were used. Some journals, symposia and conference proceedings were handsearched. The authors of the primary studies were contacted for additional data where necessary. The review authors also accessed Merck-Sante (manufacturer of acamprosate) internal trial reports of all European studies.

Study selection
Study designs of evaluations included in the review
Randomised placebo-controlled trials (RCTs) were eligible for inclusion. The studies also had to attain a Chalmers quality score of 50 to be retained in the analysis. All of the included studies were double-blinded.

Specific interventions included in the review
All of the studies included in the review compared acamprosate with placebo.

Participants included in the review
While no specific inclusion criteria were stated, it appears that to be eligible for the review the participants must have been recently detoxified alcohol-dependents. The actual participants included in the review were recently detoxified alcohol-dependents. Diagnoses were made using the 1987 and 1990 versions of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R and DSM-IV, respectively). According to these criteria, the proportion of participants classified as abusers (as opposed to dependent drinkers) ranged from 2 to 39% between studies. Most of the participants were between 20 and 60 years old (average age 43). The participants were predominantly male; the proportion of females ranged from 0 to 36%. Where reported, the proportion of participants who were married ranged from 28 to 79%. The average body mass index ranged from 23.3 to 25.1 kg/m2.

Outcomes assessed in the review
Studies that reported at least one quantitative measure of drinking behaviour were eligible for inclusion. The review authors specified continuous abstinence as the primary outcome measure used in this review. This was defined as abstinence from randomisation to study end. Since most of the studies were of 6 months' duration, continuous abstinence at 6 months was chosen as the primary end point. The secondary end points were:

- continuous abstinence at 3 and 12 months;
- point prevalence abstinence at 3, 6 and 12 months and at final study visit (defined as abstinence during the evaluation period immediately preceding the assessment point);
- the proportion of abstinent days over the total length of the study, estimated at 3, 6 and 12 months (cumulative abstinence duration proportion, CADP); and
the retention rate, calculated as the duration of patient participation compared with the expected length of the study.

No data for point prevalence at 3 months were reported in the review.

How were decisions on the relevance of primary studies made?
[A:Three reviewers independently assessed trials for relevance].

Assessment of study quality
The quality of the studies was assessed using a validated scale developed by Chalmers et al. (1981). This scale covered aspects of sample size, randomisation methods, methods to preserve blinding, selection and withdrawal criteria, outcome criteria and statistical analyses. The scores range from 0 to 100, with 100 representing the highest level of study quality. Validity judgements were made blind (to authors, place of study and journal identifiers) and independently by three reviewers, none of whom were involved in the conduct or analysis of any of the studies. Instead of resolving discrepancies, mean scores were calculated.

Data extraction
[A:Three reviewers extracted data from the individual trials].

Additional data were retrieved from the original study reports provided by the drug manufacturer, where required.

Data were extracted from the papers to allow an intention-to-treat analysis. Study withdrawals were considered treatment failures unless their participation was terminated because of the development of an adverse event. For the primary end point of continuous abstinence at 6 months, where necessary the data were recalculated to achieve a result for all studies. Where follow-up was terminated before 6 months, the result was calculated using the last observation carried forward methodology (LOCF). The CADP was also recalculated in order to standardise between studies.

Methods of synthesis
How were the studies combined?
The studies were combined in a meta-analysis. For continuous and point prevalence abstinence, estimates of efficacy were pooled using a random-effects model (DerSimonian and Laird), with weighting by the inverse of their variance. The effect size of CADP was estimated using the Hedges and Olkin parametric method of meta-analysis and the Kraemer and Andrews non-parametric method of meta-analysis. The results of the non-parametric method were reported if a more conservative estimate was achieved. The number-needed-to-treat (NNT) was also calculated from the difference in success rates. Potential publication bias was investigated using funnel plots and regression analysis.

How were differences between studies investigated?
A statistical test (unspecified) for heterogeneity was performed for the primary end point. Sensitivity analyses investigated the effect of: excluding trials of less than 6 months (which used LOCF methods); adding additional data from the drug manufacturer; and conducting the analysis on the per protocol population. Meta-regression was used to model the effect of sample size, diagnosis classification, age, gender and attrition rates on the primary end point.

Results of the review
Seventeen double-blind RCTs (4,087 participants) were included in the review.

No evidence of publication bias was reported. The trials scored between 65 and 83 on the Chalmers scale for study quality. Most aspects of trial design were well-executed. However, the drop-out rates were generally high (about 50%), and the proportion of individuals classified as abusers and dependent drinkers varied quite widely between trials (from 2 to 39%).

Treatment with acamprosate significantly increased continuous abstinence at 3, 6 and 12 months compared with placebo. The relative risk (RR) for continuous abstinence was 1.33 (95% confidence interval, CI: 1.20, 1.47) at 3 months and 1.47 (95% CI: 1.29, 1.69) at 6 months. However, whilst there was statistically significant variability
between trials for this result, no significant effects for the covariates of age, severity of dependence, attrition rates, gender, sample size or the finding of no beneficial treatment effect were found. At 12 months, data on continuous abstinence were available from 5 trials (1,670 participants). Acamprosate was found to have a beneficial effect in both an intention-to-treat analysis (RR 1.95, 95% CI: 1.58, 2.42) and a per protocol analysis (RR 1.73, 95% CI: 1.41, 2.11).

Point prevalence abstinence at 6 and 12 months was also improved with acamprosate. The RR was 1.40 (95% CI: 1.24, 1.59) at 6 months and 1.62 (95% CI: 1.37, 1.92) at 12 months.

CADP was also significantly improved with acamprosate at 3, 6 and 12 months.

For acamprosate, the NNT to achieve one beneficial outcome was 7.78 at 6 months and 7.5 at 12 months.

Retention rates were significantly higher in acamprosate than placebo treatment groups.

Authors' conclusions
Acamprosate had a significant beneficial effect in enhancing abstinence in recently detoxified alcohol-dependent individuals.

CRD commentary
Overall this was a well-conducted review. The inclusion criteria were clearly specified in terms of the interventions, outcomes and study designs. The literature search was thorough with efforts being made to minimise both publication and language bias. No details of how the studies were selected for the review, or how many reviewers performed the selection, were reported. It was therefore not possible to judge how much room for subjectivity and bias there was at the stage of selecting studies for the review. There was also no information on how the data were extracted for the review, or how many reviewers performed the data extraction. This makes it impossible to assess the risk of bias and error in data extraction. The quality of the primary studies was appropriately assessed. The review authors performed quite extensive manipulations and extrapolations of the data from the included trials, using LOCF methodology for continuous abstinence at 6 months, and standardising the estimate of CADP between trials. It was unclear how this might have affected the reliability of the estimates of treatment effect. However, when this was explored in a sensitivity analysis the result for continuous abstinence at 6 months was not changed. Further appropriate sensitivity analyses to explore the effect of different covariates was undertaken, with the results for continuous abstinence at 6 months remaining unchanged. A large proportion of the participants in the included trials were not available for assessment, and this may somewhat limit the robustness of the review results. However, methods used to handle missing data appear appropriate. Overall, the authors' conclusions seem reasonable, although it was not made clear that they related to alcohol abusers as well as dependents.

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

Research: The authors stated that further analytical work is needed to explain the disparities in effect sizes between studies; to explore the effect of treatment on retention rates; to identify potential predictors of treatment effect; and to assess the significance of possible interactions with treatment.

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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.