Acamprosate for alcohol dependence

Review information

Review No

34

Authors

Susanne Rösner[1], Andrea Hackl-Herrwerth[2], Stefan Leucht[2], Philippe Lehert[3], Simona Vecchi[4], Michael Soyka[1]

[1]Psychiatric Hospital, University of Munich, Munich, Germany

[2]Klinik und Poliklinik für Psychiatrie und Psychotherapie, Technische Universität München Klinikum rechts der Isar, München, Germany

[3]Statistics & Computer Sciences Dept, University of Mons, Mons, Belgium

[4]Department of Epidemiology, ASL RM/E, Rome, Italy

Citation example: Rösner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. Cochrane Database of Systematic Reviews 2003 , Issue 3 . Art. No.: CD004332. DOI: 10.1002/14651858.CD004332 .

Contact person

Susanne Rösner

Psychologist
Psychiatric Hospital
University of Munich
Nußbaumstr. 7
Munich
80336
Germany

E-mail: susanne.roesner@med.uni-muenchen.de
E-mail 2: susan.roesner@web.de

Dates

Assessed as Up-to-date: 30 July 2009
Date of Search: 31 January 2009
Next Stage Expected: 30 November 2010
Protocol First Published: Issue 3 , 2003
Review First Published: Not specified
Last Citation Issue: Issue 3 , 2003

What's new

Date	Event	Description
9 March 2010	Amended	comments from authors have been included

History

Date	Event	Description
23 January 2007	New citation: major change	Substantive amendment

Abstract

Background

Alcohol dependence is among the main leading health risk factors in most developed and developing countries. Therapeutic success of psychosocial programs for relapse prevention is moderate, but could potentially be increased by an adjuvant treatment with the glutamate antagonist acamprosate.

Objectives

To determine the effectiveness and tolerability of acamprosate in comparison to placebo and other pharmacological agents.

Search strategy

We searched the Cochrane Drugs and Alcohol Group (CDAG) Specialized Register, PubMed, EMBASE and CINAHL in January 2009 and inquired manufacturers and researchers for unpublished trials.

Selection criteria

All double-blind randomised controlled trials (RCTs) which compare the effects of acamprosate with placebo or active control on drinking-related outcomes.

Data collection and analysis

Two authors independently extracted data. Trial quality was assessed by one author and cross-checked by a second author. Individual patient data (IPD) meta-analyses were used to verify the primary effectiveness outcomes.

Main results

24 RCTs with 6915 participants fulfilled the criteria of inclusion and were included in the review. Compared to placebo, acamprosate was shown to significantly reduce the risk of any drinking RR 0.86 (95% CI 0.81 to 0.91); NNT 9.09 (95% CI 6.66 to 14.28) and to significantly increase the cumulative abstinence duration MD 10.94 (95% CI 5.08 to 16.81), while secondary outcomes (gamma-glutamyltransferase, heavy drinking) did not reach statistical significance. Diarrhea was the only side effect that was more frequently reported under acamprosate than placebo RD 0.11 (95% 0.09 to 0.13); NNTB 9.09 (95% CI 7.69 to 11.11). Effects of industry-sponsored trials RR 0.88 (95% 0.80 to 0.97) did not significantly differ from those of non-profit funded trials RR 0.88 (95% CI 0.81 to 0.96). In addition, the linear regression test did not indicate a significant risk of publication bias (p = 0.861).

Authors' conclusions

Acamprosate appears to be an effective and safe treatment strategy for supporting continuous abstinence after detoxification in alcohol dependent patients. Even though the sizes of treatment effects appear to be rather moderate in their magnitude, they should be valued against the background of the relapsing nature of alcoholism and the limited therapeutic options currently available for its treatment.

Plain language summary

Acamprosate for alcohol dependent patients

Alcohol dependence is an important health risk factor that can lead to disability and death for people in developed and developing countries. Alcohol consumption is potentially avoidable, which emphasizes the need for effective strategies to help people who are dependent on alcohol to reduce excessive drinking and maintain abstinence following detoxification. Psychosocial programs have limited success in preventing relapse after detoxification programs. The addition of a pharmacological agent could provide support in achieving or maintaining abstinence or to cut down alcohol consumption. The synthetic glutamate antagonist acamprosate and naltrexone, which is an opioid antagonist, are used for this purpose.

This systematic review shows that acamprosate appears to be an effective and safe treatment in alcohol dependent patients for supporting continuous abstinence after detoxification from alcohol. When added to psychosocial treatment strategies, acamprosate reduced the risk of returning to any drinking after detoxification compared with treatment with a placebo (number need to treat (NNT) for one person to benefit was nine). The cumulative abstinence time was also clearly increased. Return to heavy drinking did not change. Even though the size of the treatment effect was moderate, the benefit should be valued because of the relapsing nature of alcoholism and the limited treatment options that are currently available. Diarrhea was the most frequently reported side effect with acamprosate. Overall, side effects did not cause more participants to stop treatment when taking acamprosate compared with placebo.

These conclusions are based on 24 randomised controlled trials with 6915 participants who were treated as outpatients in all but one trial that involved adolescent inpatients. The majority of participants were men, median age 42 years. Most studies were conducted in Europe; two studies were conducted in the United States and one study in each of South Korea,Australia and Brazil. The effects of acamprosate did not differ in industry-sponsored and non-profit funded trials.

Three trials compared acamprosate and naltrexone and did not indicate a superiority of one or the other drug on return to any drinking, return to heavy drinking and cumulative abstinence duration.

Background

Appendix 1 shows the abbreviations used in the text

Description of the condition

Alcohol dependence is among the main leading health risk factors in most developed and developing countries (Alonso 2004). The one year prevalence of alcohol-use disorders in people aged between 15 to 64 years is estimated at 5.2% in the American Region, 5.5% in European countries and at over 10% in the Eastern European countries (Rehm 2009). According to the World Health Organisation (WHO 2002), the misuse of alcohol belongs to the globally leading health risk factors, causing 20-30% of oesophageal cancer, liver disease, epilepsy, motor vehicle accidents, homicide and other intentional injuries. In the year 2004, 3.8% of all global deaths and 4.6% of

global disability-adjusted life-years were attributable to alcohol (Rehm 2009). The costs attributable to alcohol consumption are estimated at more than 1% of the gross domestic products in high-income and middle-income countries (Konnopka 2007; Rehm 2009). At the same time, alcohol consumption belongs to major potentially avoidable health risk factors, underscoring the need for effective strategies to reduce excessive drinking and to support abstinence in patients who are dependent on alcohol.

Description of the intervention

Relapse prevention for alcohol dependence was exclusively dominated by psychosocial treatment strategies for many decades. Even though elaborated techniques from different theoretical and therapeutical backgrounds have been developed, treatment effects obtained by an exclusive application of psychosocial treatment are limited: A considerable high proportion of patients does not respond to the interventions at all and of those who respond, only a small portion succeeds in maintaining abstinence in a long-term perspective (Moos 2006).

With the investigation of the neurobiological mechanism of alcohol dependence, various pharmacological agents have been examined in their potential to support alcohol dependent patients in achieving abstinence or in cutting down their alcohol consumption. Some of these agents showed promising effects in first small size trials, but could not be confirmed by multicenter trials, while two substances were repeatedly shown to be effective: The opioid antagonist naltrexone and the glutamate antagonist acamprosate.

Acamprosate is a synthetic molecule with a chemical structure similar to that of the endogenous amino acid N-acetyl homotaurine (Zornoza 2003), a small, highly flexible molecule with analogy to many amino acids, most notably glutamate, gamma-aminobutyric acid, aspartate, glycine, and taurine (Spanagel 1997; Mann 2008). In animal models of alcohol dependence, acamprosate was shown to diminish the temporary increase in voluntary alcohol intake observed during a reinstated access to alcohol after a period of deprivation (Czachowski 2001; Heyser 1998; LeMagnen 1987;Olive 2002; Spanagel 1996) - the so-called "alcohol deprivation effect" (ADE), which serves as model of relapse. Besides its effects demonstrated in the limited access paradigm, acamprosate was shown to attenuate self-administration of alcohol under free-choice conditions (Spanagel 2003) and to inhibit the development of the conditioned place preference in rats (McGeehan 2003). It was also shown to selectively reduce alcohol-seeking behavior elicited by environmental stimuli predictive of alcohol availability (Bachteler 2005).

Until today, various clinical studies have been conducted, with the majority of trials demonstrating superiority of acamprosate compared to placebo. Indicated for the maintenance of abstinence in alcohol dependent patients, acamprosate was first mainly used in European Countries, but was approved by the US Food and Drug Administration (FDA) in 2004. It is meanwhile prescribed in 40 countries worldwide and in clinical use for more than 20 years.

How the intervention might work

Acamprosate's precise mechanism of action is still under investigation. Current evidence suggests a multiple mediation of effects, with modulations of the N-methyl-D-aspartic acid (NMDA) receptor, which was early identified as one central mode of operation (Zeise 1993), being still considered as the primary mechanism of action (Littleton 2003). Acamprosate acts as a partial co-agonist with enhanced functioning at low levels of endogenous activators, and inhibitation at high levels (Lipha 2002; Naassila 1998). The increased calcium influx through NMDA glutamate receptors during alcohol withdrawal induces a state of neuronal hyperexcitability associated with physical symptoms of withdrawal and an increased desire to start drink again. By inhibiting the calcium influx, acamprosate is restoring the balance between inhibitory and excitatory neurotransmitters. Besides its effects on acute withdrawal, acamprosate additionally attenuates conditioned reactions ("pseudo-withdrawal") and opponent processes associated with drinking related cues (Cole 2000; Littleton 1995), the latter explaining the potency of the substance to prevent a relapse after physical symptoms of withdrawal have disappeared. Evidence suggests that besides its effects on withdrawal-related processes, acamprosate's reductive effect on drinking is also attributable, at least in part, to its potential to reduce rewarding effects of alcohol (Cano-Cebrian 2003; McGeehan 2003).

Why it is important to do this review

Acamprosate has already been subject to various meta-analyses, which indicate small to moderate, but significant effects of the substance in maintaining abstinence in alcohol dependent patients (Berglund 2003; Bouza 2004; Chick 2003; Hopkins 2002; Kranzler 2001; Mann 2004; Rosner 2008; Schoechlin 2000). Within the last years, the primary database for acamprosate has been extended and some of the newer trials partly differ from the previous research in terms of the study design, the trial setting and the source of financial sponsoring. Thus, an update of the database by integrating newer acamprosate trials is likely to increase the validity of conclusions. Besides the statistical integration of primary effects, a systematic assessment of bias risks allows to discuss the demonstrated effects against the background of methodological considerations.

The present review is the first review on acamprosate undertaken within the framework of the Cochrane Collaboration. Available Cochrane reviews on alcoholism treatment evaluate 12-step programmes for alcohol dependence (Ferri 2006), brief interventions for heavy alcohol users admitted to general hospital wards (McQueen 2009) and for primary care populations (Kaner 2007) as well as opioid antagonists for the treatment of alcohol dependence (Srisurapanont 2005).

Objectives

To determine the effectiveness and tolerability of acamprosate in comparison to placebo and other pharmacological agents.

Methods

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) with a double-blind design, which compare the effects of acamprosate (monotherapy and combined therapy) with placebo or active control (other pharmacological treatments for alcohol dependence) on drinking-related outcomes. Randomization was required to be restricted to procedures which consider the individual patient as the unit of allocation, excluding group or cluster randomisation studies. Cross-over and multi-phase designs were only considered if medication-free periods ensured the washout of previous treatments.

Types of participants

Individuals with alcohol dependence according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders (*DSM) or the *International Statistical Classification of Diseases* (ICD) irrespective of any other characteristics. Patient samples including both, patients with alcohol dependence and alcohol abuse, were only included if patients with alcohol dependence constituted the majority of the sample (>50%).

Types of interventions

1. Experimental intervention: acamprosate
2. Control interventions: placebo; other pharmacological treatments for alcohol dependence.

A minimum treatment duration of four weeks was required to ensure an adequate implementation of the intervention. Any dose, any mode of administration and any combination of therapies was included.

Types of outcome measures

The selection of the primary and secondary outcomes of the review was constituted in consideration of the availability of outcomes, their clinical relevance and their theoretical and conceptual foundation (Keller 1972).

The study end-points of the primary effectiveness outcomes were considered as constitutive for effectiveness conclusions, while the secondary effectiveness outcomes had only complementary value in the interpretation of results. The primary end-points were evaluated with both, meta-analyses based on literature (MAL) and individual patient database (IPD) analyses, while secondary outcomes were exclusively estimated on the base of MAL. For reasons of clarity and conciseness, post-treatment evaluations were restricted to the primary outcomes of the review. Rates of drop-out and drop-out due to side effects were discussed as potential moderators of effect sizes, but were not included in the evaluation of effectiveness.

Primary outcomes

1. Return to any drinking
2. Cumulative abstinence duration.

Return to *any drinking* (complementary event: continuous abstinence) was considered as the primary endpoint for most of the previous RCTs and meta-analyses on acamprosate. It is a binary variable containing the information whether a patient returned to drinking after detoxification, or whether a patient remained fully abstinent. The *cumulative abstinence duration (CAD)* is the total sum of days a patient remained abstinent in the course of a trial (including continuous as well as interrupted abstinence intervals) related to the entire duration of the study, multiplied with the factor 100. To allow clinically relevant conclusions on treatment stability, post-treatment evaluations (follow-up after treatment termination) had to include at least 12 weeks of observation.

Secondary outcomes

1. Return to heavy drinking;
2. Gamma-glutamyl transpeptidase (GGT)
3. Side effects.

Heavy drinking was considered as predetermined by the definitions in the clinical trials. *Gamma-glutamyl transpeptidase* (GGT) levels were uniquely transformed into "units per liter". All side effects presented in the trial publications were extracted, while only those with significant group differences were considered as clinically relevant.

Search methods for identification of studies

Electronic searches

The electronic search was conducted using the following bibliographic databases in descending order:

- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* issue 2 2009) which also contains the Cochrane Drugs and Alcohol Group's Trials Register;

- MEDLINE (from 1966 to January 2009);
- EMBASE (from 1988 to January 2009);
- CINAHL (from 1982 to January 2009).

Search strategies were developed and applied by the trial search coordinator (SV) of the Cochrane Drugs and Alcohol Group (CDAG). For the MEDLINE search, the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE (sensitivity maximizing version) was applied as outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Lefebvre 2008). No operators and no restrictions in language, date, gender, age or tag terms were used. Search strategies for further databases were invariably based on the strategy developed for MEDLINE but revised for the specific requirements of each database.

Details of the search strategies are provided in Appendix 2.

We searched for ongoing clinical trials and unpublished studies via Internet on the following sites:

1. http://www.controlled-trials.com;
2. http://clinicaltrials.gov;
3. http://www.clinicalstudyresults.org;
4. http://www.centrewatch.com

For relevant trials with a completion data before 30 April 2009, the principal investigators were contacted and requested to provide reports, manuscripts or unpublished results in advance.

Searching other resources

Key informants, experts, public sponsors and the drug manufacturer, Merck Serono (Geneve), were contacted with the request to indicate further studies of potential relevance. For this purpose, reference lists with identified studies and criteria of inclusion and exclusion of the review were provided. Finally, hand searching of reference lists of included studies and current reviews was conducted to complete and to verify the preceding searches.

Data collection and analysis

Selection of studies

The eligibility and relevance of trials was assessed on the base of their abstracts retrieved from the electronic searches. For studies that met the criteria of inclusion according to the abstract information, full text versions were retrieved for a closer inspection in a second step of the study selection. On their base, the relevance and eligibility of studies was assessed by one author (SR), in case of uncertainties a author (AH) was consulted. The process of study identification and its results are outlined as a flow diagram (Figure 1) according to the PRISMA statement (Moher 2009).

After request, the manufacturer Merck Serono (Geneve) provided unconditioned access to a database with individual patient data (IPD) on acamprosate. The set of studies identified with the search strategies described above was compared with the study base of the IPD file. For studies, not included in the IPD file, investigators were contacted and requested to provide access to the raw data bases.

Data extraction and management

Aggregated data extraction and management

Information considered in the study tables was extracted by one author (SR) and cross-checked by a second author (AH), while outcome statistics were coded from the study reports by two authors (SR & AH) parallel and independently. If necessary, extracted statistics were standardized and converted for the meta-analyses, including a) the application of the intention-to-treat (ITT) principle on binary outcome data in studies which have not considered this principle in their primary analyses; b) the pooling of outcome data provided for patients subgroups or different dosage forms and c) the standardization of units of the measurement. If the alcohol content of standard drink units (SDUs) was not specified in the trial publications, country-specific values as provided by the International Drinking Guidelines (ICAP 2003) were applied. All outcome statistics and calculation steps were entered into electronic data templates (Microsoft Excel) and compared value by value. In case of disagreements, the following sequential procedures were undertaken in descending order:

1. comparison of published and extracted information to identify transcription and comprehension errors;
2. explication of the coding decisions by each reviewer, followed by consensus discussion and arbitration.

Finally, after comparisons and corrections were concluded, data were transformed into Review Manager 5 (The Nordic Cochrane Centre 2008).

Individual patient data (IPD) acquisition and management

The IPD base on acamprosate, which was used to additionally assess the primary outcomes of the review on the base of non-aggregate data, has been established in the course of a collaborative, multistage research project, started in 2005 and initiated from the Plinius Major Society, a private initiative of European alcoholism investigators. The database is constituted on raw data files, which were obtained from the primary study investigators and data centres in the course of the research project. Computerized data entry files, which were available in various mainframe formats and various devices, were combined in the course of a standardization process. Data checking against the original case report forms (CRFs) was performed, using a so-called "military standard control"-process, based on the assessment of a random sampling of values of the file. In this test, the

acceptable quality level (AQL) was fixed to a value of AQL =0.001 for main endpoints. Data transferred from the original data files to the centralized IPD base included study specific dates (e.g. date of publication), patient characteristics (e.g. age, sex, weight, marital status) and various outcome statistics. The harmonization of the raw data files was conducted by a team of researchers, familiar with the clinical guidelines in the respective countries in which the trials have been conducted. The funds for establishing and maintaining the database were coming from non-industry national grants as well as a grant from Merck Serono (Geneve), which provided unconditioned access to the data for the purpose of the review. The database was updated according to the study set identified with the study search for the review (Search methods for identification of studies).

Assessment of risk of bias in included studies

The risk of bias was assessed in accordance with the *Cochrane Collaboration's risk of bias assessment tool* (Higgins 2008). Besides the bias domains prespecified by the tool, the risk of *baseline imbalance* and *differential medication compliance* were considered as further bias risks (item "free of other bias").

Risk of bias tables were completed by one author (SR) and cross-checked by a second author (AH). Methods for bias control were only considered as applied, if these were adequately described in the study publication or the informal investigator report. Otherwise the associated bias risk was rated as "uncertain". The following criteria were considered as constitutive for the rating of bias risks:

Sequence generation (Selection bias)

Methods used for *sequence generation* were rated as adequate if based on a random process, which is providing an equal chance for every study participant to be assigned to each of the treatment conditions. In contrast, methods that would permit any prediction of assignment in advance (e.g. sequence generation by day of birth), were considered as inadequate.

Allocation concealment (Selection bias)

Strategies applied for *allocation concealment* were considered as adequate if a) randomisation and drug preparation was undertaken centralized and remote from patient recruitment centres; AND if b) allocation codes were protected against identification by the use of sealed randomisation envelopes.

Blinding (Detection bias, performance bias)

Blinding was rated as adequate, if a) at least patients and research staff were specified as being included in the blinding procedures; AND if b) active medication and placebo were of identical appearance. If different active substances were used within one study, a double-dummy design was required. For studies, which checked and confirmed the integrity of blinding at the end of the treatment, blinding was rated as adequate irrespective of the criteria outlined above.

Handling of incomplete outcome data (Attrition bias)

Handling of incomplete outcome data was considered as adequate if a) all randomised patients or at least those who have received at least one dose of treatment were included in the statistical analyses; AND if b) the methods of handling drop-outs or lost to follow-ups adequately considered the association between attendence to study visits and drinking status, either by generally assigning missing participants to the relapse category (substitution by "worst case") or by analysing the pattern of missingness (e.g. pattern-mixture analyses). The handling of incomplete outcome data was rated separately for binary and continuous outcomes; for reasons of clarity and conciseness, the summary rating of the attrition bias risk was restricted to the primary effectiveness outcomes only.

Selective reporting (Reporting bias)

A trial publication was considered as free of *selective reporting* if all outcomes listed in the protocol or the methods section of the publication were adequately reported in the results section.

Other bias

A study was rated as being "free of other bias" if baseline equivalence between groups and equivalence of medication compliance were ensured:

Baseline equivalence (Selection bias)

Baseline equivalence was rated as being equivalent between groups, if treatment groups were compared in potentially effect-determining baseline characteristics (age AND gender AND baseline drinking AND (drinking OR treatment history)). If differences between groups became evident, these had be adequately controlled in the statistical analyses.

Treatment exposure (Performance bias)

Treatment groups were considered as *equally exposed* to interventions, if they were shown not to significantly differ in medication compliance.

Funding bias

The risk of funding bias was assessed by comparing the "risk for return to any drinking" between trials that a) were sponsored, organized and conducted by the pharmaceutical industry, b) have received grants and facilities

by the manufacturer, who has not been involved in the study management and data analyses and c) were investigator-driven and completely non-profit funded.

Publication bias

The risk of publication bias was graphically and statistically examined as outlined in the section Assessment of reporting biases.

Measures of treatment effect

Treatment effects of acamprosate on dichotomous effectiveness outcomes were measured by risk ratio (RR), relating the risk of any drinking or heavy drinking observed in the intervention group to the corresponding risk in a reference group. Risk differences (RD) between treatment groups were calculated to assess side effects. Treatment effects on continuous outcomes (cumulative abstinence duration, gamma-glutamyl transpeptidase) were measured by mean differences (MD) of standardized units. For all treatment effects, 95% confidence intervals (CI) were provided. For binary outcomes with statistical significance, the numbers needed to treat for an additional beneficial outcome (NNTB) and the numbers needed to treat for an additional harmful outcome (NNTH) were calculated as the inverse of the absolute risk reduction (ARR). A P value of 0.05 and below was chosen to indicate the statistical significance of effects.

Unit of analysis issues

Only parallel group designs were considered in the review and from repeated measurements, only one time-point (study endpoint) was included in the evaluation of effectiveness. Thus, the unit of allocation invariably corresponds to the unit of analysis.

Dealing with missing data

For the analyses of binary outcome data (return to any drinking, return to heavy drinking), all randomised patients were included in the statistical analyses, with drop-outs or lost to follow ups being assigned to the relapse category.

For the MAL analyses of continuous effectiveness outcomes (cumulative abstinence duration, GGT), means and standard deviations were included as provided by the study publications irrespective of the handling of missing data in the primary analysis. For IPD analyses of cumulative abstinence duration, any time between the last study visit of an early terminating patient and the end of the trial was considered as a non-abstinent interval (irrespective of the reasons for dropping out) and related to the entire study duration.

Assessment of heterogeneity

Inconsistency across studies was quantified with the I^2-statistic (Higgins 2003), using a variability of 50% as the threshold value for substantial heterogeneity (Deeks 2008) and the Tau^2-statistic for providing an estimate of between-study variance (Rucker 2008) independent of the sample size.

Assessment of reporting biases

The risk of publication bias was graphically illustrated with the funnel plot method (Light 1984) and statistically examined with a linear regression test (Egger 1997), determining the linear regression coefficient between log odds ratio (OR) and its standard error for "return to any drinking". The linear regression test was performed non-weighted and weighted by precision. The risk of outcome reporting bias (Pocock 1987; Tannock 1996; Chan 2004; Williamson 2005) was not quantitatively analysed, but considered in the discussion of results.

Data synthesis

For synthesizing aggregate outcome measures, a random-effects model (DerSimonian 1986) was chosen according to the recommendation of Brockwell 2001, with study effects being weighting with the Mantel-Haenzel approach (Mantel 1959). For outcomes with low effect heterogeneity ($I^2 < 30\%$), a fixed effect model was additionally applied within the scope of sensitivity analyses.

IPD analyses were carried out using a multi-level one-stage approach (Riley 2007). For continuous outcome data, a two-level model including study-level and patient-level, with random treatment effects and fixed study effects was applied (Higgins 2001). Analyses of binary outcomes were conducted within the multilevel framework as introduced by Turner 2000. IPD analyses were performed with the "R" statistical package (version 2.6.2).

Subgroup analysis and investigation of heterogeneity

Subgroup analyses

Due to the low availability of subgroup outcomes in the trial publications, subgroup analyses could not be conducted on a meta-analytic level of evidence.

Investigation of heterogeneity

As a preliminary exploration of heterogeneity indicated a low statistical power due to the high missing rates for selected design characteristics (e.g. quality of blinding, allocation concealment, handling of missing outcome data), which were foreseen as predictors in the regression model as well as the high sensitivity of the results to the presumptions of the model, the authors of the review decided to obtain the missing information from the

investigators and to deliver the meta-regression at a later stage.

Sensitivity analysis

Sensitivity analyses were conducted to determine the influence of the underlying statistical model, by comparing effect sizes for low heterogeneity outcomes (I^2 < 30%) calculated on the base of random effects models versus fixed effect models.

Results

Description of studies

Results of the search

The study search for the review yielded 414 potentially relevant references, of which 384 were identified through bibliographic databases and 30 through other sources (personal communication: n = 1, database of ongoing trials: n = 29). 203 of the 414 identified references were identified as duplicates and removed. The remaining 211 records were screened and 163 records were excluded on the base of the information provided in the abstracts. For the remaining 48 records, full-text articles were obtained and on their base, another 24 studies were excluded. Reasons for exclusions was an open study design (n = 12), the missing of a control group (n = 5), a treatment duration below 30 days (n = 4), a non-dependent study sample (n = 1), a cross-over design (n = 1) and a single-blinded design. Finally 24 RCTS were considered as eligible for the review and included in the meta-analyses. The steps of trial identifying and their results are outlined in Figure 1 as flow-diagram according to the PRISMA statement (Moher 2009).

Included studies

A total of 24 RCTs with 6894 patients were included in the review. Of those, 3563 patients were treated with acamprosate, 2929 patients with placebo and 402 with naltrexone.

Comparisons

In 18 of the 24 RCTs, which met the inclusion criteria of the review, patients were either randomised to acamprosate or to placebo. Four trials included three treatment arms, comparing different dose regimes of acamprosate with each other and with placebo (Mason 2006; Paille 1995; Pelc 1997) or comparing acamprosate with placebo and the opioid antagonist naltrexone (Morley 2006). Two studies were based on a four-armed design (Anton 2006; Kiefer 2003), considering acamprosate monotherapy, naltrexone monotherapy, placebo and a combined treatment with naltrexone and acamprosate.

Patients

To participate in a clinical study, patients were required to fulfil the criteria of alcohol dependence (according to DSM-III-R, DSM-IV or ICD-10) and to have a minimum age of 18 years, apart from one study (Niederhofer 2002), which examined acamprosate`s effectiveness in a sample of adolescent patients. In the remaining studies, the mean age of the sample varied between 40 and 47 years, with a median of 42 years. Two studies included patients with alcohol dependence and alcohol abuse (Morley 2006; Rousseaux 1996). Samples were mostly of mixed gender, with men constituting the majority, while two trials (Baltieri 2003; Borg 2003) exclusively included male patients.

Funding and design

11 of the 24 RCTs (Barrias 1997; Borg 2003; Chick 2000; Geerlings 1997; Gual 2001; Lhuintre 1985; Mason 2006 ; Namkoong 2003; Pelc 1992; Rousseaux 1996; Sass 1996) were sponsored, organized and conducted by the pharmaceutical industry within the scope of new drug application processes, while six studies have received grants and facilities by the manufacturer, who was not involved in the management, analyses, and interpretation of data (Besson 1998; Ladewig 1993; Lhuintre 1990; Poldrugo 1997; Tempesta 2000; Whitworth 1996) and seven trials were investigator-driven research (ICDR) with non-proft funding (Anton 2006; Baltieri 2003; Kiefer 2003; Morley 2006; Niederhofer 2002; Paille 1995; Pelc 1992). 18 of the 24 RCTs included in the review used a multicenter design, 6 trials (Baltieri 2003; Borg 2003; Kiefer 2003; Lhuintre 1985; Niederhofer 2002; Rousseaux 1996) a single-center design. Sample sizes varied from 10 patients (Borg 2003) to 1383 patients (Anton 2006), with the COMBINE-study (Anton 2006) being the largest trial included in the review. Treatment was provided in outpatient settings, with the exception of one trial (Niederhofer 2002), which provided treatment on an inpatient base. Psychosocial treatment was concurrently applied, but not specified in most trial publications. In multi-centre trials, psychosocial treatment was applied centre-specific (Chick 2000; Geerlings 1997; Barrias 1997; Besson 1998; Paille 1995). In eight studies (Baltieri 2003; Barrias 1997; Besson 1998; Chick 2000; Mason 2006; Namkoong 2003; Pelc 1997; Tempesta 2000) patients were additionally encouraged to participate in Alcoholics Anonymous (AA) groups.

Countries in which the studies were conducted

Most studies (n = 19) were conducted in Europe, two studies were conducted in the United States (Anton 2006; Mason 2006) and one study each in South Korea (Namkoong 2003), Australia (Morley 2006) and Brazil (Baltieri 2003).

Treatment regimen and duration

Before treatment, patients were detoxified, whereby a minimum of 3 to 7 days of continuous abstinence was required to enter randomisation with the exception of two studies (Kiefer 2003; Sass 1996), which demanded 12 days and 14 days of baseline abstinence and one study (Mason 2006), which did not require detoxification at all. In this study, about half of the sample was actively drinking before treatment started.

One trial started with a placebo run-in week (Chick 2000) and in the study of Gual 2001, acamprosate was prescribed from the start of the alcohol withdrawal phase. At the beginning of the treatment, patients were randomly assigned to either intervention or control. Treatment was applied in a double-blind fashion and in the course of the study, drinking-related outcomes and side effects were repeatedly measured.

Most studies dosed acamprosate weight dependent, providing a daily dose of 1332 mg to patients with a body weight lower than 60 kg and 1998 mg to those who weighted more than 60 kg (Barrias 1997; Besson 1998; Ladewig 1993; Namkoong 2003; Pelc 1992; Poldrugo 1997; Sass 1996; Whitworth 1996). With 1332 mg acamprosate per day, dosing was lowest in the studies of Lhuintre 1990 and Niederhofer 2002, while the highest doses of 3000 mg were applied in the US trials (Anton 2006; Mason 2006). Lhuintre 1985 gave one capsule per 10 kg body weight, keeping a minimum dose of 1000 mg and a maximum dose of 2250 mg. In three studies, high dose regimes of 3000 mg per day (Mason 2006) or low dose regimes of 1332 mg per day (Paille 1995; Pelc 1997) were tested against the standard dose of 1998 mg, respectively 2000 mg.

Treatment duration varied from eight weeks (Namkoong 2003) to one year (Barrias 1997; Besson 1998; Paille 1995; Sass 1996; Whitworth 1996), with a duration of six months being most common (Borg 2003; Chick 2000; Geerlings 1997; Gual 2001; Ladewig 1993; Mason 2006; Niederhofer 2002; Pelc 1992; Poldrugo 1997; Tempesta 2000).

Outcomes

The most frequently considered outcome was “return to any drinking” (or its complementary event "continuous abstinence"), available for 24 RCTs, followed by cumulative abstinence duration, available for 19 RCTs. The secondary outcomes of the review, "return to heavy drinking" and GGT values were less frequently provided; anyhow, information on these outcomes was available for six trials (heavy drinking: Anton 2006; Chick 2000; Kiefer 2003; Mason 2006; Morley 2006; Namkoong 2003) and seven trials (GGT: Kiefer 2003; Lhuintre 1985; Lhuintre 1990; Namkoong 2003; Paille 1995; Rousseaux 1996; Sass 1996). Most of the outcome information was available from the trial publications with the following exceptions: "Return to any drinking”-rates were extracted from the manufacturer report for three trials (Lhuintre 1990; Mason 2006; Tempesta 2000) and subsequently provided by the investigator (Anton 2006) and the study sponsor (Borg 2003) for one trial at a time; cumulative abstinence duration was extracted the manufacturer report in the case of three trials (Barrias 1997; Ladewig 1993; Chick 2000) and provided by the sponsor for one trial (Borg 2003). Post-treatment "return to any drinking", available for 7 RCTS (Baltieri 2003; Geerlings 1997; Ladewig 1993; Paille 1995; Sass 1996; Tempesta 2000; Whitworth 1996) and post-treatment cumulative abstinence duration, available for 9 RCTs (Anton 2006; Barrias 1997; Geerlings 1997; Ladewig 1993; Paille 1995; Poldrugo 1997; Sass 1996; Tempesta 2000; Whitworth 1996), was exclusively extracted from trial publications.

For the definition of heavy drinking, a cut-off value of five SDUs was chosen in most studies (Anton 2006; Chick 2000; Kiefer 2003; Namkoong 2003), one trial (Morley 2006) considered six drinks as critical threshold for heavy drinking. Kiefer 2003 also assigned patients to the heavy drinking category if drinking occurred on five or more days a week.

Methods of data assessment

Assessment of drinking was mostly based on retrospective quantity/ frequency reports (Chick 2000; Kiefer 2003; Mason 2006; Morley 2006; Pelc 1997; Sass 1996; Tempesta 2000; Whitworth 1996) or drinking cards (Chick 2000; Kiefer 2003; Mason 2006; Morley 2006; Pelc 1997; Sass 1996; Tempesta 2000; Whitworth 1996), on which patients were to record drinking patterns and drinking amount on a daily basis. Four studies (Anton 2006; Mason 2006; Morley 2006; Namkoong 2003) assessed drinking with the Time Line Follow-Back method (Sobell 1988; Sobell 1992), a semi-structured interview that uses calendar format to record the quantity and frequency of drinking.

For 17 of 24 RCTs, patient-reported drinking was validated by objective measures. To verify patients` self reports, GGT values were used in most studies (Besson 1998; Gual 2001; Ladewig 1993; Lhuintre 1985; Niederhofer 2002; Mason 2006; Paille 1995; Poldrugo 1997; Sass 1996; Whitworth 1996). Alternatively, Anton 2006 and Tempesta 2000 used carbohydrate-deficient transferrin (CDT) as a validity check for self-reported drinking data, Lhuintre 1985, Niederhofer 2002 and Whitworth 1996 used the mean corpuscular volume (MCV), Chick 2000; Kiefer 2003; Mason 2006; Namkoong 2003 and Sass 1996 the breath alcohol concentration, Chick 2000; Kiefer 2003; Morley 2006 and Pelc 1997 the urine alcohol concentration and Mason 2006; Sass 1996 and Whitworth 1996 used collateral reports.

To systematically assess side effects, checklists (Barrias 1997; Kiefer 2003; Ladewig 1993; Niederhofer 2002; Lhuintre 1990; Pelc 1992; Tempesta 2000), an open ended inquiry (Morley 2006), a rating scale (Baltieri 2003) and the Systematic Assessment for Treatment Emergent Effects (SAFTEE) developed by Levine 1986 and Rabkin 1992 were used (Anton 2006; Namkoong 2003).

Compliance was assessed by pill count in most trials (Anton 2006, Besson 1998; Chick 2000, Geerlings 1997, Gual 2001; Kiefer 2003, Mason 2006; Morley 2006; Namkoong 2003; Paille 1995; Pelc 1992; Pelc 1997; Sass

1996; Tempesta 2000), in one study (Mason 2006), acamprosate plasma levels were examined to validate compliance estimates based on pill count. Post-treatment drinking status was assessed at intervals of 3 months (Baltieri 2003; Kiefer 2003; Tempesta 2000), 6 months (Barrias 1997; Geerlings 1997; Ladewig 1993; Poldrugo 1997) and 12 months (Anton 2006; Besson 1998; Sass 1996; Whitworth 1996) after treatment was discontinued.

Excluded studies

24 trials were excluded on the basis of their full-text versions. Reasons for exclusion was the use of an open label study design in 12 studies (Buri 2007; Croissant 2006, de Sousa 2005, Florez 2008, Fuchs 2002, Kampman 2009, Kiritze-Topor 2004, Laaksonen 2008, Nespor 2006, Pelc 2002; Rychlik 2001; Soyka 2002), the lack of placebo or active control group in five studies (De Wildt 2002; Feeney 2002; Hammarberg 2004; Han 2008; Reid 2005), a treatment duration below 30 days in four studies (Boeijinga 2004; Johnson 2003; Ooteman 2007; Staner 2006), a study sample of non-dependent drinkers (Mason 2002), the non-availability of data from the first treatment period in a cross-over design (Gerra 1992) and the use of a single-blind design (Rubio 2001). Results after treatment were excluded because of a post-treatment duration of 4 weeks (Chick 2000) and 8 weeks (Mason 2006) and the use of a single-blind placebo design (Paille 1995).

Risk of bias in included studies

See Figure 2, Figure 3

Allocation

Sequence generation

For 6 of the 24 RCTs included in the review (Anton 2006; Kiefer 2003; Morley 2006; Namkoong 2003; Niederhofer 2002; Whitworth 1996), the methods used for sequence generation were specified in the trial publications. All of the reported strategies were considered as adequate: Five trials (Kiefer 2003; Morley 2006; Namkoong 2003; Niederhofer 2002; Whitworth 1996) have used computer-generated randomisation lists to create random sequences and in one study (Anton 2006), an interactive voice response system was applied. For the remaining 18 RCTs, methods used for sequence generation were not reported and remained unclear.

Allocation concealment

3 of 24 RCTs included in the review (Kiefer 2003; Mason 2006; Morley 2006) met both criteria of adequate allocation concealment (centralized randomisation and drug preparation, sealed envelopes). Randomization was described as centralized and conducted by an independent support unit remote from patient recruitment centres in four trials (Anton 2006; Kiefer 2003; Mason 2006; Morley 2006), while in three of these trials (Kiefer 2003; Mason 2006; Morley 2006), drug containers were additionally described as being prepared by an independent pharmacy. The second criteria for adequate allocation concealment, the use of sealed envelopes, was reported in six trials (Kiefer 2003; Mason 2006; Morley 2006; Sass 1996; Tempesta 2000; Whitworth 1996).

Blinding

From the 24 RCTs included in the review, 7 RCTs (Anton 2006; Kiefer 2003; Mason 2006; Morley 2006; Namkoong 2003; Paille 1995; Rousseaux 1996) fulfilled both criteria of adequate blinding (blinding of patients and research stuff, identically matched placebo). 13 trials reported to have used placebo and active medication with identical appearance (Anton 2006; Baltieri 2003; Barrias 1997; Besson 1998; Chick 2000; Kiefer 2003; Lhuintre 1990; Mason 2006; Morley 2006; Namkoong 2003; Paille 1995; Poldrugo 1997; Rousseaux 1996) and seven of these trials (Anton 2006; Kiefer 2003; Mason 2006; Morley 2006; Namkoong 2003; Paille 1995; Rousseaux 1996) have additionally specified patients and research stuff as being included in the double-blinding procedures. Two trials (Kiefer 2003; Morley 2006) additionally tested and confirmed the integrity of blinding by inquiries on patients and therapists. In studies with an active control group (Anton 2006; Kiefer 2003; Morley 2006), blinding was ensured with a double-dummy design signifying that an identically matched placebo was available for each drug, and participants in each group took the same number of pills per day.

Incomplete outcome data

Binary outcomes

The handling of missing binary data was considered as adequate for 19 of the 24 RCTs. In these trials, all randomised patients or at least those who received treatment, were included in the data analysis and assigned to the relapse-category. The problem of incomplete binary outcome data was considered as inadequately addressed in two trials, which either excluded patients who dropped out early (Lhuintre 1985) or which only considered those who had at least one outcome criteria available (Mason 2006). Bias risks were rated as "uncertain" in three trials, which did not provide information on the handling of missing binary outcome data (Anton 2006; Borg 2003) or which classified drop-outs according to the reason of their drop-out (Besson 1998).

Continuous outcomes

For 13 of the 19 RCTs, which considered cumulative abstinence duration as an outcome, the handling of missing data was considered as adequate. If a patient was absent from a study visit or reported any alcohol use during a given study period, the complete interval was coded as a non-abstinent period for cumulative abstinence duration calculation in these trials. Bias risks were rated as "unclear" in six trials, which did either not provide any information on how missing abstinence durations were handled (Borg 2003; Chick 2000, Kiefer 2003; Namkoong

2003) or which only rated the drop-out interval as non-abstinent, if the early discontinuation was verified to be unrelated to alcohol use (Mason 2006; Besson 1998).

The handling of missing GGT values was rated as inadequate for one trial (Lhuintre 1985), which excluded missing participants. For the remaining trials (Kiefer 2003; Lhuintre 1990; Namkoong 2003; Paille 1995; Rousseaux 1996; Sass 1996), the handling of missing end-point GGT remained unclear.

Selective reporting

The comparison between prespecified and presented outcomes did not indicate inconsistencies for any of the included studies.

Other potential sources of bias

13 of 24 RCTs included in the review (Anton 2006; Barrias 1997; Chick 2000; Gual 2001; Kiefer 2003; Lhuintre 1985; Mason 2006; Morley 2006; Namkoong 2003; Poldrugo 1997; Sass 1996; Tempesta 2000; Whitworth 1996) were considered as "free" of other potential sources of bias, ensuring the equivalence of baseline characteristics (age, gender, baseline drinking, drinking or treatment history) and the equivalence of medication compliance between groups. For the remaining 11 RCTs, the risk of other potential sources of bias remained "unclear".

Publication bias

Plotting of log odds ratio for "return to any drinking" and its standard error showed a slight asymmetry with a gap in the bottom corner of the graph *see* Figure 4 or Analysis 5.1, while the linear regression test (Egger 1997) did not indicate a considerable risk of publication bias, neither for the non-weighted regression (R^2 = 0.23; p = 0.342; SE = 1.440; n = 25) nor for the weighted regression (R^2 = 0.46; p = 0.861; SE = 1.412; n = 25), *see* Figure 4

Founding sources

Synthesis of effects "return to any drinking" according to their sponsoring indicated the highest magnitude of effects for partially industry-supported trials RR 0.84 (95% CI 0.78 to 0.89), the lowest magnitude for fully industry-sponsored trials RR 0.88 (95% CI 0.80 to 0.97) and a value in between for non-profit sponsored, investigator-driven trials RR 0.86 (95% CI 0.81 to 0.91), *see* Figure 5 or Analysis 5.1.

Effects of interventions

Comparison 1: Acamprosate versus placebo

Primary outcomes

Return to any drinking: A statistically significant difference was shown between groups; acamprosate reduced the risk to return to any drinking after detoxification to 86% of the risk in the placebo group, RR 0.86 (95% CI 0.81 to 0.91) *see* Analysis 1.1 or Figure 6. The numbers needed to treat for an additional prevention of drinking was estimated at NNTB 9.09 (95% CI 6.66 to 14.28).

Cumulative abstinence duration: A statistically significant difference was shown between groups; acamprosate on average increased the cumulative abstinence duration by 11% compared to placebo, MD 10.9 (95% CI 5.08 to 16.81) *see* Analysis 1.2 or Figure 7.

Secondary outcomes

Return to heavy drinking: No statistically significant difference was shown between groups; the risk to return to heavy drinking was 1% lower in the acamprosate group than in the placebo group, RR 0.99 (95% CI 0.94 to 1.04) *see* Analysis 1.3.

GGT: No statistically significant difference was shown between groups; acamprosate was associated with a reduction of the GGT by about 12 units per liter compared to placebo, MD -11.91 (95% CI -24.12 to 0.30) *see* Analysis 1.4.

Side effects: Among 38 side effects, only diarrhoea was more frequently reported under acamprosate than under placebo, RD 0.11 (95% CI 0.10 to 0.13) *see* Analysis 1.5. The numbers needed to treat for an additional case of experiencing diarrhoea as a side effect of acamprosate was estimated at NNTH 9.09 (95% CI 7.69 to 11.11). For further adverse events *see* Analysis 1.6; Analysis 1.7; Analysis 1.8; Analysis 1.9; Analysis 1.9; Analysis 1.10; Analysis 1.11; Analysis 1.12; Analysis 1.13; Analysis 1.14.

Drop-out due to adverse events: A statistically significant difference was shown between groups; the risk to drop-out early from a study due to side effects was 35% higher in the acamprosate group than in the placebo group, RR 1.35 (95% CI 1.01 to 1.80) *see* Analysis 1.15.

Drop-out for any cause: A statistically significant difference was shown between groups; the risk of dropping out irrespective of reasons was 9% lower in the acamprosate group than in the placebo group, RR 0.91 (95% CI 0.83 to 0.99) *see* Analysis 1.16.

Post-treatment outcomes: A statistically significant difference between groups was shown three to twelve months after treatment was discontinued; patients who were in the acamprosate group had a 9% lower risk to return to any drinking than those who were in the placebo group, RR 0.91 (95% CI 0.87 to 0.96) *see* Analysis 1.17 and a 9% higher continuous abstinence duration MD 8.92 (95% CI 5.08 to 12.77) *see* Analysis 1.18. The numbers needed

higher continuous abstinence duration MD 8.92 (95% CI 5.08 to 12.77) *see* Analysis 1.18. The numbers needed to treat for an additional prevention of drinking until the post-treatment evaluation was estimated at NNTB 12.50 (95% CI 9.09 to 25.00).

Sensitivity analyses

If data synthesis for "return to heavy drinking" (I^2 < 30%) was based on a fixed-effect model, with RR 0.97 (95% CI 0.92 to 1.03) *see* Analysis 1.19, the magnitude of effects was marginally higher compared than that calculated with the random-effects model RR 0.99 (95% CI 0.94 to 1.04), but the selection of the statistical model did not have an impact on the significance of effects.

Heterogeneity

With the exception of the effect variance for "return to heavy drinking", which was exclusively explained by sampling error (I^2 0%, Analysis 1.3), with proportions of between-study heterogeneity over 75%, I^2 statistics indicated a considerable level of heterogeneity (Deeks 2008). High levels of heterogeneity for the continuous outcomes of the review (cumulative abstinence duration: I^2 94%, Analysis 1.2 and GGT: I^2 80%, Analysis 1.4) were confirmed by τ^2statistics (cumulative abstinence duration: τ^2 138.67; GGT: τ^2 197.21), while the τ^2statistics indicate moderate heterogeneity for the binary outcome "return to any drinking" (τ^2 0.01).

Comparison 2: Acamprosate versus naltrexone

Primary outcomes

Return to any drinking: No statistically significant difference was shown between groups; the risk to return to any drinking was 3% higher in the acamprosate group than in the naltrexone group, RR 1.03 (95% CI 0.96 to 1.10), *see* Analysis 2.1 or Figure 8. If effects are compared on an individual study base, effects on return to any drinking demonstrated in the studies of Anton 2006 and Kiefer 2003 favoured naltrexone, while those found in the study of Morley 2006 indicated a superiority of acamprosate.

Cumulative abstinence duration: No statistically significant difference was shown between groups; acamprosate on average increased the cumulative abstinence duration by 3% compared to naltrexone MD 2.98 (95% CI -7.45 to 13.42) *see* Analysis 2.2, or Figure 9. If effects are considered on an individual study base, effects on cumulative abstinence duration in the study of Anton 2006 favoured naltrexone, while those found in the study of Morley 2006 indicated a superiority of acamprosate.

Secondary outcomes

Return to heavy drinking: No statistically significant difference was shown between groups; the risk to return to heavy drinking was 4% higher in the acamprosate group than in the naltrexone group, RR 1.04 (95% CI 0.95 to 1.15) *see* Analysis 2.3.

GGT: A statistically significant difference was shown between groups; acamprosate was associated with a 9.7 units higher GGT compared to naltrexone, MD 9.7 (95% CI 5.18 - 14.22) *see* Analysis 2.4; the effect is based on one trial only (Kiefer 2003).

Side effects: Acamprosate was associated with a higher risk of diarrhoea than naltrexone RD 0.27 (95% CI 0.21 to 0.33) *see* Analysis 2.5, while naltrexone caused more often nausea RD -0.08 (95% CI -0.13 to -0.03) *see* Analysis 2.6, fatigue RD -0.13 (95% CI -0.26 to -0.10), somnolence RD -0.07 (95% CI -0.13 to -0.01) and vomiting RD -0.06 (95% CI -0.11 to 0.01) *see* Analysis 2.7.

Drop-out due to adverse events: No statistically significant difference was shown between groups; acamprosate was associated with a 24% lower risk of terminating a study early because of adverse events than naltrexone, RR 0.76 (95% CI 0.37 to 1.58) *see* Analysis 2.8.

Drop-out for any cause: No statistically significant difference was shown between groups; acamprosate was associated with a 9% higher risk of terminating the study early irrespective of reasons than naltrexone, RR 1.09 (95% CI 0.91 to 1.3) *see* Analysis 2.9.

Comparison 3: Acamprosate + naltrexone versus placebo

Primary outcomes

Return to any drinking: No statistically significant difference was shown between groups; the risk to return to any drinking was 30% lower under combined treatment with acamprosate and naltrexone than under placebo, RR 0.70 (95% CI 0.35 to 1.39) *see* Analysis 3.1 or Figure 10.

Cumulative abstinence duration: No statistically significant difference was shown between groups; the combined treatment with acamprosate and naltrexone on average increased the cumulative abstinence duration by 2% compared to placebo, MD 2.20 (95% CI -1.90 to 6.30) *see* Analysis 3.2 or Figure 11

Secondary outcomes

Return to heavy drinking: No statistically significant difference was shown between groups; the risk to return to heavy drinking was 29% lower under combined treatment with acamprosate and naltrexone than under placebo, RR 0.71 (95% CI 0.38 to 1.35) *see* Analysis 3.3

GGT: No statistically significant difference was shown between groups; the combined treatment with acamprosate and naltrexone was associated with a 8.7 units lower GGT compared to placebo, MD -8.70 (95% CI -24.86 to 7.46) *see* Analysis 3.4

Side effects: The combined therapy with acamprosate and naltrexone caused significantly more often diarrhoea RD 0.20 (95% CI 0.13 to 0.27) *see* Analysis 3.5, with decreased appetite RD 0.11, (95% CI 0.05 to 0.17), nausea RD 0.20 (95% CI 0.14 to 0.26) and vomiting RD 0.09 (95% CI 0.03 to 0.14) *see* Analysis 3.6.

Drop-out due to adverse events: A statistically significant difference was shown between groups; the combined therapy with acamprosate and naltrexone was associated with an almost four times higher risk of terminating a study early because of adverse events than placebo, RR 3.75 (95% CI 1.33 to 10.55) *see* Analysis 3.7.

Drop-out for any cause: No statistically significant difference was shown between groups; the combined therapy with acamprosate and naltrexone was associated with a 17% lower risk of terminating a study irrespective of reasons than placebo, RR 0.83 (95% CI 0.28 to 2.49) *see* Analysis 3.8.

Comparison 4: Acamprosate + naltrexone versus acamprosate

Primary outcomes

Return to any drinking: No statistically significant difference was shown between groups; the risk to return to any drinking was 20% lower under combined treatment with acamprosate and naltrexone than under acamprosate alone, RR 0.80 (95% CI 0.49 to 1.30) *see* Analysis 4.1 or Figure 12

Cumulative abstinence duration: No statistically significant difference was shown between groups; the combined treatment with acamprosate and naltrexone on average increased the cumulative abstinence duration by 2% compared to acamprosate alone, MD 2.10 (95% CI -2.03 to 6.23) *see* Analysis 4.2 or Figure 13.

Secondary outcomes

Return to heavy drinking: No statistically significant difference was shown between groups; the risk to return to heavy drinking was 19% lower under combined treatment with acamprosate and naltrexone than under acamprosate alone, RR 0.81 (95% CI 0.50 to 1.34) *see* Analysis 4.3.

GGT: No statistically significant difference was shown between groups; the combined treatment with acamprosate and naltrexone was associated with a 1 units lower GGT compared to acamprosate alone, MD 1.00 (95% CI - 8.65 to 10.65) *see* Analysis 4.4.

Side effects: The combined therapy with acamprosate and naltrexone caused significantly more often nausea, RD 0.18 (95% CI 0.11 to 0.24) and vomiting, RD 0.08 (95% CI 0.03 to 0.13) than acamprosate alone *see* Analysis 4.6.

Drop-outs due to adverse events: No statistically significant difference was shown between groups; the combined therapy with acamprosate and naltrexone was associated with a 41% higher risk of terminating a study early because of adverse events than acamprosate alone, RR 1.41 (95% CI 0.68 to 2.90) *see* Analysis 4.7.

Drop-out for any cause: No statistically significant difference was shown between groups; the combined therapy with acamprosate and naltrexone was associated with a 16% lower risk of terminating a study irrespective of reasons than acamprosate alone, RR 0.84 (95% CI 0.49 to 1.44) *see* Analysis 4.8.

Discussion

Summary of main results

A total of 24 RCTs with 6915 participants were included in the review. Effects on both primary effectiveness outcomes clearly support the abstinence-promoting effects of acamprosate when compared to placebo: Added to psychosocial treatment strategies, the glutamate antagonist was shown to reduce the risk to return to any drinking after detoxification to 86% of the risk in the placebo group RR 0.86 (95% CI 0.80 to 0.91), NNTB 9.09 (95% CI 6.66 to 14.28) and to increase abstinence duration by about 11%, MD 10.94 (95% CI 5.08 to 16.81). Treatment effects estimated on the base of individual patient data (IPD) confirmed the statistical significance of the primary effectiveness outcomes based on literature, indicating a marginally higher magnitude of effects for return to any drinking RR 0.83 (95%CI 0.79 to 0.87); NNTB 7.14 (95% CI 5.15 to 11.76) and a slightly lower magnitude for the cumulative abstinence duration MD 9.82 (95% CI 8.05 to 11.35). Post-treatment evaluations, available from a subset of ten RCTs, showed that effect sizes were lower after treatment with acamprosate was discontinued; nevertheless, 3 to 12 months after the end of the treatment period, effects still reached statistical significance (return to any drinking RR 0.91 (95% CI 0.87 to 0.96); NNTB 12.50 (95% CI 9.09 to 25.00); cumulative abstinence duration MD 8.92 (95% CI 5.08 to 12.77)).

At the same time, acamprosate was shown to be safe to use. The only side-effect, which was more frequently reported in the acamprosate group, was diarrhoea RD 0.11 (95% CI 0.09 to 0.13); NNTH 9.09 (95% CI 7.69 to 11.11). Side effects did not more often lead to an early termination of the treatment under acamprosate than under placebo RR 1.35 (95% CI 1.01 to 1.80), indicating that most patients accept the experienced adverse events as a tolerable part of alcoholism treatment.

Nevertheless, primary and secondary outcomes of the review did not provide a completely consistent picture: While the effectiveness of acamprosate was confirmed by the primary outcomes of the review, the secondary outcomes, gamma-glutamyltransferase (GGT) MD -11.91 (95% CI -24.12 to 0.30) and "return to heavy drinking"

RR 0.99 (95% CI 0.94 to 1.04), did not reach statistical significance. Thereby the non-significance of the summary GGT was mainly caused by one outlier value, whereas non-superiority of acamprosate to avoid heavy drinking was attributable to the majority of primary studies. It should also be considered in this context that acamprosate is mainly indicated for supporting continuous abstinence, rather than to avoid a relapse to heavy drinking.

The meta-analytic integrations based on head-to-head comparisons between acamprosate and naltrexone did not indicate a superiority of one or the other drug (return to any drinking RR 1.03 (95% CI 0.96 to 1.10); cumulative abstinence duration MD 2.98 (95% CI -7.45 to 13.42); return to heavy drinking RR 1.04 (95% CI 0.95 to 1.15)), but the corresponding study base of three RCTs is too sparse to draw final conclusions. The same applies to the effects of combined treatments with acamprosate and naltrexone, based on two RCTs, which are promising, but need to be confirmed by further effectiveness and safety studies (heavy drinking RR 0.71 (95% CI 0.38 to 1.35); any drinking RR 0.70 (95% CI 0.35 to 1.39); drinking days MD -2.20 (95% CI -6.30 to 1.90).

The high heterogeneity of effects ($I^2 > 75\%$) is emphasizing the diverse nature of evidence in terms of treatment characteristics, patient characteristics and features of the study designs, supporting the need to develop theoretically well-considered models to further explore the variability of effects.

Overall completeness and applicability of evidence

Completeness of the database

The evaluation of primary outcomes of the review refers to almost complete databases: meta-analysis based on literature (MAL) for "return to any drinking" includes data from all 24 RCTs and cumulative abstinence duration analysis includes all but five trials (Baltieri 2003; Kiefer 2003; Lhuintre 1985; Lhuintre 1990; Rousseaux 1996), for which no aggregate data were available. IPD analyses on both outcomes consider all RCTs apart from one small sample size trial (Niederhofer 2002) with 26 patients. In contrast, databases of secondary outcomes as well as post-treatment outcomes, reported by a limited subset of trials, are rather incomplete: Outcome data on GGT were based on seven RCTs (Kiefer 2003; Lhuintre 1985; Lhuintre 1990; Namkoong 2003; Paille 1995; Rousseaux 1996; Sass 1996), heavy drinking rates on six RCTs (Anton 2006; Chick 2000; Kiefer 2003; Mason 2006; Morley 2006; Namkoong 2003), and post-treatment primary effectiveness outcomes on a total of 11 RCTs (Anton 2006; Baltieri 2003; Barrias 1997; Geerlings 1997; Kiefer 2003; Ladewig 1993; Paille 1995; Poldrugo 1997; Sass 1996; Tempesta 2000; Whitworth 1996).

Applicability of the results

With the acamprosate trials included in the review, treatment durations, types of psychosocial interventions and intensity of co-treatments are represented with high variability. Additionally, inclusion criteria were defined in a non-restrictive way and thus samples can be assumed to reflect a mix of different characteristics of the population of interest. Limitations in the generalizability might arise from the proceeding to screen out patients with concurrent psychiatric illnesses from acamprosate trials. In contrast, some features of the study design, including the pretreatment of patients, the dosing of acamprosate as well as the settings of treatment, did not considerably vary between studies: With few exceptions, patients were detoxified before treatment, dosing was between 4 and 6 tables (à 333 mg) and treatment was realized in outpatient programs. Thus, the generalizability of the demonstrated results might not be provided, if the frame conditions in clinical practice differ from those applied in research.

Quality of the evidence

Within the acamprosate trials included in the review, various features of the study design have been adequately implemented to ensure a high level of validity: Patients were randomly assigned to treatment groups to prevent selection bias. Active medication and placebo with identical appearance were used to mask treatment allocation and to reduce the general susceptibility of outcomes to bias effects; objective measures of drinking were considered (Wood 2008), either to validate patient-reported outcomes or as a discrete outcome criteria in the majority of studies.

Treatment groups did not differ in relevant baseline characteristics and if so, group differences were controlled in statistical analyses of treatment effects. Group differences in medication compliance were indeed demonstrated in some selected trials, but all in all, appear more likely to be generated by chance than by systematic influences. The risk of attrition bias, associated with the appearance of high and differential drop-out rates, has adequately been encountered in the majority of trials: Data analyses were conducted in accordance with the original ITT principle (Newell 1992) or a modified version (treatment received analysis), which takes into account the high initial drop-out in addiction treatment by including all patients who received treatment (Lehert 1993). To replace missing end-point data, these were substituted by "worst-case" scenarios - a proceeding which has been well established in addiction research. Because of its good tolerability, the risk that specific side effects unmask blinding - a methodological limitation that was also discussed for antidepressant therapy (Moncrieff 2004) - appears to be low for acamprosate. Furthermore, quantitative analyses of bias risks did neither suggest a difference between industry sponsored trials and investigator-driven research (sponsoring bias) nor indicate that non-significant trials have been omitted from publication (publication bias).

Nevertheless, some uncertainties still persist. As some features of the study designs were omitted from trial reports, it remains unclear whether these have not been implemented or whether they were implemented, but not reported. The poor reporting of the study design mainly concerns the methods used for generating random

sequences, the specification of person groups included in the blinding process and the methods applied for allocation concealment. Particularly the latter, unclear concealment, has repeatedly been shown to be associated with bias effects in various fields of clinical research (Schulz 1995; Huwiler-Muntener 2002; Pildal 2007). The fact that a considerable portion of included trials has been initiated before 1996, when the Good Clinical Practice (GCP) guidelines were published by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH 1996), might at least explain the poor reporting in earlier trials.

Potential biases in the review process

To lower the risk of bias in the review process, all outcome statistics were extracted by two authors independently (SR & AH). To prevent confirmation bias (Nickerson 1998), at least one author has participated in each review step, who has not been involved in addiction treatment or research before.

Agreements and disagreements with other studies or reviews

Small to moderate, but significant effects have already been demonstrated for acamprosate by former meta-analyses (Schoechlin 2000; Kranzler 2001; Hopkins 2002; Berglund 2003; Chick 2003; Slattery 2003; Mann 2004; Bouza 2004; Verheul 2005; Rosner 2008). In contrast to most available meta-analyses on the glutamate antagonist, which considered continuous abstinence as the primary dichotomous effectiveness outcome, with "return to any drinking", the complementary of continous abstinence was chosen in the review at hand. The defintion of the outcome follows the recommendation of the Cochrane Collaboration (Deeks 2008) to consider the onset of a disease as the event of interest, if participants are "well" at the beginning of the study (in the majority of included trials, a successful detoxification of study participants was required to enter the treatment phase). The selection of the primary dichotomous effectiveness outcome also goes in line with the outcome definition in the Cochrane review on opioid antagonists for alcohol dependence (Srisurapanont 2005).

Nevertheless, in contrast to the relative risk (RR), the numbers needed to treat for an additional beneficial outcome (NNTB) was related to continuous abstinence. With NNTB 9.09 (95% CI 6.55 to 14.28), the magnitude of absolute effects varies within the range of values estimated by previous analyses. Based on 17 RCTs and 4087 patients, the meta-analysis by Mann 2004 found a NNTB value of 7.8 (95% CI 6.0 to 12.2) after 6 months of treatment and of 7.5 (95% CI 5.3 to 12.8) after 12 months. A former meta-analysis conducted by the authors of the review (Rosner 2008), based on a total of 21 RCTs with 5280 patients, identified a RR for "return to any drinking" of 0.84 (95% CI 0.78 to 0.91) and a corresponding NNTB of 7.7 (95% CI 5.6 to 13.0), while the meta-analysis of the Spanish Agency for Health Technology Assessment (Bouza 2004) with 11 RCTs and 3324 patients, estimated a NNTB of 10 (95% CI 7.0 to 14.0). The marginally lower magnitude of treatment effects estimated by the meta-analysis at hand compared to Mann 2004 and Rosner 2008 can be explained by the inclusion of newer studies with negative results (e.g. Anton 2006; Mason 2006; Morley 2006).

Authors' conclusions

Implications for practice

Based on comprehensive evidence from 24 RCTs with 6915 participants, the review confirms the effectiveness of acamprosate in alcoholism treatment. Acamprosate was shown to reduce the risk of any drinking after detoxification to 86% of the risk a patient would have under placebo and to increase the number of abstinent days by about three additional days a month. In a population of alcohol dependent patients, acamprosate is expected to prevent drinking after detoxification in one out of nine patients (NNTB = 9), who would otherwise have relapsed.

However, when translating research into clinical practice, it needs to be taken into consideration that the low levels of medication compliance and the high rates of patients dropping-out early from treatment in addiction treatment additionally impede the demonstration of therapeutic effects in clinical trials. For patients, who take acamprosate regularly, therapeutic benefits are likely to exceed those demonstrated in the review. Secondly, it should be kept in mind that acamprosate was applied as an adjunctive therapy to psychosocial and psychotherapeutic interventions. Thus, strictly speaking, effect sizes rather reflect the additional benefit of adding acamprosate to psychosocial treatments than its benefit compared to placebo - a fact which often remained unconsidered in the interpretation of treatment effects. Nevertheless, despite these obstacles and restrictions, demonstrated treatment effects for acamprosate are comparable in their magnitude with those obtained in other areas of psychiatric research (see Adams 2007; Arroll 2009; Citrome 2008).

All in all, acamprosate does not appear to be magic bullet in the treatment of alcohol dependence and - considering the complexity of processes involved in the development and maintenance of addiction - there will probably never be a single strategy that can "cure" alcohol dependence. But, after summarizing and appraising the availbale evidence, the glutamate antagonist appears to be an helpful and effective mean to support abstinence in alcohol dependent patients. Nevertheless, the principle that therapeutic decisions should be shared decisions between physicians and patients applies to pharmacological relapse prevention in a particular way; this is not only to respect a patient's` free choice of treatment, but also to ensure commitment and compliance. Patients' doubts and reservations against a therapeutic strategy which uses a substance to treat dependency from another one, should be taken seriously when informing patients about their treatment options and the associated risks and benefits. At the same time, therapeutic strategies which have been shown to work in well-controlled trials, should not kept back from patients, particularly if these concern the treatment of a disease that is known

to have a high impact on health and quality and duration of life and for which alternative therapeutic options are of limited effectiveness.

Implications for research

Treatment of alcohol dependence is a complex therapeutic process and research on its effectiveness meets with particular difficulties. One of the main methodological challenges in addiction research results from the high magnitude of drop-out rates. The inclusion of all randomized patients in the data analyses according to the intention-to-treat (ITT) principle and a handling of missing data, which accounts for the close linkage between treatment attendance and consumption in patients with substance use disorders, appear to be essential means for preventing attrition bias in addiction research. Nevertheless, as even the most elaborated methods for substituting incomplete patient data are associated with error, persistent efforts should be made to validly assess the drinking status of drop-outs and to ensure the validity of self-reports by objective measures. For those patients who were lost to follow-up, substitution by “worst case” appears as one the most appropriate method to handle missing data in addiction research.

Because of the good tolerability of acamprosate, the risk that specific side effects unmask blinding was considered as comparatively low in the trials included in the review. Nevertheless, the use of side effects imitating placebo could help to ensure the integrity of blinding; if not realizable, the assessment of blinding quality by inquiries on patients, treatment providers and investigators should be used to identify threats to blinding quality.

The reporting of clinical trials with acamprosate was clear and comprehensible in most study publications; nevertheless some deficits became apparent. A stricter adherence to methodological standards of reporting as outlined in the CONSORT statement (Moher 2001) would help to remove remaining doubts and uncertainties.

Finally, the review at hand refers to gaps in knowledge, that need to be addressed by future research. Further head-to-head comparisons between acamprosate and naltrexone are needed to determine the relative effectiveness of both substances and their specific profile of effectiveness. Thereby a conceptual distinction between different achievements in drinking control such as a patient's ability to maintain continuously abstinent or his/her ability to stop drinking once started (Keller 1972) will help to specify differential efficacy profiles. The identification of patient characteristics which determine a patient's responsiveness to the availbale psychosocial and pharmacological interventions is indispensable for the deduction of elaborated techniques of combining therapeutic strategies and their tailoring to the individual treatment goals and therapeutic needs of patients.

Acknowledgements

We thank the team of the Cochrane Drugs and Alcohol Group (CDAG, Rome, Italy) for their support in the preparation and conduction of this review. We also thank Anton RF (Center for Drug and Alcohol Programs, Medical University of South Carolina, Charleston, USA), Baltieri D (Psychiatric Institute, University of Sao Paulo, Sao Paulo, Brazil), Barrias JA (Regional Alcohol Studies Center, Porto, Portugal), Gual A (Unitat d’ Alcohologia de la Generalitat, Barcelona, Spain), Morley KC (Central Clincial School of Medicine, University of Sydney, Sydney, Australia), Namkoong K (Yongdong Severance Hospital, Seoul, South Korea) and Merck Serono (Geneva, Switzerland) for the disposal of unreported data and information*. Our gratitude also goes to V Hesslbrock V (Alcohol Research Center, University of Connecticut Health Center, Farmington, USA) for the reference to ongoing studies and to P Thomson (CSR Incorporated, Arlington, USA), for providing advice for analyses of the COMBINE data set.

* authors of primary studies not mentioned in this section were either not requested as all relevant data and information were available from the trial publication or were unable to provide the requested data or information.

This work was financially supported by the Federal Ministry of Education and Research (BMBF) under the grant number 01KG0724. All responsibilities for the contents of this publications remain with the authors.

Contributions of authors

SUSANNE RÖSNER:

- protocol elaboration
- study selection
- data extraction
- data management
- analysis of data (MAL)
- interpretation and discussion of results
- writing the review
- securing funding

ANDREA HACKL-HERRWERTH:

- study selection
- data extraction

STEFAN LEUCHT:

- protocol elaboration
- interpretation and discussion of results

SIMONA VECCHI:

- development of search strategies
- study search

PHILIPPE LEHERT:

- Analysis of data (IPD)

MICHAEL SOYKA:

- protocol elaboration
- interpretation and discussion of results (clinical perspective)
- securing funding

Declarations of interest

Rösner, S: No conflict of interest known

Hackl-Herrwerth, A: No conflict of interest known

Leucht, S: Received speaker/consultancy/advisory board honoraria from Sanofi-Aventis, BMS, EliLilly, Janssen/Johnson and Johnson, Lundbeck and Pfizer

Vecchi, S: No conflict of interest known

Lehert, P: Received speaker/consultancy/advisory board honoraria from Lundbeck, SanofiAventis, Merck,

Soyka, M: Reveived speaker/consultancy/advisory board honoraria from Lipha Pharmaceuticals, Forest Laboratories, Sanofi-Aventis, Essex Pharma, Eli Lilly, Prempharm and AstraZeneca

Differences between protocol and review

Authors

Andrea Hackl-Herrwerth, Simona Vecchi and Philippe Lehert have not been considered as authors in the protocol as their contribution was not known at the protocol stage.

Selection of outcomes

The selection of the primary and secondary outcomes in the protocol was mainly based on theoretical considerations concerning different compounds of drinking control (Keller 1972) and their clinical relevance. In the process of data extraction, limitations in the availability of outcomes became evident, which required changes in the outcome selection. Accordingly, heavy drinking rates, available from six trials only, were removed from the primary outcome list of the protocol and considered as a secondary outcome in the review. Cumulative abstinence duration was in contrast included as a primary outcome, as it was more frequently reported in the trial publications (n = 19). Drop-out rates were considered as potential moderators of effectiveness in the review, but were not included in the evaluation of effectiveness as originally outlined in the protocol. The decision is based on the fact that various indicators of drinking behavior are available, which were assumed to be more closely related to therapeutic success than drop-out rates.

IPD analyses

The IPD analyses were not foreseen in the protocol, as the authors did not have access to the IPD data set at the time, the protocol was elaborated.

Assessment of heterogeneity

The inclusion of τ^2-statistic in the assessment of heterogeneity, which was additionally applied to I^2-statistic in the review to provide a measure of variability independent of the sample size, is based on considerations outlined by Rucker 2008, which were not known to the authors at the time the protocol was elaborated.

Publication bias

Besides the graphical illustration with the funnel plot method (Light 1984), the risk of publication bias was additionally quantified with a linear regression test (Egger 1997) in the review. The authors did not consider this option when writing the protocol.

Sensitivity analyses

The investigation of *within-study selective outcome reporting bias* by sensitivity analyses was not conducted as outlined in the protocol due to the low availability of unreported outcomes. Instead, a sensitivity analysis was conducted to examine the influence of the funding source on the study outcomes.

Published notes

Characteristics of studies

Characteristics of included studies

Anton 2006

Methods	**Allocation:** random; **blinding:** double-blind; **principle of analysis:** ITT; **study duration:** 16 weeks (treatment); 12 months (post-treatment); **setting:** outpatient; **study sites:** 11; **Country:** USA
Participants	**Diagnosis:** alcohol dependence (DSM-IV); **required abstinence:** 4 to 21 days; **baseline characteristics:** 70% male; mean age: 44.0 years; 42% married: 71% employed; **pre-baseline drinking:** 75% days drinking; 12.4 drinks per drinking day; ADS score (Skinner 1982; Skinner 1984): 16.8; percentage of individuals abstinent for at least 4 days: 99% **Exclusionary psychiatric conditions:** 1. a concurrent drug abuse or dependence; 2. a dependence or abuse from opioids (last 6 months) ro a chronic treatment with any opiate-containing medications (last 30 days) or urine positive for opioids; 3. a concurrent major psychiatric disorder; 4. prior use of study medication in the last 30 days
Interventions	1. 3000 mg acamprosate + MM (n = 152) 2. 3000 mg acamprosate + MM + CBI (n = 154) 3. 100 mg naltrexone + MM (n = 153) 4. 100 mg naltrexone + MM + CBI (n = 155) 5. 3000 mg acamprosate + 100 mg naltrexone + MM (n = 148) 6. 3000 mg acamprosate + 100 mg naltrexone + MM + CBI (n = 157) 7. placebo + MM (n = 153) 8. placebo + CBI (n = 156) 9. CBI only (n = 157) **Psychosocial treatment:** a) group 1 to 7: medial management (MM); **applied manual:** Pettinati 2004; **aim:** flexible (with recommendation to abstinence); b) group 2, 4, 6, 8 and 9: combined behavioral intervention (CBI); **applied manual:** integrates aspects of cognitive behavioral therapy (CBT) (Kadden 1992) as applied in Project MATCH (Project Match Research Group 1997), motivational enhancement (ME) MIller 1994, 12-step facilitation (Nowinski 1995), etc. **Dosing:** flexible dosing allowed
Outcomes	1. Return to heavy drinking* 2. percent days abstinent 3. good clinical outcome (abstinence; moderate drinking**) 4. time to first heavy drinking* 5. side effects * relapse / heavy drinking: drinking ≥ 5 (4) SDU for men (women); ** moderate drinking: ≥ 14 (11) SDU for men (women) per week, with no more than two days on ≥ 5 (4) SDU for men (women)
Missing data rates	**Treatment phase / drop-out rates:** acamprosate: 38.5% (n = 116); naltrexone: 35% (n = 108); naltrexone + acamprosate: 40.7% (n = 124); ; placebo: 28.5% (n = 88); group difference: not reported; **lost to follow-up rates**: acamprosate: 4.6% (n = 14); naltrexone: 6.1% (n = 19); naltrexone + acamprosate: 6.2% (n = 19); placebo: 5.8% (n = 18); group difference: not significant **Post-treatment phase / drop-out rates:** acamprosate: 49.2 (n = 149); naltrexone: 46.0% (n = 142); naltrexone + acamprosate: 53.1% (n = 162); placebo: 38.2% (n = 118); group difference: not significant
Financial support	National Institute on Alcohol Abuse and Alcoholism (NIAAA); active control substances and placebo were donated by Lipha Pharmaceuticals; Lipha Pharmaceuticals conducted monitoring visits to the clinical sites

Data assessment methods	**Assessment of drinking:** TLFB interview (Sobell 1988; Sobell 1992; nine times during 16 weeks of treatment and at week 10, 36, 42 during post-treatment); **assessment of side effects:** SAFTEE (Levine 1986, Rabkin 1992); **assessment of compliance:** pill count; **validation of patient-reported outcomes:** CDT (week 8, 16) was used as a validity check for self-reported drinking; **laboratory assessment of drop-outs:** not reported
Notes	The COMBINE study group provided access to the COMBINE data set, which was used for the calculation of "return to any drinking" for the review

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Participants are randomly assigned to treatment by a stratified random block design controlling for clinical centres; the randomization was implemented via a central telephone based interactive voice response system at a coordinating centre
Allocation concealment?	Unclear	Randomization was performed at the coordinating centre; no further information provided
Blinding?	Yes	**Persons blinded:** double-blind, including patients, investigators, research staff, evaluators, health care practitioners and therapists; **placebo appearance:** double-dummy design (an identically matched placebo was available for each drug, and participants in each group took the same number of pills per day); acamprosate and acamprosate placebo differed in appearance from naltrexone and naltrexone placebo
Incomplete outcome data addressed? binary outcomes	Unclear	**Principle of analysis:** ITT; **handling of missing data:** not reported; it was assumed for the meta-analysis that lost to follow-ups have been classified as relapsers
Incomplete outcome data addressed? continuous outcomes	Yes	**Principle of analysis:** ITT; **handling of missing data (CAD):** for the calculation of abstinent days, patients lost to follow-up were assumed to have relapsed to heavy drinking on the day after their last contact **Handling of missing data (GGT):** outcome not considered in the study
Free of selective reporting?	Yes	**Outcome reporting:** a study protocol is available and the primary outcomes listed in the protocol are reported adequately in the study publication
Free of other bias?	Yes	**1. Baseline equivalence:** 67 pretreatment characteristics were compared across groups and no evidence for baseline imbalance was found; socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes **2. Treatment exposure: compliance rates** (% of prescribed medication taken): acamprosate: 84.2%; naltrexone: 85.4%; group difference in compliance rates: not significant

Baltieri 2003

Methods	**Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks (treatment); 12 weeks (post-treatment); **principle of analysis:** ITT (modified); **setting:** outpatient; **study sites:** 1; **country:** Brazil
Participants	**Diagnosis:** alcohol dependence (ICD-10); **required abstinence:** 7 days; **baseline characteristics:** 100% male; mean age: 44.2 (SD = 8.28) years; **pre-baseline drinking:** 360.0 (SD = 150.7) grams alcohol per day **Exclusionary of psychiatric conditions:** 1. a concurrent psychiatric disorder; 2. a previous psychosis; 3. a condition that requires psychiatric medication
Interventions	1. 1998 mg acamprosate (n = 40) 2. placebo (n = 35) **Psychosocial treatment:** psychosocial orientation; patients were encouraged to participate in Alcoholics Anonymous (AA) groups; **aim:** abstinence
Outcomes	1. Time to first drink (survival curve) 2. return to any drinking 3. side effects
Missing data rates	**Drop-out rates**: acamprosate: 25.0% (n = 10); placebo: 20% (n = 7); group difference in drop-out rates: not reported; group difference in reasons for drop-out: not reported; **lost to follow-up rates**: acamprosate: 17.5% (n = 7); placebo: 11.4% (n = 4); group difference in lost to follow-up rates: not reported
Financial support	Investigator-driven trial with non-profit funding
Data assessment methods	**Assessment of drinking:** retrospective quantity / frequency report (week 1, 2, 3, 4, 6, 8, 12, 16, 20, 24); **assessment of side effects:** UKU side effect rating scale (Louzã, 2000); **assessment of compliance:** not reported; **validation of patient-reported outcomes:** GGT, collateral reports; **laboratory assessment of drop-outs:** *not reported*
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	No information provided
Blinding?	Unclear	**Persons blinded:** double-blind; no detailed information provided; **placebo appearance:** identical to active medication
Incomplete outcome data addressed? binary outcomes	Yes	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication were excluded from the analyses (= treatment-received analysis); **handling of missing data:** lost to follow-ups have been categorized as relapsers in the primary analysis
Incomplete outcome data addressed? continuous outcomes	Unclear	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication were excluded from the analyses (= treatment-received analysis); **handling of missing data (CAD, GGT):** outcomes not considered in the study
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Unclear	**1. Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes **2. Treatment exposure: compliance rate:** not reported; group difference in compliance rates: *not reported*

Barrias 1997

Methods	**Allocation:** random; **blinding:** double-blind; **study duration:** 12 months (treatment); 6 months (post-treatment); **principle of analysis:** ITT (modified); **setting:** outpatient; **study sites**: 9; **country:** Portugal
Participants	**Diagnosis:** alcohol dependence (DSM-III); **required abstinence:** ≥ 5 days; **baseline characteristics:** 92% male; mean age: 40.3 years; 73.2% married; **pre-baseline drinking:** 97.7% (96%) of patients were physically (psychologically) dependent on alcohol; 88.4% consumed alcohol every day; 64.9% consumed more than 10 SDU a day; MAST score (Selzer 1971): 31.9 **Exclusionary of psychiatric conditions:** 1. a concurrent major psychiatric disorder; 2. a concurrent use of psychotropic medications besides stable medication of benzodiazepines and use of oxazepam and tetrazepam for periods < 2 weeks
Interventions	1. 1332 mg/ 1998 mg acamprosate (n = 150) 2. placebo (n = 152) **Psychosocial treatment:** not specified; patients were encouraged to participate in AA groups; **aim:** abstinence; **dosing:** 1. weight dependent; 2. flexible: dose reduction in case of side effects
Outcomes	1. Time to first drink (survival curve) 2. return to any drinking 3. return to heavy drinking 4. cumulative abstinence duration (CAD) 5. craving 6. gamma-glutamyltransferase (GGT) 7. mean corpuscular volume (MCV) 8. side effects
Missing data rates	**Treatment phase / drop-out rates**: acamprosate: 42.7% (n = 64); placebo: 45.4% (n = 69); group difference in drop-out rates: not significant; group difference in reasons for drop-out: significantly more patients refused to continue treatment in the placebo group than in the acamprosate group; **lost to follow-up rates:** acamprosate: 39% (n = 58); placebo: 43% (n = 66); group difference in missing end point data rates: not significant **Post-treatment phase / drop-out rates**: 53% of the entire sample dropped out during the treatment and post-treatment phase; no group specific values provided
Financial support	Sponsored and organized by Merck Lipha within the scope of a new drug application processes
Data assessment methods	**Assessment of drinking:** retrospective quantity / frequency report (week 4, 12, 24, 36, 48, 60*, 72*); *post-treatment evaluation; **assessment of side effects:** side effect checklist (44 symptoms); **assessment of compliance:** not reported; **validation of patient-reported outcomes:** not reported; **laboratory assessment of drop-outs:** not reported
Notes	CAD was extracted from the manufacturer report

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	No information provided
Blinding?	Unclear	**Persons blinded:** double-blind; no detailed information provided; **placebo appearance:** identical to active medication
Incomplete outcome data addressed? binary outcomes	Yes	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication were excluded from the primary analysis (= treatment-received analysis); **handling of missing data:** lost to follow-ups have been categorized as relapsers in the primary analysis
Incomplete outcome data addressed? continuous outcomes	Yes	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication were excluded from the primary analysis (= treatment-received analysis); **handling of missing data (CAD):** if a patient was absent from the visit or reported any alcohol use during a given study period, the complete interval was coded as a non-abstinent period for the calculation of cumulative abstinence duration; **handling of missing data (GGT):** outcome not considered in the study
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section were adequately reported
Free of other bias?	Yes	**1. Baseline equivalence:** socio-demographic variables: yes (with a trend for more participants in the naltrexone group being unemployed than in the placebo group); drinking frequency and intensity: yes; drinking history or treatment history: yes **2. Treatment exposure: compliance rate**: acamprosate: 94.4%; placebo: 92.8%; group difference in compliance rates: not significant

Besson 1998

Methods	**Allocation:** random; **blinding:** double-blind; **study duration:** 12 months (treatment); 12 months (post-treatment); **principle of analysis:** ITT modified; **setting:** outpatient; **study sites:** 3; **country:** Switzerland
Participants	**Diagnosis:** alcohol dependence (DSM-III); **required abstinence:** ≥ 5 days; **baseline characteristics:** 80% male; mean age: 42.5 years; **pre-baseline drinking:** 60.1% had previous alcohol detoxifications; 50% had previous psychotherapy; 15.0 years of alcohol dependence; MAST score (Selzer 1971): 31.6 **Exclusionary of psychiatric conditions:** 1. a concurrent major psychiatric disorder requiring medication; 2. a concurrent use of psychotropic medications; benzodiazepines administered during detoxification had to be discontinued by the 14th day of the study and were then prohibited until the end of the study
Interventions	1. 1332 mg/ 1998 mg acamprosate (n = 55) 2. placebo (n = 55) **Psychosocial treatment:** not specified; patients were allowed to participate in AA groups; **aim:** abstinence; **dosing:** 1. weight dependent; 2. flexible: dose reduction in case of side effects; **permitted medication:** voluntary use of disulfiram
Outcomes	1. Time to first drink (survival curve) 2. return to any drinking 3. cumulative abstinence duration (CAD) 4. craving 5. gamma-glutamyltransferase (GGT) 6. mean corpuscular volume (MCV) 7. side effects
Missing data rates	**Treatment phase / drop-out rates**: acamprosate: 65.5% (n = 36); placebo: 65.5% (n = 36); group difference in drop-out rates: not significant; group difference in reasons for drop-out: not significant; **lost to follow-up rates**: acamprosate: 16.4% (n = 9); placebo: 14.5% (n = 8); group difference in lost to follow-up rates: not significant **Post-treatment phase / drop-out rates**: acamprosate: 81.8% (n = 45); placebo: 85.5% (n = 47); only 18 patients (10 previously on acamprosate and 8 previously on placebo) completed the post-treatment phase
Financial support	The study has received grants and facilities by the manufacturer (Lipha Pharmaceuticals), but the manufacturer had no role in the management, analyses and interpretation of data
Data assessment methods	**Assessment of drinking:** retrospective quantity / frequency report (week 4, 12, 24, 36, 48, 60*, 72*, 84*, 96*); *post-treatment evaluation; **assessment of side effects:** spontaneous reports; **assessment of compliance:** pill count; **validation of patient-reported outcomes:** a GGT equal or above 1.3 times the upper laboratory normal was considered as suggestive of possible relapse drinking; **laboratory assessment of drop-outs:** not reported
Notes	Because of the small sample (n=18), no outcomes were provided for the follow-up period (day 361 to day 720)

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Balanced randomization between placebo and acamprosate, stratified for the voluntary intake of disulfiram; no further details provided
Allocation concealment?	Unclear	No information provided
Blinding?	Unclear	**Persons blinded:** double-blind; no detailed information provided; **placebo appearance:** identical to active medication
Incomplete outcome data addressed? binary outcomes	Unclear	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication (n = 8; no group specific values provided) were excluded from the primary analysis (= treatment-received analysis); **handling of missing data:** unless for reasons clearly unrelated to study treatment (intercurrent illness and protocol violation unrelated to treatment), all patients who discontinued the treatment before study completion were considered as non-abstinent
Incomplete outcome data addressed? continuous outcomes	Unclear	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication (n = 8; no group specific values provided) were excluded from the primary analysis (=treatment-received analysis); **handling of missing data (CAD):** unless for reasons clearly unrelated to study treatment (intercurrent illness and protocol violation unrelated to treatment), the complete intervals of missing participants were coded as a non-abstinent periods; **handling of missing data (GGT):** outcome not considered in the study
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Unclear	**1. Baseline equivalence:** socio-demographic variables: yes (with a trend for more participants in the naltrexone group being unemployed than in the placebo group); drinking frequency and intensity: yes; drinking history or treatment history: no* * baseline differences were found for previous psychotherapy, with more patients in the acamprosate having psychotherapy experience than in the placebo group; as no further indicators of treatment history indicated significant group differences, the difference was not considered as being of clinical relevance **2. Treatment exposure: compliance rate**: not reported; group difference in compliance rates: not sognificant, with exception of the last study visit, when compliance in the placebo group was significantly lower than in the acamprosate group

Borg 2003

Methods	**Allocation:** random; **blinding:** double-blind; **study duration:** 3 months; **principle of analysis:** ITT (modified); **setting:** outpatient; **study sites:** 1; **country:** Sweden
Participants	**Diagnosis:** alcohol dependence; **required abstinence:** no information available; **baseline characteristics:** no information available; **pre-baseline drinking:** no information available **Exclusionary of psychiatric conditions:** no information available
Interventions	1. 1998 mg acamprosate (n = 5) 2. placebo (n = 5)
Outcomes	1. Patients who return to any drinking 2. Cumulative abstinence duration (CAD)
Missing data rates	**Drop-out rates**: no information available; **lost to follow-up rates**: no information available
Financial support	Merck Lipha; sponsored, organized and conducted within the scope of new drug application processes
Data assessment methods	**Assessment of drinking / side effects / compliance:** no information available; **validation of patient-reported outcomes:** no information available; **laboratory assessment of drop-outs:** no information available
Notes	Unpublished trial; information subsequently provided by Lipha Pharmaceuticals

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information available
Allocation concealment?	Unclear	No information available
Blinding?	Unclear	**Persons blinded:** no detailed information available; **placebo appearance:** no information available
Incomplete outcome data addressed? binary outcomes	Unclear	**Principle of analysis:** no information available; **handling of missing data:** no information available
Incomplete outcome data addressed? continuous outcomes	Unclear	**Principle of analysis:** no information available; **handling of missing data:** no information available
Free of selective reporting?	Unclear	No information available
Free of other bias?	Unclear	No information available

Chick 2000

Methods	**Allocation:** random; **blinding:** double-blind; **study duration:** 6 months (treatment); 4 weeks (post-treatment); **principle of analysis:** ITT modified (treatment-received analysis); **setting:** outpatient; **study sites:** 20; **country:** United Kingdom
Participants	**Diagnosis:** alcohol dependence (DSM-III); **required abstinence:** 5 to 35 days; **baseline characteristics:** 83.5% male; mean age: 43.3 years; 56% married: 51% employed; **pre-baseline drinking:** 25.4 units (à 8 grams) per day; SADQ score: 33.5; MAST score (Selzer 1971): 37.5; 38.2% of patients drank alcohol during the wash-out period **Exclusionary of psychiatric conditions:** 1. a drug abuse or dependence (last 12 months); 2. a concurrent major psychiatric disorder; 3. a concurrent use of disulfiram or calcium carbimide or other drugs known to induce hepatic enzymes with the exception of tranquillizers on a regular base
Interventions	1. 1998 mg acamprosate (n = 289) 2. placebo (n = 292) **Psychosocial treatment:** centre specific; cognitive-behavioral group therapy was applied in 13 of 16 centres; patients were encouraged to participate in AA groups; **aim:** abstinence; **dosing:** flexible: dose reduction in case of side effects **Trial started with a placebo run-in week**
Outcomes	1. Time to first drink (survival curve) 2. return to any drinking 3. return to heavy drinking* 4. cumulative abstinence duration (CAD) 5. craving 6. gamma-glutamyltransferase level (GGT) 7. aspartate aminotransferase 8. mean corpuscular volume (MCV) 9. side effects * relapse / heavy drinking: drinking ≥ 5 (3) SDU per drinking day for men (women) or a single day ≥ 8 (6) SDU for men (women)
Missing data rates	**Drop-out rates**: acamprosate: 65.4% (n = 189); placebo: 64.7% (n = 189); group difference in drop-out rates: not significant; group difference in reasons for drop-out: not reported; **lost to follow-up rates**: acamprosate: 23% (n = 66); placebo: 25% (n = 73); group difference in lost to follow-up rates: not significant
Financial support	Sponsored and organized by Lipha Pharmaceuticals within the scope of a new drug application processes
Data assessment methods	**Assessment of drinking:** diary cards; retrospective quantity / frequency report (week 1, 2, 4, 6, 8, 12, 16, 20, 24, 28*); *post-treatment evaluation; **assessment of side effects:** spontaneous reports; **assessment of compliance:** pill count; **validation of patient-reported outcomes:** breathalyzer test; urine alcohol level; **laboratory assessment of drop-outs:** not reported
Notes	CAD was extracted from the manufacturer report Subgroups: compliant subgroup analysis

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomization in blocks of eight; no further information provided
Allocation concealment?	Unclear	No information provided
Blinding?	Unclear	**Persons blinded:** double-blind: no detailed information provided; **placebo appearance:** identical to active medication
Incomplete outcome data addressed? binary outcomes	Yes	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication were excluded from the primary analysis (= treatment-received analysis); **handling of missing data:** lost to follow-ups have been categorized as relapsers in the primary analysis
Incomplete outcome data addressed? continuous outcomes	Unclear	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication were excluded from the primary analysis (= treatment-received analysis); **handling of missing data (CAD):** not reported; **handling of missing data (GGT):** outcome not considered in the study
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**1. Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes* * significant baseline differences between groups (prior drinking, place of detoxification) were considered as covariates in the statistical analyses and were shown not have a significant influence on treatment effects **2. Treatment exposure: compliance rates** (patients who took at least 90% of their medication): acamprosate: 27%; placebo: 28%; group difference in compliance rates: not significant

Geerlings 1997

Methods	**Allocation:** random; **blinding:** double-blind; **study duration:** 6 months (treatment); 6 months (post-treatment); **principle of analysis:** ITT (modified); **setting:** outpatient; **study sites:** 22; **country:** Netherlands, Belgium, Luxembourg
Participants	**Diagnosis:** alcohol dependence (DSM-III); **required abstinence:** ≥ 5 days; **baseline characteristics:** 76% male; mean age: 41.0 (SD=8.6) years; 50.6% married; **pre-baseline drinking:** 74% consumed alcohol every day; 66% consumed more than 10 SDU a day; 53% (61%) of patients were physically (psychologically) dependent on alcohol; mean duration of the prior detoxification period: 19.2 (SD = 19) days **Exclusionary of psychiatric conditions:** a concurrent use of psychotropic medication (antidepressants, neuroleptics, benzodiazepines, barbiturates, meprobamate, anti-epileptic drugs, clomethiazole and disulfiram)
Interventions	1. 1332 mg/ 1998 mg acamprosate (n = 128) 2. placebo (n = 134) **Psychosocial treatment:** centre specific, no further information provided; **aim:** abstinence
Outcomes	1. Time to first drink (survival curve) 2. return to any drinking 3. cumulative abstinence duration (CAD) 4. gamma-glutamyltransferase (GGT) 5. mean corpuscular volume (MCV) 6. aspartate aminotransferase (AST) 7. alanine aminotransferase (ALT) 8. side effects
Missing data rates	**Treatment phase / drop-out rates**: acamprosate: 59.4% (n = 76); placebo: 68.5% (n = 92); group difference in drop-out rates: significant; group difference in reasons for drop-out: not reported; **lost to follow-up rates:** not reported **Post-treatment phase / drop-out rates**: acamprosate: 76.6% (n = 98); placebo: 82.8% (n = 111)
Financial support	Sponsored and organized by Merck Lipha (Belgium) within the scope of a new drug application processes
Data assessment methods	**Assessment of drinking:** not reported (week 4, 8, 12, 18, 24, 36*, 48*); *post-treatment evaluation; **assessment of side effects:** not reported; **assessment of compliance:** pill count; **validation of patient-reported outcomes:** not reported; **laboratory assessment of drop-outs:** not reported
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Balanced randomisation in groups of 4 + 4; no further details provided
Allocation concealment?	Unclear	No information provided
Blinding?	Unclear	**Persons blinded:** double-blind; no detailed information provided; **placebo appearance:** not reported
Incomplete outcome data addressed? binary outcomes	Yes	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication were excluded from the primary analysis (= treatment-received analysis); **handling of missing data:** lost to follow-ups have been categorized as relapsers in the primary analysis
Incomplete outcome data addressed? continuous outcomes	Yes	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication were excluded from the primary analysis (= treatment-received analysis); **handling of missing data (CAD):** if a patient was absent from the visit or reported any alcohol use during a given study period, the complete interval was coded as a non-abstinent period for the calculation of cumulative abstinence duration; **handling of missing data (GGT):** outcome not considered in the study
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Unclear	**1. Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: no* * patients in the acamprosate group had a significantly longer alcohol-free period after previous detoxifications than in the placebo group **2. Treatment exposure: compliance rates** (% of medication taken): acamprosate: 86%; placebo: 88%; group difference in compliance rates: not significant

Gual 2001

Methods	**Allocation:** random; **blinding:** double-blind; **study duration:** 6 months; **principle of analysis:** ITT (modified); **setting:** outpatient; **study sites:** 11; **country:** Spain
Participants	**Diagnosis:** alcohol dependence (DSM-III-R); **required abstinence:** ≥ 7 days; **baseline characteristics:** 79% male; mean age: 41.0 (SD = 9.2) years; 67.7% married; **pre-baseline drinking:** 84% consumed alcohol every day; 66.3%% consumed more than 10 SDU a day; 12.8 (SD = 7.9) years of alcohol dependence; MAST score (Selzer 1971): 27.8 (SD = 8.5) **Exclusionary of psychiatric conditions:** 1. a drug abuse or (other than alcohol or nicotine) during the preceding 6 months; 2. a concurrent major psychiatric disorder that would require treatment during the trial. 3. a concurrent use of disulfiram
Interventions	1. 1998 mg acamprosate (n = 141) 2. placebo (n = 147) **Psychosocial treatment:** no information provided; **aim:** abstinence; **permitted medication:** Tetrabamate, chlomethiazole, amitriptyline, imipramine, chlordiazepoxide, clorazepate, triazolam, temazepam; **dosing:** acamprosate was prescribed from the start of alcohol withdrawal
Outcomes	1. Cumulative abstinence duration (CAD) 2. stable recovery duration 3. return to any drinking 4. time to first drink 5. craving 6. gamma-glutamyltransferase (GGT) 7. carbohydrate-deficient transferrin (CDT) 8. side effects
Missing data rates	**Drop-out rates**: acamprosate: 31.9% (n = 45); placebo: 38.8% (n = 57); group difference in drop-out rates: not reported; group difference in reasons for drop-out: not reported; **lost to follow-up rates**: acamprosate: 14.2% (n = 21); placebo: 18.2% (n = 27); group difference in lost to follow-up rates: not reported
Financial support	Sponsored and organized by Merck Lipha (Spain) within the scope of a new drug application processes
Data assessment methods	**Assessment of drinking:** retrospective quantity / frequency report (week 4, 8, 12, 18, 24); **assessment of side effects:** not reported; **assessment of compliance:** pill count; **validation of patient-reported outcomes:** a GGT equal or above 1.3 times the upper laboratory normal was considered as suggestive of possible relapse drinking; **laboratory assessment of drop-outs:** not reported
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	No information provided
Blinding?	Unclear	**Persons blinded:** double-blind; no detailed information provided; **placebo appearance:** not reported
Incomplete outcome data addressed? binary outcomes	Yes	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication were excluded from the primary analysis (= treatment-received analysis); **handling of missing data:** lost to follow-ups have been categorized as relapsers in the primary analysis
Incomplete outcome data addressed? continuous outcomes	Yes	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication were excluded from the primary analysis (= treatment-received analysis); **handling of missing data (CAD):** if a patient was absent from the visit or reported any alcohol use during a given study period, the complete interval was coded as a non-abstinent period for the calculation of cumulative abstinence duration; **handling of missing data (GGT):** outcome not considered in the study
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**1. Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes **2. Treatment exposure: compliance rates** (% of medication taken): acamprosate: 91.5%; placebo: 91.4%; group difference in compliance rates: not significant

Kiefer 2003

Methods	**Allocation:** random; **Blinding:** double-blind; **Study duration:** 12 weeks (treatment); 12 weeks (post-treatment); **Principle of analysis:** ITT; **Setting:** outpatient; **study sites:** 1; **country:** Germany
Participants	**Diagnosis:** alcohol dependence; **required abstinence:** 12 to 15 days; **baseline characteristics:** 73.7% male; mean age: 46.2 (SD=9.3) years; 28% married: 61% employed; **pre-baseline drinking:** 254.9 (SD = 129.4) grams alcohol per day; 2.7 (SD = 4.0) previous detoxifications **Exclusionary psychiatric conditions:** 1. a history of opioid or cocaine abuse; 2. a concurrent major psychiatric impairment or disorder requiring psychotropic medication or inpatient treatment or a history of psychosis; 3. a concurrent use of psychotropic medications or disulfiram
Interventions	1. 1998 mg acamprosate (n = 40) 2. 50 mg naltrexone (n = 40) 3. 50 mg naltrexone and 1998 mg acamprosate (n = 40) 4. placebo plus psychosocial treatment (n = 40) **Psychosocial treatment:** cognitive behavioral therapy (CBT); **applied manual:** Marlatt 1985; **aim:** abstinence
Outcomes	1. Time to first drink (survival curve) 2. time to first relapse* (survival curve) 3. days abstinent 4. craving 5. gamma-glutamyltransferase (GGT) 6. carbohydrate-deficient transferrin (CDT) 7. mean corpuscular volume (MCV) 8. side effects * relapse: drinking ≥ 5 (4) SDU per drinking for men (women) or having ≥ 5 drinking days per week
Missing data rates	**Drop-out rates:** acamprosate: 57.5% (n = 23); naltrexone: 45% (n = 18); naltrexone + acamprosate: 35.0% (n = 14); placebo: 75% (n = 30); group difference in drop-out rates: not reported, but appear significant; group difference in reasons for drop-out: not reported
Financial support	University of Hamburg
Data assessment methods	**Assessment of drinking**: drinking diary (weekly); **assessment of side effects:** adverse effect checklist; **assessment of compliance:** pill count; **validation of patient-reported outcomes:** breath alcohol concentrations were randomly registered; **laboratory assessment of drop-outs:** not reported
Notes	Post-treatment results were presented in Kiefer 2004

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Randomized; computer-generated randomisation lists
Allocation concealment?	Yes	Randomization was centralized; allocation codes were provided in sealed envelopes for each patient at the pharmacy of the university hospital, where formulation and blinding was conducted
Blinding?	Yes	**Persons blinded:** double-blind, including patients and research staff; **placebo appearance:** double-dummy design (an identically matched placebo was available for each drug, and participants in each group took the same number of pills per day) The integrity of the double-blind procedure was confirmed by obtaining a prediction from each patient at the end of the trial
Incomplete outcome data addressed? binary outcomes	Yes	**Principle of analysis:** ITT; **handling of missing data:** lost to follow-ups have been categorized as relapsers in the primary analysis
Incomplete outcome data addressed? continuous outcomes	Unclear	**Principle of analysis:** not reported; **handling of missing data (CAD, GGT):** not reported
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**1. Baseline equivalence:** socio-demographic variables: yes (besides gender); drinking frequency: *not reported;* drinking intensity: *no*;* drinking history or treatment history: *no** * baseline differences between groups (amount of alcohol consumed per day, history of drinking problems, GGT) were considered as covariates in the MANCOVA and were shown not have a significant influence on the treatment effects **2. Treatment exposure: compliance rates** (% of prescribed medication taken): 81.1%; no group specific values provided; group difference in compliance rates: not significant

Ladewig 1993

Methods	**Allocation:** random; **blinding:** double-blind; **study duration:** 6 months (treatment); 6 months (post-treatment); **principle of analysis:** ITT; **setting:** outpatient; **study sites:** 3; **country:** Switzerland
Participants	**Diagnosis:** alcohol dependence (DSM-III); **required abstinence:** ≥ 5 days; **baseline characteristics:** 75.8% male; mean age: 46.8 (SD = 10.2) years; **pre-baseline drinking:** 85.5% had at least one prior alcohol detoxification; 12.3 (SD = 1.8) years of drinking; MAST score (Selzer 1971): 37.9 (SD = 39.1) **Exclusionary of psychiatric conditions:** a concurrent major psychiatric disorder
Interventions	1. 1332 mg/ 1998 mg acamprosate (n = 29) 2. placebo (n = 32) **Psychosocial treatment:** no information provided; **aim: abstinence; dosing:** weight dependent
Outcomes	1. Time to first drink (survival curve) 2. return to any drinking 3. patients who remain abstinent between study visits 4. cumulative abstinence duration (CAD) 5. side effects
Missing data rates	**Treatment phase / drop-out rates**: acamprosate: 34.5% (n = 10); placebo: 34.4% (n = 11); group difference in drop-out rates: not significant; group difference in reasons for drop-out: not reported; **lost to follow-up rates**: acamprosate: 6.9% (n = 2); placebo: 3% (n = 1); group difference in lost to follow-up rates: not significant **Post-treatment phase / drop-out rates**: 34% of the entire sample dropped out during the treatment and post-treatment phase; no group specific values were provided
Financial support	The study has received grants and facilities by the manufacturer (Lipha Pharmaceuticals), but the manufacturer had no role in the management, analyses and interpretation of data
Data assessment methods	**Assessment of drinking:** retrospective quantity / frequency report (week 4, 12, 24, 363, 483); *post-treatment evaluation; **assessment of side effects:** side effect checklist (44 symptoms); **assessment of compliance:** not reported; **validation of patient-reported outcomes:** GGT; **laboratory assessment of drop-outs:** not reported
Notes	CAD was extracted from the manufacturer report

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	No information provided
Blinding?	Unclear	**Persons blinded:** double-blind; no detailed information provided; **placebo appearance:** not reported
Incomplete outcome data addressed? binary outcomes	Yes	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication were excluded from the primary analysis (= treatment-received analysis); **handling of missing data:** lost to follow-ups have been categorized as relapsers in the primary analysis
Incomplete outcome data addressed? continuous outcomes	Yes	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication were excluded from the primary analysis (= treatment-received analysis); **handling of missing data (CAD):** if a patient was absent from the visit, the complete interval was excluded for the calculation of cumulative abstinence; **handling of missing data (GGT):** outcome not considered in the study
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Unclear	**1. Baseline equivalence:** socio-demographic variables: yes (besides gender); drinking frequency: *not reported;* drinking intensity: yes; drinking history or treatment history: *no** * patients in the acamprosate group had more previous treatments than patients in placebo group; the difference was not reported to be controlled in the statistical analyses of treatment effects **2. Treatment exposure: compliance rates:** acamprosate: 84.8%; placebo: 92.2%; group difference in compliance rates: not significant

Lhuintre 1985

Methods	**Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks; **principle of analysis:** completer analysis, subsequently transformed into ITT analysis; **setting:** outpatient; **study sites**: 1; **country:** France
Participants	**Diagnosis:** alcohol dependence; **required abstinence:** ≥ 5 days; **baseline characteristics:** 88.6% male; mean age: 41.4 (SD = 7) years; **pre-baseline drinking:** not reported **Exclusionary of psychiatric conditions:** 1. a concurrent major psychiatric disorder; 2. more than two failed attempts of alcohol detoxification
Interventions	1. 1000 mg - 2250 mg acamprosate (n = 33 + 9*) 2. placebo (n = 37 + 6*) * patients subsequently added to the meta-analyses of binary outcomes as treatment failures **Psychosocial treatment:** no information provided; **dosing:** weight dependent (with 1 capsule per 10 kg body weight per day; minimum:1000 mg; maximum; 2250 mg)
Outcomes	1. Return to any drinking 2. patients who remain abstinent between study visits 3. gamma-glutamyltransferase (GGT) 4. mean corpuscular volume (MCV) 5. side effects
Missing data rates	**Drop-out rates**: acamprosate: 21.4% (n = 9); placebo: 14.0% (n = 6); group difference in drop-out rates: not reported; group difference in reasons for drop-out: not reported; **lost to follow-up rates**: acamprosate: 9.5% (n = 4); placebo: 11.6% (n = 5); group difference in lost to follow-up rates: not reported
Financial support	Sponsored by MERAM, France
Data assessment methods	**Assessment of drinking:** not reported; **assessment of side effects:** not reported; **assessment of compliance:** not reported; **validation of patient-reported outcomes:** GGT, MCV; **laboratory assessment of drop-outs:** not reported
Notes	Completer analyses were subsequently transformed into ITT analyses for the meta-analyses

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	No information provided
Blinding?	Unclear	**Persons blinded:** double-blind; not reported; **placebo appearance:** not reported
Incomplete outcome data addressed? binary outcomes	No	**Principle of analysis:** completer analysis, patients who did not have at least one outcome criteria available (acamprosate: n = 9; placebo: n = 6) were excluded in the primary analysis, but subsequently added to the meta-analyses of binary outcomes as treatment failures; **handling of lost to follow-ups:** individuals lost to follow-up were ere excluded from the analysis, but were subsequently categorized as relapsers in the meta-analysis
Incomplete outcome data addressed? continuous outcomes	No	**Principle of analysis:** completer analysis; **handling of missing data (CAD):** outcome not considered in the study; **handling of lost to follow-ups (GGT):** individuals lost to follow-up were excluded from the analysis
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**1. Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes **2. Treatment exposure: compliance rates:** not reported;group difference in compliance rates: not significant

Lhuintre 1990

Methods	**Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks; **principle of analysis:** not reported; **setting:** outpatient; **study sites:** 30; **country:** France
Participants	**Diagnosis:** alcohol dependence (DSM-IV); **required abstinence:** 5 to 30 days; **baseline characteristics:** 81.9% male; mean age: 42.5 (SD=9.5) years; 64.5% married: 62% employed; **pre-baseline drinking:** 194.5 (SD = 115.0) grams alcohol per day **Exclusionary of psychiatric conditions:** 1. a concurrent use of benzodiazepines (started within the last six months), high dose antidepressants and neuroleptics
Interventions	1. 1332 mg acamprosate (n = 279) 2. placebo (n = 290) **Psychosocial treatment:** not reported; **permitted medication:** benzodiazepines (if use started at least 6 months before the trial), antidepressants and neuroleptics at low doses, meprobamate, non-barbiturate hypnotics, non-benzodiazepine hypnotics
Outcomes	1. Return to any drinking 2. gamma-glutamyltransferase (GGT) 3. mean corpuscular volume (MCV) 4. aspartate aminotransferase 5. alanine aminotransferase 6. side effects
Missing data rates	**Drop-out rates**: acamprosate: 37.3% (n = 104); placebo: 37.6% (n = 109); group difference in drop-out rates: not significant; group difference in drop-out reasons: not reported; **lost to follow-up rates**: not reported
Financial support	The study has received grants and facilities by the manufacturer (Merck LIpha, France), but the manufacturer had no role in the management, analyses and interpretation of data
Data assessment methods	**Assessment of drinking:** no patient-reported drinking outcomes provided (week 4, 8, 12); **assessment of side effects:** 43-item side effect questionnaire; **assessment of compliance:** pill count; **validation of patient-reported drinking outcomes:** no patient-reported drinking outcomes provided
Notes	Rates of any drinking were extracted from the manufacturer report

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	No information provided
Blinding?	Unclear	**Persons blinded:** double-blind; no detailed information provided; **placebo appearance:** identical to active medication
Incomplete outcome data addressed? binary outcomes	Yes	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication were excluded from the primary analysis (= treatment-received analysis); **handling of missing data:** lost to follow-ups have been categorized as relapsers in the primary analysis
Incomplete outcome data addressed? continuous outcomes	Unclear	**Principle of analysis:** not reported; **handling of missing data (CAD):** outcome not considered in the study; **handling of missing data (GGT):** not reported
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Unclear	**1. Baseline equivalence**: socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes **2. Treatment exposure**: **compliance rates:** not reported; group difference in compliance rates: not reported

Mason 2006

Methods	**Allocation:** random; **blinding:** double-blind; **study duration:** 6 months (treatment); 8 weeks (post-treatment); **principle of analysis:** ITT modified (first visit non-attendants excluded); **setting:** outpatient; **study sites:** 21; **country:** USA
Participants	**Diagnosis:** alcohol dependence (DSM-IV); **required abstinence:** abstinence was not explicitly required for admission to the study; 49.6% of patients were abstinent at baseline; **baseline characteristics:** 67.9% male; mean age: 44.5 (SD = 10.1) years; 47% married; 57.2% employed full-time; **pre-baseline drinking:** 67.3 % drinking days; 6.2 (SD = 3.8) drinks per day; 12.8 (SD = 9.0) years of heavy drinking **Exclusionary of psychiatric conditions:** 1. a clinically significant psychiatric condition; 2. need for psychoactive medication; 3. use of any investigational drug, disulfiram or naltrexone in the month prior to screening; 4. dependence on illicit drugs or unable to provide a pre-randomization urine sample
Interventions	1. 2000 mg acamprosate (n = 253 + 5*) 2. 3000 mg acamprosate (n = 82 + 1*) 3. placebo (n = 257 + 3*) * patients subsequently added to the meta-analyses of binary outcomes as treatment failures **Psychosocial treatment:** cognitive behavioral techniques and motivational enhancement for medication compliance; **applied manual:** www.alcoholfree.info; **aim:** abstinence
Outcomes	1. Cumulative abstinence duration (CAD) 2. drinks per week 3. drinking days per week 4. side effects
Missing data rates	**Drop-out rates**: acamprosate: 56.3% (n = 192); placebo: 44.4% (n = 114); group difference in drop-out rates: significantly higher drop-out in the acamprosate group; **lost to follow-up rates**: acamprosate: 15.5% (n = 51); placebo: 10.1% (n = 26); group difference in lost to follow-up rates: not reported
Financial support	Sponsored and organized by Lipha Pharmaceuticals within the scope of a new drug application processes
Data assessment methods	**Assessment of drinking:** TLFB interview (Sobell 1988; Sobell 1992; diary cards; retrospective quantity / frequency reports; **assessment of side effects:** open-ended questionnaire; **assessment of compliance:** pill count; acamprosate plasma levels; **validation of patient-reported outcomes:** 1. breath alcohol concentration; 2. GGT; 3. collateral reports; **laboratory assessment of drop-outs:** not reported
Notes	Rates of any drinking, rates of heavy drinking and standard deviations (SD) for CAD were extracted from the manufacturer report No results provided for the post-treatment evaluation

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Yes	Identical blister-cards of double-blind medication were centrally prepared and labelled by study number; randomisation numbers were centrally prepared for each site in blocks of 7 and used to randomly assign participants to treatment groups; information on randomisation was provided in sealed envelopes
Blinding?	Yes	**Persons blinded:** double-blind, including patients and research staff; **placebo appearance:** identical to active medication
Incomplete outcome data addressed? binary outcomes	No	**Principle of analysis:** ITT - modified; patients who did not have at least one outcome criteria available (acamprosate: n = 6; placebo: n = 3) were excluded, but subsequently considered in the meta-analysis; **handling of missing data:** lost to follow-ups have been categorized as relapsers in the primary analysis
Incomplete outcome data addressed? continuous outcomes	No	**Principle of analysis:** ITT - modified; patients who did not have at least one outcome criteria available (acamprosate: n = 6; placebo: n = 3) were excluded in the primary analysis, but subsequently added to the meta-analyses of binary outcomes as treatment failures; **handling of missing data (CAD):** if a patient was absent from the visit or reported any alcohol use during a given study period, the complete interval was coded as a non-abstinent period for the calculation of *drinking days;* if the early discontinuation was verified as not associated with alcohol use, the time was excluded (the denominator in such cases was the actual time on study); **handling of missing data (GGT):** outcome not considered in the study
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**1. Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes* * there was a non-significant trend for the lower dose acamprosate group for higher alcoholism severity than in other groups **2. Treatment exposure: compliance rates** (% 80% of the prescribed medication taken): acamprosate: 88.9%; placebo: 92.6%;group difference in compliance rates: not significant

Morley 2006

Methods	**Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks; **principle of analysis:** ITT; **setting:** outpatient; **study sites:** 3; **country:** Australia
Participants	**Diagnosis:** alcohol dependence; alcohol abuse; **required abstinence:** 3 to 21 days; **baseline characteristics:** 70.4% male; mean age: 44.9 (SD = 9.0) years; 35% married: 66% employed; **pre-baseline drinking:** 14.8 (SD = 7.9) drinks per drinking day; 15.8 (SD = 10.8) years of problematic drinking; ADS score (Skinner 1982; Skinner 1984): 20.5 (SD = 8.7); mean duration of abstinence: 4.8 (SD = 3.8) days **Exclusionary psychiatric conditions:** 1. a concurrent drug abuse or dependence; 2. a concurrent major psychiatric disorder with psychosis and significant suicide risk; 3. a treatment with naltrexone or acamprosate within 3 months before randomization
Interventions	1. 50 mg naltrexone (n = 53) 2. 1998 mg acamprosate (n = 55) 3. placebo (n = 61) **Psychosocial treatment:** brief intervention; compliance training
Outcomes	1. Return to any drinking 2. Return to heavy drinking* 3. days abstinent 4. drinks per drinking day 5. time to first drink 6. craving 7. gamma-glutamyltransferase (GGT) 8. side effects *relapse / heavy drinking: drinking ≥6 (4) SDU for men (women)
Missing data rates	**Drop-out rates**: acamprosate: 25.5% (n = 14); naltrexone: 32.1% (n = 17); placebo: 34.4% (n = 21); group difference in drop-out rates: not significant; group difference in reasons for drop-out: not reported; **lost to follow-up rates**: acamprosate: 3.3% (n = 2); naltrexone: 3.8% (n = 2); placebo: 1.6% (n = 1); group difference in lost to follow-up rates: not significant
Financial support	National Health and Medical Research Council of Australia, University of Sydney Sesqui Fund
Data assessment methods	**Assessment of drinking:** TLFB interview (Sobell 1988; Sobell 1992; week 1, 2, 6, 12); daily monitoring cards; **assessment of side effects:** open-ended enquiry; **assessment of compliance:** pill count; **validation of patient-reported outcomes:** urine alcohol concentrations were examined in a randomly selected sample of 10% of the study population; **laboratory assessment of drop-outs:** not reported
Notes	Subgroups: 1. completed and compliant patients. Further publication used for data extraction: Richardson (2008); information on the study design was provided by the investigator

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Randomized; computer-generated randomisation lists (information provided by the investigator)
Allocation concealment?	Yes	The randomisation was conducted by an independent support unit; prior to the start of the trial all medication packages were collated and packaged by a member of staff not involved in the study; each sealed envelope contained the medication had a subject code, which corresponded to the allocation that was kept in a spreadsheet held by a member of staff not involved in the study; the naltrexone and naltrexone placebo were packaged similarly as were the acamprosate and acamprosate placebo (information provided by the investigator)
Blinding?	Yes	**Persons blinded:** double-blind including patients, researchers, therapists; **placebo appearance:** an identically matched placebo was available for each drug, and participants in each group took the same number of pills per day The validity of the double-blind procedure was examined and confirmed at the end of the trial
Incomplete outcome data addressed? binary outcomes	Yes	**Principle of analysis:** ITT; **handling of lost to follow-up data:** patients lost to follow-up were assumed to have relapsed from the last date of contact
Incomplete outcome data addressed? continuous outcomes	Yes	**Principle of analysis:** ITT; **handling of lost to follow-up data (CAD):** for the calculations of *drinking days*, individuals lost to follow-up were assumed to have relapsed from the last date of contact (drinking days); **handling of missing data (GGT):** outcome not considered in the study
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**1. Baseline equivalence:** socio-demographic variables: yes (except age*); drinking frequency and intensity: no*; drinking history or treatment history: yes * baseline imbalance was found for age and consecutive abstinent days before treatment and considered as covariate in the statistical analyses **2. Treatment exposure: compliance rates** (patients who took at least 80% of the prescribed medication): 79.7% (of study completers); no group specific values provided; group difference in compliance rates: not significant

Namkoong 2003

Methods	**Allocation:** random; **blinding:** double-blind; **study duration:** 8 weeks; **principle of analysis:** : ITT (modified); **setting:** outpatient; **study sites:** 12; **Country:** South Korea
Participants	**Diagnosis:** alcohol dependence (DSM-IV); **required abstinence:** not reported; **baseline characteristics:** 95.8% male; mean age: 44 (SD = 8.3) years; 76.1% married: 59.9% employed; **pre-baseline drinking:** 52.7 (SD = 32.7) drinking days; 18.0 (SD = 11.7) drinks per drinking occasion; 4.6 (SD = 6.0) previous admissions to alcoholism in-patient programmes; 42% had previous alcohol detoxifications; ADS score (Skinner 1982; Skinner 1984): 21.5 (SD = 8.4) **Exclusionary of psychiatric conditions:** 1. a concurrent drug abuse or dependence (other than alcohol or nicotine); 2. a concurrent major psychiatric disorder; 3. a concurrent use of psychotropic medications or disulfiram or a previous treatment with acamprosate
Interventions	1. 1332 mg/ 1998 mg acamprosate (n = 72) 2. placebo (n = 70) **Psychosocial treatment:** brief psychotherapy; patients were encouraged to participate in AA groups or cognitive behavioral therapy; **dosing:** weight dependent
Outcomes	1. Return to any drinking 2. return to heavy drinking* 3. percent days abstinent 4. percent heavy drinking days 5. drinks per drinking occasion 6. craving 7. gamma-glutamyltransferase (GGT) 8. aspartate aminotransferase 9. alanine aminotransferase 10. side effects * relapse / heavy drinking: drinking ≥ 5 (4) SDU for men (women)
Missing data rates	**Drop-out rates**: acamprosate: 26.4% (n = 19); placebo: 31.4% (n = 22); group difference in drop-out rates: not significant; group difference in reasons for drop-out: not reported; **lost to follow-up rates**: acamprosate: 5.6% (n = 4); placebo: 14.3% (n = 10); group difference in lost to follow-up rates: not reported
Financial support	Sponsored by Whan-In Pharmaceutical (South Korea)
Data assessment methods	**Assessment of drinking:** TLFB interview (Sobell 1988; Sobell 1992; weekly for the first 4 weeks, afterwards biweekly); **assessment of side effects:** SAFTEE (Levine 1986, Rabkin 1992); **assessment of compliance:** pill count; **validation of patient-reported outcomes:** breathalyzer test; **laboratory assessment of drop-outs:** not reported
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Randomized; computer-generated randomisation lists
Allocation concealment?	No	Patients were randomised by the principal investigator; no further information provided
Blinding?	Yes	**Persons blinded:** double-blind, including patients and investigators; **placebo appearance:** identical to active medication
Incomplete outcome data addressed? binary outcomes	Yes	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication were excluded from the primary analysis (= treatment-received analysis); **handling of missing data:** lost to follow-ups have been categorized as relapsers in the primary analysis
Incomplete outcome data addressed? continuous outcomes	Unclear	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication were excluded from the primary analysis (= treatment-received analysis); **handling of missing data (CAD, GGT):** not reported
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**1. Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes **2. Treatment exposure: compliance rate** (% of tablets taken): acamprosate: 80.5%; placebo: 74.3%; group difference in compliance rates: not significant

Niederhofer 2002

Methods	**Allocation:** random; **blinding:** double-blind; **study duration:** 6 months; **principle of analysis:** ITT (modified); **setting:** inpatient; **study sites:** 1; **country:** Austria
Participants	**Diagnosis:** alcohol dependence (DSM-IV); **required abstinence:** ≥ 5 days; **baseline characteristics:** 65.4% male; mean age: 17.1 (SD = 1.1) years; **pre-baseline drinking:** no details provided **Exclusionary of psychiatric conditions:** concurrent psychiatric disorders that might require specific drug treatment
Interventions	1. 1332 mg acamprosate (n = 13) 2. placebo (n = 13) **Psychosocial treatment:** not reported
Outcomes	1. Return to any drinking 2. cumulative abstinence duration (CAD) 3. side effects
Missing data rates	**Drop-out rates**: acamprosate: 46.2% (n = 6); placebo: 38.5% (n = 5); group difference in drop-out rates: not significant; group differences in reasons for drop-out: not significant; **lost to follow-up rates**: not reported
Financial support	Investigator-driven trial with non-profit funding
Data assessment methods	**Assessment of drinking:** not reported; **assessment of side effects:** side effect checklist (44 items); **assessment of compliance:** self-report; **validation of patient-reported outcomes:** GGT, MCV (week 1, 2, 3, 4, 6, 8, 10, 12); **laboratory assessment of drop-outs:** not reported
Notes	Inpatient programme; sample: alcohol dependent adolescents

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Randomized; computer-generated randomisation lists
Allocation concealment?	Unclear	Allocation codes were provided in sealed envelopes; no further information provided
Blinding?	Unclear	**Persons blinded:** double-blind; not reported; **placebo appearance:** not reported
Incomplete outcome data addressed? binary outcomes	Yes	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication (n = 7) were excluded from the primary analysis (= treatment-received analysis); **handling of missing data:** lost to follow-ups have been categorized as relapsers in the primary analysis
Incomplete outcome data addressed? continuous outcomes	Yes	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication (n = 7) were excluded from the primary analysis (= treatment-received analysis); **handling of missing data (CAD):** if a patient was absent from the visit or reported any alcohol use during a given study period, the complete interval was coded as a non-abstinent period for the calculation of cumulative abstinence duration; **handling of missing data (GGT):** outcome not considered in the study
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Unclear	**1. Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes **2. Treatment exposure: compliance rate:** not reported; group difference in compliance rates: *not reported*

Paille 1995

Methods	**Allocation:** random; **blinding:** double-blind; **study duration:** 12 months (treatment); 6 months (single-blind placebo); **principle of analysis:** ITT (modified); **setting:** outpatient; **study sites:** 31; **country:** France
Participants	**Diagnosis:** alcohol dependence (DSM-III-R); **required abstinence:** 7 to 30 days; **baseline characteristics:** 80% male; mean age: 43.2 (SD = 8.6) years; 76% living with family; 68.2% employed; **pre-baseline drinking:** 200 grams alcohol per day; 9.5 (SD = 7.1) years of alcohol dependence; 73% had been drinking more than 10 SDU per day **Exclusionary of psychiatric conditions:** 1. a concurrent major psychiatric disorders; 2. more than three attempted detoxifications in the last 2 years
Interventions	1. 1300 mg acamprosate (n = 188) 2. 2000 mg acamprosate (n = 173) 3. placebo (n = 177) **Psychosocial treatment:** supportive psychotherapy; no further information provided; **permitted medication:** maprotiline, lorazepam and any symptomatic therapy which had been started more than 3 months prior to the study
Outcomes	1. Time to first drink (survival curve) 2. Return to any drinking 3. patients who remain abstinent between study visits 4. cumulative abstinence duration (CAD) 5. craving 6. gamma-glutamyltransferase (GGT) 7. mean corpuscular volume (MCV) 8. side effects
Missing data rates	**Drop-out rates**: acamprosate: 51.5% (n = 186); placebo: 65.0% (n = 115); group difference in drop-out rates: significant; group difference in reasons for drop-out: significant (more patients in the placebo group took medication that was not permitted); **lost to follow-up rates**: acamprosate: 15.3% (n = 55); placebo: 15.8% (n = 28); group difference in lost to follow-up rates: not significant
Financial support	Investigator-driven trial with non-profit funding
Data assessment methods	**Assessment of drinking:** retrospective quantity / frequency report (week 4, 8, 12, 16, 20, 24, 32, 40, 48, 56*, 64*, 72*); *post-treatment evaluation; **assessment of side effects:** not reported; **assessment of compliance:** pill count; **validation of patient-reported outcomes:** GGT; **laboratory assessment of drop-outs:** not reported
Notes	If a patient stopped taking the treatment for more than 30 days, the protocol called for withdrawal from the trial The post-treatment phase does not fulfil the criteria of inclusion and are thus not included in the review

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; predetermined lists; no further information provided
Allocation concealment?	Unclear	No information provided
Blinding?	Yes	**Persons blinded:** double-blind, including patients and research staff; **placebo appearance:** identical to active medication
Incomplete outcome data addressed? binary outcomes	Yes	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication were excluded from the primary analysis (= treatment-received analysis); **handling of missing data:** lost to follow-ups have been categorized as relapsers in the primary analysis
Incomplete outcome data addressed? continuous outcomes	Yes	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication were excluded from the primary analysis (= treatment-received analysis); **handling of missing data (CAD):** if a patient was absent from the visit or reported any alcohol use during a given study period, the complete interval was coded as a non-abstinent period for the calculation of cumulative abstinence duration; **handling of missing data (GGT):** not reported
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Unclear	**1. Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes **2. Treatment exposure:** compliance rates (% of pills taken): acamprosate: 50.9%; placebo: 35.6%; group difference in compliance rates: *not reported*

Pelc 1992

Methods	**Allocation:** random; **blinding:** double-blind; **study duration:** 6 months; **principle of analysis:** ITT; **setting:** outpatient; **study sites:** 5; **country:** Belgium
Participants	**Diagnosis:** alcohol dependence (DSM-III); **required abstinence:** ≤ 23 days; **baseline characteristics:** 70% male; mean age: 42.6 (SD = 8.4); **pre-baseline drinking:** no detailed information provided **Exclusionary of psychiatric conditions:** 1. a concurrent mental psychiatric disorder; 2. a concurrent use of psychotropic medications and disulfiram
Interventions	1. 1332 mg/ 1998 mg acamprosate (n = 55) 2. placebo (n = 47) **Psychosocial treatment:** supportive psychotherapy; no further information provided; **dosing:** weight dependent
Outcomes	1. Return to any drinking 2. patients who remain abstinent between study visits 3. cumulative abstinence duration (CAD) 4. gamma-glutamyltransferase (GGT) 5. clinical global impression 6. side effects
Missing data rates	**Drop-out rates**: acamprosate: 52.7% (n = 29); placebo: 79% (n = 37); group difference in drop-out rates: significant; group difference in reasons for drop-out: not reported; **lost to follow-up rates**: acamprosate: 56.4% (n = 31); placebo: 78.7% (n = 37); group difference in lost to follow-up rates: significant
Financial support	Investigator-driven trial with non-profit funding
Data assessment methods	**Assessment of drinking:** not reported (week 1, 2, 4, 12, 24); **assessment of side effects:** side effect check-list (45 items); **assessment of compliance:** pill count; **validation of patient-reported outcomes:** not reported; **laboratory assessment of drop-outs:** not reported
Notes	In case of relapse ≤ 3 days, patients were advised to continue treatment; in case of relapse > 3 days, patients were admitted to in-patient detoxification

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no further information provided
Allocation concealment?	Unclear	No information provided
Blinding?	Unclear	**Persons blinded:** double-blind; no further information provided; **placebo appearance:** identical to active medication
Incomplete outcome data addressed? binary outcomes	Yes	**Principle of analysis:** ITT; **handling of missing data:** lost to follow-ups have been categorized as relapsers in the primary analysis
Incomplete outcome data addressed? continuous outcomes	Yes	**Principle of analysis:** ITT; **handling of missing data (CAD):** if a patient was absent from the visit or reported any alcohol use during a given study period, the complete interval was coded as a non-abstinent period for the calculation of cumulative abstinence duration; **handling of missing data (GGT):** outcome not considered in the study
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Unclear	**1. Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: *not reported;* drinking history or treatment history: *not reported* **2. Treatment exposure:** compliance rates: not reported; group difference in compliance rates: *not reported*

Pelc 1997

Methods	**Allocation:** random; **blinding:** double-blind; **study duration:** 3 months; **principle of analysis:** ITT (modified); **setting:** outpatient; **study sites:** 11; **country:** Belgium, France
Participants	**Diagnosis:** alcohol dependence (DSM-III-R); **required abstinence:** 14 days; **baseline characteristics** 85% male; mean age: 41.3 (SD = 25.7); years; 49.5% married; **pre-baseline drinking:** 76.6% consumed more than 10 SDU a day; 100% had previous detoxifications **Exclusionary of psychiatric conditions:** 1. a concurrent major psychiatric disorder; 2. prior treatment(s) with acamprosate
Interventions	1. 1332 mg acamprosate (n = 63) 2. 1998 mg acamprosate (n = 63) 3. placebo (n = 62) **Psychosocial treatment:** supportive counselling and social support when needed; patients were encouraged to participate in AA groups
Outcomes	1. Cumulative abstinence duration (CAD) 2. time to first drink (survival curve) 3. return to any drinking 4. patients who remain abstinent between study visits 5. gamma-glutamyltransferase (GGT) 6. mean corpuscular volume (MCV) 7. aspartate aminotransferase 8. alanine aminotransferase 9. side effects
Missing data rates	**Drop-out rates**: acamprosate: 31.0% (n = 39); placebo: 48.4% (n = 30); group difference in drop-out rates: significant; group difference in reasons for drop-out: not reported; **lost to follow-up rates**: acamprosate: 9.5% (n = 12); placebo: 24.2% (n =15); group difference in lost to follow-up rates: not reported, but appear significant
Financial support	Sponsored and organized by Merck Lipha (Belgium) within the scope of a new drug application processes
Data assessment methods	**Assessment of drinking:** diary cards; retrospective quantity / frequency report (week 1, 2, 4, 6, 8, 10, 12); **assessment of side effects:** spontaneous reports (week 1, 2, 4, 6, 8, 10, 12); **assessment of compliance:** pill count; **validation of patient-reported outcomes:** urine alcohol concentration; **laboratory assessment of drop-outs:** not reported
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no further information provided
Allocation concealment?	Unclear	No information provided
Blinding?	Unclear	**Persons blinded:** double-blind; no further information provided; **placebo appearance**: not reported
Incomplete outcome data addressed? binary outcomes	Yes	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication were excluded from the primary analysis (= treatment-received analysis); **handling of missing data:** lost to follow-ups have been categorized as relapsers in the primary analysis
Incomplete outcome data addressed? continuous outcomes	Yes	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication were excluded from the primary analysis (= treatment-received analysis); **handling of missing data (CAD):** if a patient was absent from the visit or reported any alcohol use during a given study period, the complete interval was coded as a non-abstinent period for the calculation of cumulative abstinence duration; **handling of missing data (GGT):** outcome not considered in the study
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Unclear	**1. Baseline equivalence:** no significant differences between groups were present at baseline; no further information provided **2. Treatment exposure: compliance rates** (% of tablets taken): 95%; no group specific values provided; group difference in compliance rates: *not reported*

Poldrugo 1997

Methods	**Allocation:** random; **blinding:** double-blind; **study duration:** 6 months (treatment); 6 months (post-treatment); **principle of analysis:** ITT (modified); **setting:** outpatient; **study sites:** 5; **country:** Italy
Participants	**Diagnosis:** alcohol dependence (DSM-III); **required abstinence**: ≥ 5 days; **baseline characteristics:** 73% male; mean age: 43.9 (SD = 9.7) years; 58% married; **pre-baseline drinking:** 86% consumed alcohol every day; 75% consumed more than 10 SDU per day; 10.9 (SD = 1) years of alcohol dependence; MAST score (Selzer 1971): 27.1 (SD = 7.5) **Exclusionary of psychiatric conditions:** concurrent major psychiatric disorders
Interventions	1. 1332 mg/ 1998 mg acamprosate (n = 122) 2. placebo (n = 124) **Psychosocial treatment:** psychological support, group sessions, family therapy; patients were encouraged to participate in AA groups; **aim of therapy:** abstinence; **prohibited medication:** neuroleptics, barbiturates, meprobamate, valproic acid, carbamazepine, clonidine, benzodiazepines); the use of disulfiram was permitted; **dosing:** weight dependent
Outcomes	1. Time to first drink (survival curve) 2. return to any drinking 3. patients who remain abstinent between study visits 4. cumulative abstinence duration (CAD) 5. craving 6. gamma-glutamyltransferase (GGT) 7. mean corpuscular volume (MCV) 8. aspartate aminotransferase 9. alanine aminotransferase 10. side effects
Missing data rates	**Drop-out rates**: acamprosate: 46.7% (n = 57); placebo: 62.1% (n = 77); group difference in drop-out rates: significant; group difference in reasons for drop-out: not significant; **lost to follow-up rates**: acamprosate: 3.3% (n = 4); placebo: 4.0% (n = 5); group difference in lost to follow-up rates: not significant
Financial support	Study has received grants and facilities by the manufacturer (Merck Lipha, Belgium), but the manufacturer had no role in the management, analyses, and interpretation of data
Data assessment methods	**Assessment of drinking:** retrospective quantity / frequency report (week 4, 12, 24, 36*, 48*); *post-treatment evaluation; **assessment of side effects:** not reported; **assessment of compliance:** not reported; **validation of patient-reported outcomes:** GGT (with a GGT of 1.3 times upper limit of laboratory normal as a threshold value for relapse); **laboratory assessment of drop-outs:** not reported
Notes	Patients with a severe relapse during the study were admitted to a hospital for withdrawal treatment while continuing their medication and not considered as protocol violators. Only patients who needed inpatient treatment longer than 14 days were withdrawn from the study

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no further information provided
Allocation concealment?	Unclear	No information provided
Blinding?	Unclear	**Persons blinded:** double-blind; no further information provided; **placebo appearance:** identical appearance and taste to active medication
Incomplete outcome data addressed? binary outcomes	Yes	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication were excluded from the primary analysis (= treatment-received analysis); **handling of missing data:** lost to follow-ups have been categorized as relapsers in the primary analysis
Incomplete outcome data addressed? continuous outcomes	Yes	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication were excluded from the primary analysis (= treatment-received analysis); **handling of missing data (CAD):** if a patient was absent from the visit or reported any alcohol use during a given study period, the complete interval was coded as a non-abstinent period for the calculation of cumulative abstinence duration; **handling of missing data (GGT):** outcome not considered in the study
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**1. Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes **2. Treatment exposure: compliance rates:** not reported; group difference in compliance rates: not significant

Rousseaux 1996

Methods	**Allocation:** random; **blinding:** double-blind; **duration:** 12 weeks (treatment); **principle of analysis:** ITT; **setting:** outpatient; **study sites:** 1; **country:** Belgium
Participants	**Diagnosis:** alcohol dependence (65%); alcohol abuse (35%); **baseline characteristics:** 70.1% male; mean age: 42.2 years; 32.3% married: 64% employed; **pre-baseline drinking:** not reported **Exclusionary of psychiatric conditions:** a concurrent use of psychotropic medications and disulfiram
Interventions	1. 1332 mg/ 1998 mg acamprosate (n = 63) 2. placebo (n = 64) **Psychosocial treatment:** group therapy, individual therapy; **dosing:** weight dependent
Outcomes	1. Return to any drinking 2. drinks per day 3. gamma-glutamyltransferase (GGT) 4. mean corpuscular volume (MCV)
Missing data rates	**Drop-out rates:** acamprosate: 28.6% (n = 18); placebo: 26.6% (n = 17); group difference in drop-out rates: not reported; group difference in reasons for drop-out: not reported **Lost to follow-up rates**: not reported
Financial support	Sponsored and organized by Merck Lipha within the scope of a new drug application processes
Data assessment methods	**Assessment of drinking:** not reported; **assessment of side effects:** not reported; **assessment of compliance:** not reported; **validation of patient-reported outcomes:** not reported; **laboratory assessment of drop-outs:** not reported
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no further information provided
Allocation concealment?	Unclear	No information provided
Blinding?	Yes	**Persons blinded:** double-blind, including patients and research staff; **placebo appearance:** identical to active medication
Incomplete outcome data addressed? binary outcomes	Yes	**Principle of analysis:** ITT; **handling of missing data:** lost to follow-ups have been categorized as relapsers in the primary analysis
Incomplete outcome data addressed? continuous outcomes	Unclear	**Principle of analysis:** ITT; **handling of missing data (CAD):** outcome not considered in the study; **handling of missing data (GGT):** not reported
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Unclear	**1. Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: *not reported*; drinking history or treatment history: *not reported* **2. Treatment exposure: compliance rate:** not reported; group difference in compliance rates: *not reported*

Sass 1996

Methods	**Allocation:** random; **blinding:** double-blind; **study duration:** 12 months (treatment); 12 months (post-treatment); **principle of analysis:** ITT (modified); **setting:** outpatient; **study sites:** 12; **country:** Germany
Participants	**Diagnosis:** alcohol dependence (DSM-III-R); **required abstinence:** 14 to 28 days; **baseline characteristics:** 77.6% male; mean age: 41.2 (SD = 0.7) years; 46% married; **pre-baseline drinking:** 78% consumed more than 10 SDU a day; 73.1% had previous treatments or detoxifications for alcoholism **Exclusionary of psychiatric conditions:** 1. a concurrent drug abuse or dependence 2. a concurrent psychiatric impairment that would require treatment during the trial
Interventions	1. 1332 mg/ 1998* mg acamprosate (n = 136) 2. placebo (n = 136) **Psychosocial treatment:** centre specific; mostly supportive or individual therapy; **dosing:** 1. weight dependent; 2. flexible: dose reductions to 1332 mg/day in case of side effects; **prohibited medication:** antidepressants, neuroleptics, benzodiazepines, barbiturates, disulfiram, clomethiazole for more than three days
Outcomes	1. Time to first drink (survival curve) 2. return to any drinking 3. patients who remain abstinent between study visits 4. cumulative abstinence duration (CAD) 5. relapse duration 6. craving 7. gamma-glutamyltransferase (GGT) 8. carbohydrate-deficient transferrin (CDT) 9. mean corpuscular volume (MCV) 10. aspartate aminotransferase 11. alanine aminotransferase 12. side effects
Missing data rates	**Drop-out rates**: acamprosate: 41.9% (n = 57); placebo: 59.6% (n = 81); group difference in drop-out rates: significant; group difference in reasons for drop-out: significant (unwillingness to continue treatment; acamprosate: 14.7%; placebo: 33.1%); **lost to follow-up rates**: acamprosate: 19.1% (n = 26); placebo: 20.6% (n = 28); group difference in lost to follow-up rates: not significant
Financial support	Merck Lipha (Germany); sponsored, organized and conducted within the scope of new drug application processes
Data assessment methods	**Assessment of drinking:** diary cards; retrospective quantity / frequency report (week 4, 8, 12, 24, 36, 48, 96*); *post-treatment evaluation; **assessment of side effects:** not reported; **assessment of compliance:** pill count; **validation of patient-reported outcomes:** GGT, collateral information, breathalyzer test; **laboratory assessment of drop-outs:** not reported
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomization with balance of blocks was used to obtain equal numbers of treatment groups; no further information provided
Allocation concealment?	Unclear	Information on randomisation was provided in sealed envelopes; no further information provided
Blinding?	Unclear	**Persons blinded:** double-blind; no further information provided **Placebo appearance**: not reported
Incomplete outcome data addressed? binary outcomes	Yes	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication were excluded from the primary analysis (= treatment-received analysis); **handling of missing data:** lost to follow-ups have been categorized as relapsers in the primary analysis
Incomplete outcome data addressed? continuous outcomes	Yes	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication were excluded from the primary analysis (= treatment received analysis); **handling of missing data (CAD):** if a patient was absent from the visit or reported any alcohol use during a given study period, the complete interval was coded as a non-abstinent period for the calculation of cumulative abstinence duration; **handling of missing data (GGT):** not reported
Free of selective reporting?	Yes	**Outcome reporting:** the publication provides all outcomes specified in the methods section
Free of other bias?	Yes	**1. Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes **2. Treatment exposure: compliance rate** (patients who took at least 80% of the prescribed medication): acamprosate: 97%; placebo: 94%; group difference in compliance rates: not significant

Tempesta 2000

Methods	**Allocation:** random; **blinding:** double-blind; **study duration:** 6 months (treatment); 3 months (post-treatment); **principle of analysis:** ITT (modified); **setting:** outpatient; **study sites:** 18; **country:** Italy
Participants	**Diagnosis:** alcohol dependence (DSM-III-R); **required abstinence:** ≥ 5 days; **baseline characteristics:** 82.7% male; mean age: 45.9 (SD=11.2) years; 68.2% married; **pre-baseline drinking:** 85.2% consumed alcohol every day; 53.0% consumed more than 10 SDU a day; 11.5 (SD = 16.4) years of alcohol dependence; 90% had previous treatment for alcohol dependence; MAST score (Selzer 1971): 22.7 (SD = 10.6) **Exclusionary of psychiatric conditions:** concurrent major psychiatric disorders that would have required treatment during the trial
Interventions	1. 1998 mg acamprosate (n = 164) 2. placebo (n= 166) **Psychosocial treatment:** individual behavior-oriented supportive counselling; patients were encouraged to participate in AA groups
Outcomes	1. Time to first drink (survival curve) 2. return to any drinking 3. patients who remain abstinent between study visits 4. cumulative abstinence duration (CAD) 5. relapse severity 6. craving 7. gamma-glutamyltransferase (GGT) 8. aspartate aminotransferase 9. alanine aminotransferase 10. side effects
Missing data rates	**Drop-out rates**: acamprosate: 24.4% (n = 40); placebo: 26.5% (n = 44); group difference in drop-out rates: not significant; group difference in reasons for drop-out: yes (a higher portion of patients in the placebo group (9.6%) refused to continue than in the acamprosate group (5.5%); **lost to follow-up rates**: acamprosate: 9.8% (n = 16); placebo: 9% (n = 15); group difference in lost to follow-up rates: not significant
Financial support	Study has received grants and facilities by the manufacturer (Merck Lipha, France), but the manufacturer had no role in the management, analyses, and interpretation of data
Data assessment methods	**Assessment of drinking:** drinking diary (week 4, 8, 12, 16, 20, 24, 30*, 36*); *post-treatment evaluation; **assessment of side effects:** 1. spontaneous reporting; 2. side effect checklist; **assessment of compliance:** pill count; **validation of patient-reported outcomes:** collateral reports; urine was sampled for serum levels of carbohydrate-deficient transferrin (CDT), but it is not reported if the measures were used to validate patient-reported outcomes; **laboratory assessment of drop-outs:** not reported
Notes	Rates of any drinking were extracted from the manufacturer report Patients with a severe relapse during the study were admitted to a hospital for withdrawal treatment while continuing their medication and not considered as protocol violators. Only patients who needed inpatient treatment longer than 14 days were withdrawn from the study

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomization with balance of blocks was used to obtain equal numbers of treatment groups; no further information provided
Allocation concealment?	Unclear	Sealed envelope randomisation; no further information provided
Blinding?	Unclear	**Persons blinded:** double-blind; no further information provided; **placebo appearance:** not reported
Incomplete outcome data addressed? binary outcomes	Yes	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication were excluded from the primary analysis (= treatment-received analysis); **handling of missing data:** lost to follow-ups have been categorized as relapsers in the primary analysis
Incomplete outcome data addressed? continuous outcomes	Yes	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication were excluded from the primary analysis (= treatment-received analysis); **handling of missing data (CAD):** if a patient was absent from the visit or reported any alcohol use during a given study period, the complete interval was coded as a non-abstinent period for the calculation of cumulative abstinence duration; **handling of missing data (GGT):** outcome not considered in the study
Free of selective reporting?	Yes	**Outcome reporting:** the publication provides all outcomes specified in the methods section
Free of other bias?	Yes	**1. Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes **2. Treatment exposure: compliance rates** (regular intake of study medication): 76.9 - 84.5% (no group specific values provided); group difference in compliance rates: not significant

Whitworth 1996

Methods	**Allocation:** random; **blinding:** double-blind; **study duration:** 12 months (treatment); 12 months (post-treatment); **principle of analysis:** ITT (modified); **setting:** outpatient; **study sites:** 5; **country:** Austria
Participants	**Diagnosis:** alcohol dependence (DSM-III); **required abstinence:** ≥ 5 days; **baseline characteristics:** 79% male; mean age: 42.0 (SD = 8.5) years; **pre-baseline drinking:** 62.7% consumed more than 10 SDU (or 121 grams alcohol) per day; MAST score (Selzer 1971): 32.6 (SD = 8.8) **Exclusionary of psychiatric conditions:** a concurrent major psychiatric disorders that would require treatment during the trial
Interventions	1. 1332 mg/ 1998 mg acamprosate (n = 224) 2. placebo (n = 224) **Psychosocial treatment:** standardized between centres; not further information provided **Dosing:** weight dependent **Prohibited medication:** drugs that act on the central nervous system were prohibited during the trial with the exception of thioridazine and dibenzepine
Outcomes	1. Time to first drink (survival curve) 2. return to any drinking 3. patients who remain abstinent between study visits 4. cumulative abstinence duration (CAD) 5. gamma-glutamyltransferase (GGT) 6. mean corpuscular volume (MCV) 7. side effects
Missing data rates	**Drop-out rates**: acamprosate: 57.6% (n = 129); placebo: 62.1% (n = 139); group difference in drop-out rates: not significant; group difference in reasons for drop-out: not significant; **lost to follow-up rates**: acamprosate: 14.7% (n = 33); placebo: 16.1% (n = 36); group difference in lost to follow-up rates: not significant
Financial support	Study has received grants and facilities by the manufacturer (Merck Lipha), but the manufacturer had no role in the management, analyses, and interpretation of data
Data assessment methods	**Assessment of drinking:** diary cards; retrospective quantity / frequency report (week 4, 8, 12, 24, 36, 48, 60, 72, 84, 96); *post-treatment evaluation; **assessment of side effects:** side effect checklist (44 items); **assessment of compliance:** not reported; **validation of patient-reported outcomes:** GGT, MCV; **laboratory assessment of drop-outs:** not reported
Notes	Patients with a severe relapse during the study were admitted to a hospital for withdrawal treatment while continuing their medication and not considered as protocol violators; only patients who needed inpatient treatment longer than 15 days were withdrawn from the study

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Randomized; computer-generated randomisation lists
Allocation concealment?	Unclear	Allocation codes were provided in sealed envelopes for each patient; no further information provided
Blinding?	Unclear	**Persons blinded:** double-blind; no further information provided; **placebo appearance:** not reported
Incomplete outcome data addressed? binary outcomes	Yes	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication (n = 7) were excluded from the primary analysis (= treatment-received analysis); **handling of missing data:** lost to follow-ups have been categorized as re lapsers in the primary analysis
Incomplete outcome data addressed? continuous outcomes	Yes	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication (n = 7) were excluded from the primary analysis (= treatment-received analysis); **handling of missing data (CAD):** if a patient was absent from the visit or reported any alcohol use during a given study period, the complete interval was coded as a non-abstinent period for the calculation of cumulative abstinence duration; **handling of missing data (GGT):** outcome not considered in the study
Free of selective reporting?	Yes	**Outcome reporting:** the publication provides all outcomes specified in the methods section
Free of other bias?	Yes	**1. Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes **2. Treatment exposure: compliance rates:** not reported; group difference in compliance rates: not significant

Footnotes

Characteristics of excluded studies

Boeijinga 2004

Reason for exclusion	treatment duration: 15 days (effects on alcohol withdrawal)

Buri 2007

Reason for exclusion	open trial; non-randomised

Croissant 2006

Reason for exclusion	open trial

de Sousa 2005

Reason for exclusion	open trial

De Wildt 2002

Reason for exclusion	no active or placebo control group (acamprosate alone versus acamprosate + minimal intervention versus acamprosate + brief cognitive behavioral therapy)

Feeney 2002

Reason for exclusion	no active or placebo control group (acamprosate + cognitive behavioral therapy versus + cognitive behavioral therapy alone)

Florez 2008

Reason for exclusion	open trial

Fuchs 2002

Reason for exclusion	open trial

Gerra 1992

Reason for exclusion	cross-over trial, with no data from the first study period available

Hammarberg 2004

Reason for exclusion	no active or placebo control group (acamprosate + minimum intervention versus acamprosate + extended intervention)

Han 2008

Reason for exclusion	no active or placebo control group (acamprosate versus no treatment)

Johnson 2003

Reason for exclusion	treatment duration: 23 days (pharmacokinetic / pharmacodynamic study)

Kampman 2009

Reason for exclusion	open trial

Kiritze-Topor 2004

Reason for exclusion	open trial

Laaksonen 2008

Reason for exclusion	open trial

Mason 2002

Reason for exclusion	sample: healthy patients (pharmacokinetic study)

Nespor 2006

Reason for exclusion	open trial

Ooteman 2007

Reason for exclusion	treatment duration: 21 days

Pelc 2002

Reason for exclusion	open trial

Reid 2005

Reason for exclusion	no active or placebo control group (acamprosate + medical care + compliance therapy versus acamprosate + medical care)

Rubio 2001

Reason for exclusion	single-blinded

Rychlik 2001

Reason for exclusion	open trial; non-randomized

Soyka 2002

Reason for exclusion	open trial; non-randomized

Staner 2006

Reason for exclusion	treatment duration: 15 days (laboratory study)

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Gaebel

Study name	Integrative Therapy in Alcoholism
Methods	Randomized, double-blind, placebo, parallel assignment
Participants	Alcohol dependent
Interventions	Acamprosate vs. placebo
Outcomes	1. Abstinence 2. Social functioning 3. Cognitive functioning
Starting date	May 2003
Contact information	---
Principal investigator	Wolfgang Gaebel, Professor Department of Psychiatry and Psychotherapy, University of Düsseldorf
Collaborators	German Federal Ministry of Education and Research German Addiction Research Network Merck Santé University Hospital, Bonn Univeristat Duisburg-Essen University of Homburg Psychosomatic Clinic of Bergisch Gladbach
Sponsors	Heinrich-Heine University, Duesseldorf
Notes	

Garbutt

Study name	Study of Acamprosate for Alcohol Dependence in a Family Medicine Clinic
Methods	Randomized, double-blind, placebo-controlled
Participants	Alcohol dependent patients with abstinence motivation
Interventions	Acamprosate vs. placebo
Outcomes	1. Percent days abstinent 2. Adherence to medicine 3. Drop-out/loss to follow-up rate 4. Percent days complete abstinent 5. Percent heavy drinking days 6. Clinical Global Impression
Starting date	August 2006
Contact information	Amy Ford, MA aford@med.unc.edu
Principal investigator	JC Garbutt, MD, University of North Carolina, Chapel Hill
Collaborators	---
Sponsors	University of North Carolina
Notes	Acamprosate in a family medicine setting

Haber

Study name	Trial for the Treatment of Alcohol Dependence
Methods	Randomized, double-blind, controlled
Participants	Alcohol dependent patients
Interventions	Acamprosate vs. naltrexone
Outcomes	1. Time (days) to relapse 2. Time (days) to lapse 3. Days abstinence 4. Drinks per drinking day 5. Biochemical measures of liver function 6. Craving 7. Depression 8. Anxiety 9. Stress 10. Global physical health 11. Global mental health
Starting date	March 2003
Contact information	---
Principal investigator	Paul Haber, Conjoint Associate Professor, University of Sydney
Collaborators	National Health and Medical Research Council, Australia Sydney South West Area Health Service South Eastern Area Health Service Wentworth Area Health Services
Sponsors	University of Sydney
Notes	

Mann

Study name	Individually Adapted Therapy of Alcoholism
Methods	Randomized, double-blind, placebo-controlled, parallel assignment
Participants	Alcohol dependent patients with abstinent
Interventions	Acamprosate, naltrexone, placebo
Outcomes	1. Time to relapse to heavy drinking 2. percentage of days without heavy drinking 3. time to first alcohol consumption 4. percentage of days of complete abstinence from alcohol
Starting date	November 2002
Contact information	---
Principal investigator	Karl F. Mann, MD, Central Institute of Mental Health, Mannheim, Germany Michael N. Smolka, MD, Central Insitute of Mental Health, Mannheim, Germany
Collaborators	BMBF Federal Ministry of Education and Research Merck Dupont Pharmaceuticals
Sponsors	Central Institute of Mental Health, Mannheim
Notes	

Petrakis

Study name	Treatment With Acamprosate in Patients With Schizophrenia and Comorbid Alcoholism
Methods	Randomized, double-blind, placebo-controlled
Participants	Alcohol dependent patients with a diagnosis of schizophrenia, schizoaffective or psychotic disorder
Interventions	Acamprsate vs. placebo
Outcomes	1. Drinking 2. Craving 3. Psychotic symptoms 4. Cognitive functioning 5. Psychiatric distress
Starting date	September 2006
Contact information	Elizabeth Ralevski, Ph.D. elizabeth.ralevski@yale.edu
Principal investigator	Ismene L Petrakis, MD Yale University
Collaborators	Forest Laboratories
Sponsors	Yale University
Notes	

Pettinati

Study name	Acamprosate Initiated During Alcohol Detoxification
Methods	Randomized, double-blind, placebo-controlled, crossover assignment
Participants	Alcohol dependent patients
Interventions	Acamprosate vs. placebo
Outcomes	1. Days abstinent 2. Days heavy drinking 3. Adverse events 4. Treatment discontinuation 5. Total amount of oxazepam 6. Change in CIWA scores 7. Number of adverse events
Starting date	October 2006
Contact information	---
Principal investigator	Helen Pettinati, Ph.D. University of Pennsylvania
Collaborators	---
Sponsors	Forest Laboratories
Notes	

Sonne

Study name	Acamprosate in Alcoholics With Comorbid Anxiety or Depression
Methods	Randomized, double-blind, placebo-controlled
Participants	Alcohol dependent patients with a concurrent diagnosis of a mood disorders, a social anxiety or a generalized anxiety disorder
Interventions	Acamprosate vs. placebo
Outcomes	1. Total days abstinent from alcohol 2. Psychiatric assessments including MADRS,HAM-A, Liebowitz Social Anxiety Scale, and Hospital Anxiety and Depression Scale
Starting date	April 2006
Contact information	Susan C Sonne, PharmD, BCPP sonnesc@musc.edu
Principal investigator	Susan C Sonne, PharmD, BCPP, Medical University of South Carolina Jennifer S Potter, PhD, Mclean Hospital Richard Rosenthal, MD, Columbia University College of Physicians & Surgeons
Collaborators	Mclean Hospital Columbia University
Sponsors	Medical University of South Carolina
Notes	

Witte

Study name	Acamprosate Added to Escitalopram and Behavioral Treatment for Comorbid Depression and Alcoholism
Methods	Double-blind, placebo-controlled study (randomization unclear)
Participants	Patients with alcohol abuse or dependence and major depressive disorder
Interventions	Escitalopram plus acamprosate vs. escitalopram plus placebo
Outcomes	1. Reduction in alcohol use 2. Reduction in depression score
Starting date	March 2007
Contact information	Janet M. Witte, MD, MPH jwitte@partners.org
Principal investigator	Janet M Witte, MD Massachusetts General Hospital Nicholas Bolo, PhD Mclean Hospital
Collaborators	Mclean Hospital National Alliance for Research on Schizophrenia and Depression
Sponsors	Massachusetts General Hospital
Notes	

Footnotes

Summary of findings tables

Additional tables

References to studies

Included studies

Anton 2006

* Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donovan DM, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomised controlled trial. JAMA 2006;295:2003-17.

Baltieri 2003

Published and unpublished data

Baltieri D A, De Andrade A G. Acamprosate in alcohol dependence: a randomised controlled efficacy study in a standard clinical setting. Journal of studies on alcohol 2004;65:136-9.

Barrias 1997

Published and unpublished data

Barrias JA, Chabac S, Ferreira L, Fonte A, Potgieter AS, Teixeira de Sousa E. Acamprosate: multicenter Portuguese efficacy and tolerance evaluation study. Psiquiatria Clinica 1997;18:149-60.

Besson 1998

Published and unpublished data

Besson J, Aeby F, Kasas A, Lehert P, Potgieter A. Combined efficacy of acamprosate and disulfiram in the treatment of alcoholism: a controlled study. Alcoholism, Clinical and Experimental Research 1998;22:573-9.

Borg 2003

Unpublished data only

Borg S. Randomized controlled trial of acamprosate versus placebo in Swedish alcoholics. Unpublished trial 2003.

Chick 2000

Published and unpublished data

Chick J, Howlett H, Morgan M Y, Ritson B. United Kingdom Multicentre Acamprosate Study (UKMAS): a 6-month prospective study of acamprosate versus placebo in preventing relapse after withdrawal from alcohol. Alcohol and Alcoholism 2000;35:176-87.

Geerlings 1997

Geerlings PJ, Ansoms C, van den Brink W. Acamprosate and prevention of relapse in alcoholics. Results of a randomised, placebo-controlled, double-blind study in out-patient alcoholics in The Netherlands, Belgium and Luxembourg. European Addiction Research 1997;3:129-37.

Gual 2001

Gual A, Lehert P. Acamprosate during and after acute alcohol withdrawal: a double-blind placebo-controlled study in Spain. Alcohol and Alcoholism 2001;36:413-8.

Kiefer 2003

Kiefer F, Jahn H, Tarnaske T, Helwig H, Briken P, Holzbach R, et al. Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism: a double-blind, placebo-controlled study. Archives of General Psychiatry 2003;60:92-9.

Ladewig 1993

Ladewig D, Knecht T, Leher P, Fendl A. Acamprosate--a stabilizing factor in long-term withdrawal of alcoholic patients. Therapeutische Umschau 1993;50:182-8.

Lhuintre 1985

Lhuintre J P, Daoust M, Moore ND, Chretien P, Saligaut C, Tran G, et al. Ability of calcium bis acetyl homotaurine, a GABA agonist, to prevent relapse in weaned alcoholics. Lancet 1985;1:1014-6.

Lhuintre 1990

Lhuintre JP, Moore N, Tran G, Steru L, Langrenon S, Daoust M, et al. Acamprosate appears to decrease alcohol intake in weaned alcoholics. Alcohol and Alcoholism 1990;25:613-22.

Mason 2006

Published and unpublished data

Mason BJ, Goodman AM, Chabac S, Lehert P. Effect of oral acamprosate on abstinence in patients with alcohol dependence in a double-blind, placebo-controlled trial: the role of patient motivation. Journal of Psychiatric Research 2006;40:383-93.

Morley 2006

Morley KC, Teesson M, Reid SC, Sannibale C, Thomson C, Phung N, et al. Naltrexone versus acamprosate in the treatment of alcohol dependence: A multi-centre, randomised, double-blind, placebo-controlled trial. Addiction 2006;101:1451-62.

Namkoong 2003

Namkoong K, Lee BO, Lee PG, Choi MJ, Lee E. Acamprosate in Korean alcohol-dependent patients: a multi-centre, randomised, double-blind, placebo-controlled study. Alcohol and Alcoholism 2003;38:135-41.

Niederhofer 2002

Niederhofer H, Staffen W. Acamprosate and its efficacy in treating alcohol dependent adolescents. European Child & Adolescent Psychiatry 2003;12:144-8.

Paille 1995

Published and unpublished data

Paille FM, Guelfi JD, Perkins AC, Royer RJ, Steru L, Parot P. Double-blind randomised multi centre trial of acamprosate in maintaining abstinence from alcohol. Alcohol and Alcoholism 1995;30:239-47.

Pelc 1992

Published and unpublished data

Pelc I Le Bon O Lehert P Verbanck P. Acamprosate in the treatment of alcohol dependence: A six month post detoxification study. In: Naranjo C, Sellers E, editors(s). Novel pharmacological interventions for alcoholism. New York: Springer, 1992:348-52.

Pelc 1997

Published and unpublished data

Pelc I, Verbanck P, Le Bon O, Gavrilovic M, Lion K, Lehert P. Efficacy and safety of acamprosate in the treatment of detoxified alcohol-dependent patients. A 90-day placebo-controlled dose-finding study. British Journal of Psychiatry 1997;171:73-7.

Poldrugo 1997

Published and unpublished data

Poldrugo F. Acamprosate treatment in a long-term community-based alcohol rehabilitation programme. Addiction 1997;92:1537-46.

Rousseaux 1996

Roussaux JP, Hers D, Ferauge M. Does acamprosate diminish the appetite for alcohol in weaned alcoholics? Journal de Pharmacie de Belgique 1996;51:65-8.

Sass 1996

Published and unpublished data

Sass H, Soyka M, Mann K, Zieglgansberger W. Relapse prevention by acamprosate. Results from a placebo-controlled study on alcohol dependence. Archives of General Psychiatry 1996;53:673-80.

Tempesta 2000

Published and unpublished data

Tempesta E, Janiri L, Bignamini A, Chabac S, Potgieter A. Acamprosate and relapse prevention in the treatment of alcohol dependence: a placebo-controlled study. Alcohol and Alcoholism 2000;35:202-9.

Whitworth 1996

Published and unpublished data

Whitworth AB, Fischer F, Lesch OM, Nimmerrichter A, Oberbauer H, Platz T, et al. Comparison of acamprosate and placebo in long-term treatment of alcohol dependence. Lancet 1996;347:1438-42.

Excluded studies

Boeijinga 2004

Boeijinga PH, Parot P, Soufflet L, Landron F, Danel T, Gendre I, et al. Pharmacodynamic effects of acamprosate on markers of cerebral function in alcohol-dependent subjects administered as pretreatment and during alcohol abstinence. Neuropsychobiology 2004;50(1):71-7.

Buri 2007

Buri C, Moggi F, Giovanoli A, Strik W. Prescription procedures in medication for relapse prevention after inpatient treatment for alcohol use disorders in Switzerland. Alcohol and Alcoholism 2007;42(4):333-9.

Croissant 2006

Croissant B, Diehl A, Klein O, Zambrano S, Nakovics H, Heinz A, et al. A pilot study of oxcarbazepine versus acamprosate in alcohol-dependent patients. Alcoholism: Clinical and Experimental Research 2006;30(4):630-5.

de Sousa 2005

de Sousa A. An open randomised study comparing disulfiram and acamprosate in the treatment of alcohol dependence. Alcohol and Alcoholism 2005;40(6):545-8.

De Wildt 2002

De Wildt WA, Schippers GM, Van Den Brink W, Potgieter A S, Deckers F, Bets D. Does psychosocial treatment enhance the efficacy of acamprosate in patients with alcohol problems? Alcohol and Alcoholism 2002;37(4):375-82.

Feeney 2002

Feeney GF, Young RM, Connor JP, Tucker J, McPherson A. Cognitive behavioural therapy combined with the relapse-prevention medication acamprosate: are short-term treatment outcomes for alcohol dependence improved? Australian and New Zealand Journal of Psychiatry 2002;36(5):622-8.

Florez 2008

Florez G, Garcia-Portilla P, Alvarez S, Saiz P A, Nogueiras L, Bobes J. Using topiramate or naltrexone for the treatment of alcohol-dependent patients. Alcoholism: Clinical and Experimental Research 2008;32(7):1251-9.

Fuchs 2002

Fuchs WJ, Riebenfeld D. Acamprosate and psychosocial intervention. An integrative treatment approach for prevention of alcohol dependent patients in Switzerland. Praxis (Bern 1994) 2002;91(17):735-42.

Gerra 1992

Gerra G, Caccavari R, Delsignore R. Effects of fluoxetine and Ca-acetyl-homotaurinate on alcohol intake in familial and nonfamilial. Current Therapeutic Research 1992;52:291-5.

Hammarberg 2004

Hammarberg A, Wennberg P, Beck O, Franck J. A comparison of two intensities of psychosocial intervention for alcohol dependent patients treated with acamprosate. Alcohol and Alcoholism 2004;39(3):251-5.

Han 2008

Han DH, Lyool I K, Sung YH, Lee SH, Renshaw PF. The effect of acamprosate on alcohol and food craving in patients with alcohol dependence. Drug and Alcohol Dependence 2008;93(3):279-83.

Johnson 2003

Johnson BA, O'Malley SS, Ciraulo DA, Roache JD, Chambers RA, Sarid-Segal O, et al. Dose-ranging kinetics and behavioral pharmacology of naltrexone and acamprosate, both alone and combined, in alcohol-dependent subjects. Journal of Clinical Psychopharmacoly 2003;23(3):281-93.

Kampman 2009

Kampman KM, Pettinati HM, Lynch KG, Xie H, Dackis C, Oslin D W, et al. Initiating acamprosate within-detoxification versus post-detoxification in the treatment of alcohol dependence. Addictive Behaviors 2009;34(6-7):581-6.

Kiritze-Topor 2004

Kiritze-Topor P, Huas D, Rosenzweig C, Comte S, Paille F, Lehert P. A pragmatic trial of acamprosate in the treatment of alcohol dependence in primary care. Alcohol and Alcoholism 2004;39(6):520-7.

Laaksonen 2008

Laaksonen E, Koski-Jannes A, Salaspuro M, Ahtinen H, Alho H. A randomised, multi centre, open-label, comparative trial of disulfiram, naltrexone and acamprosate in the treatment of alcohol dependence. Alcohol and Alcoholism 2008;43(1):53-61.

Mason 2002

Mason BJ, Goodman AM, Dixon RM, Hameed MH, Hulot T, Wesnes K, et al. A pharmacokinetic and pharmacodynamic drug interaction study of acamprosate and naltrexone. Neuropsychopharmacology 2002;27(4):596-606.

Nespor 2006

Nespor K, Csemy L. Treatment and prevention of alcohol-related problems and evidence based medicine. Casopis Lekaru Ceskych 2006;145(12):964-5.

Ooteman 2007

Ooteman W, Koeter MW, Verheul R, Schippers GM, van den Brink W. The effect of naltrexone and acamprosate on cue-induced craving, autonomic nervous system and neuroendocrine reactions to alcohol-related cues in alcoholics. European Neuropsychopharmacoly 2007;17(8):558-66.

Pelc 2002

Pelc I, Ansoms C, Lehert P, Fischer F, Fuchs W J, Landron F, et al. The European NEAT program: an integrated approach using acamprosate and psychosocial support for the prevention of relapse in alcohol-dependent patients with a statistical modelling of therapy success prediction. Alcoholism Clinical and Experimental Research 2002;26(10):1529-38.

Reid 2005

Reid SC, Teesson M, Sannibale C, Matsuda M, Haber PS. The efficacy of compliance therapy in pharmacotherapy for alcohol dependence: a randomised controlled trial. Journal of Studies on Alcohol 2005;66(6):833-41.

Rubio 2001

Rubio G, Jimenez-Arriero MA, Ponce G, Palomo T. Naltrexone versus acamprosate: one year follow-up of alcohol dependence treatment. Alcohol and Alcoholism 2001;36(5):419-25.

Rychlik 2001

Rychlik R, Paschen B, Kirchhoff D, Daniel D, Pfeil T, Kilburg A. Adjuvant drug treatment of alcoholism with acamprosate: between sectorial budgets and disease management. Deutsche Medizinische Wochenschrift 2001;126(33):899-904.

Soyka 2002

Soyka M, Preuss U, Schuetz C. Use of acamprosate and different kinds of psychosocial support in relapse prevention of alcoholism. Results from a non-blind, multicentre study. Drugs in Road Traffic 2002;3(1):1-12.

Staner 2006

Staner L, Boeijinga P, Danel T, Gendre I, Muzet M, Landron F, et al. Effects of acamprosate on sleep during alcohol withdrawal: A double-blind placebo-controlled polysomnographic study in alcohol-dependent subjects. Alcoholism: Clinical and Experimental Research 2006;30(9):1492-9.

Studies awaiting classification

Ongoing studies

Gaebel

Unpublished data only [ClinicalTrials.gov: NCT00159107; Other: 01EB0133]

Garbutt

[ClinicalTrials.gov: NCT00381043; Other: CMP-MD-06]

Haber

Unpublished data only [ClinicalTrials.gov: NCT00120601.; Other: X99-0277]

Mann

[ClinicalTrials.gov: NCT00317031; Other: PREDICT]

Petrakis

[ClinicalTrials.gov: NCT00463346 ; Other: CMP-MD-13]

Pettinati

[ClinicalTrials.gov: NCT00360594; Other: 804481]

Sonne

[ClinicalTrials.gov: NCT00330174; Other: CMP-MD-04]

Witte

[ClinicalTrials.gov: NCT00452543; Other: 2006-P-001592/1]

Other references

Additional references

Adams 2007

Adams CE, Awad G, Rathbone J, Thornley B. Chlorpromazine versus placebo for schizophrenia. Cochrane Database of Systematic Reviews 2007, Issue 1.10.1002/14651858.

Alonso 2004

Alonso J, Angermeyer MC, Bernert S, Bruffaerts R, Brugha TS, Bryson H. Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatrica Scandinavia Supplement 2004;420:21-7.

Arroll 2009

Arroll B, Elley CR, Fishman T, Goodyear-Smith F A, Kenealy T, Blashki G. Antidepressants versus placebo for depression in primary care. Cochrane Database of Systematic Reviews 2009, Issue 1.10.1002/14651858.

Bachteler 2005

Bachteler D, Economidou D, Danysz W, Ciccocioppo R, Spanagel R. The effects of acamprosate and neramexane on cue-induced reinstatement of ethanol-seeking behavior in rat. Neuropsychopharmacology 2005;30(6):1104-10.

Berglund 2003

Berglund MA, Franck J, Fridell M, Hakanson I, Johansson BA. Treatment of alcohol and drug abuse - an evidence-based review. Swedish Council on Technology Assessment in Health Care (SBU) 2003;156(1).

Bouza 2004

Bouza C, Angeles M, Munoz A, Amate JM. Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a systematic review. Addiction 2004;99(7):811-28.

Brockwell 2001

Brockwell SE, Gordon IR. A comparison of statistical methods for meta-analysis. Statistics in Medicine 2001;20(6):825-40.

Cano-Cebrian 2003

Cano-Cebrian MJ, Zornoza-Sabina T, Guerri C, Polache A, Granero L. Acamprosate blocks the increase in dopamine extracellular levels in nucleus accumbens evoked by chemical stimulation of the ventral hippocampus. Naunyn Schmiedebergs Archives of Pharmacology 2003;368(4):324-7.

Chan 2004

Chan AW, Hrobjartsson A, Haahr MT, Gotzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomised trials: comparison of protocols to published articles. JAMA 2004;291(20):2457-65.

Chick 2003

Chick J, Lehert P, Landron F. Does acamprosate improve reduction of drinking as well as aiding abstinence? Journal of Psychopharmacology 2003;17(4):397-402.

Citrome 2008

Citrome L. Compelling or irrelevant? Using number needed to treat can help decide. Acta Psychiatrica Scandinavia 2008;117(6):412-9.

Cole 2000

Cole JC, Littleton JM, Little HJ. Acamprosate, but not naltrexone, inhibits conditioned abstinence behaviour associated with repeated ethanol administration and exposure to a plus-maze. Psychopharmacology (Berl) 2000;147(4):403-11.

Czachowski 2001

Czachowski CL, Legg BH, Samson HH. Effects of acamprosate on ethanol-seeking and self-administration in the rat. Alcoholism Clinical and Experimental Research 2001;25(3):344-50.

Deeks 2008

Deeks J, Higgins JPT, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, editors(s). Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK): Johm Wiley & Sons, 2008:243-293.

DerSimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials 1986;7(3):177-88.

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315(7109):629-34.

Ferri 2006

Ferri M, Amato L, Davoli M. Alcoholics Anonymous and other 12-step programmes for alcohol dependence. Cochrane Database of Systematic Reviews 2006, Issue 3. 10.1002/14651858.CD005032.pub2.

Heyser 1998

Heyser CJ, Schulteis G, Durbin P, Koob GF. Chronic acamprosate eliminates the alcohol deprivation effect while having limited effects on baseline responding for ethanol in rats. Neuropsychopharmacology 1998;18(2):125-33.

Higgins 2001

Higgins JP, Whitehead A, Turner RM, Omar RZ, Thompson SG. Meta-analysis of continuous outcome data from individual patients. Statistics in Medicine 2001;20(15):2219-41.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557-60.

Higgins 2008

Higgins JPT, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, editors(s). Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK): Johm Wiley & Sons, 2008:243-296.

Hopkins 2002

Hopkins JS, Garbutt JC, Poole CL, West SL, Carey TS. Naltrexone and acamprosate: Meta-analysis of two medical treatments for alcoholism. Alcoholism: Clinical and Experimental Research 2002;26(Suppl):130A.

Huwiler-Muntener 2002

Huwiler-Muntener K, Juni P, Junker C, Egger M. Quality of reporting of randomised trials as a measure of methodologic quality. JAMA 2002;287(21):2801-4.

ICAP 2003

ICAP International Center for Alcohol Policies. International Drinking Guidelines [(http://www.icap.org/)]. Report Nr. 14 2003.

ICH 1996

International Conference on Harmonisation. Guideline for Good ClinicalPractice E6(R1).. (http://www.ich.org/LOB/media/MEDIA482.pdf) 1996;Jun [cited 2009 Jan 20].

Kadden 1992

Kadden R, Carroll K, Donovan D, Cooney N, Monti P, Abrams D, Litt M, Hester R. NIAAA Project MATCH Monograph Series. National Institute on Alcoholism and Alcohol Abuse edition. Vol. 3. Rockville: Matson ED, 1992.

Kaner 2007

Kaner EF, Beyer F, Dickinson HO, Pienaar E, Campbell F, Schlesinger C, Heather N, Saunders J, Burnand B. Effectiveness of brief alcohol interventions in primary care populations. Cochrane Database of Systematic Reviews 2007, Issue 2. 10.1002/14651858.CD004148.pub3.

Keller 1972

Keller M. On the loss-of-control phenomenon in alcoholism. British Journal of Addiction 1972;67:153-66.

Kiefer 2004

Kiefer F, Andersohn F, Otte C, Wolf K, Jahn H, Wiedemann K. Long-term effects of pharmacotherapy on relapse prevention in alcohol dependence. Acta Neuropsychiatrica 2004;16:233-8.

Konnopka 2007

Konnopka A, König HH. Direct and indirect costs attributable to alcohol consumption in Germany. Pharmacoeconomics 2007;25(7):605-18.

Kranzler 2001

Kranzler HR, Van Kirk J. Efficacy of naltrexone and acamprosate for alcoholism treatment: a meta-analysis. Alcoholism: Clinical and Experimental Research 2001;25(9):1335-41.

Lefebvre 2008

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for Studies. In: Higgins JPT, Green S, editors(s). Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK): Johm Wiley & Sons, 2008:95-150.

Lehert 1993

Lehert P. Review and discussion of statistical analysis of controlled clinical trials in alcoholism. Alcohol and Alcoholism Supplement 1993;2:157-63.

LeMagnen 1987

LeMagnen J, Tran G, Durlach J. Lack of effects of Ca-acetyl homotaurinate on chronic and acute toxicities of ethanol in rats. Alcohol and Alcohilsm 1987;4(2):103-8.

Levine 1986

Levine J, Schooler NR. SAFTEE: a technique for the systematic assessment of side effects in clinical trials. Psychopharmacol Bulletin 1986;22(2):343-81.

Light 1984

Light RJ, Pillemer BD. The science of reviewing research. Cambridge (MA): Harvard University Press, 1984.

Lipha 2002

Lipha Pharmaceuticals Inc. Clincial Background Materials for Psychopharmacologic Drugs Advisory Committee Meeting. NDA 21-431 2002.

Littleton 1995

Littleton J. Acamprosate in alcohol dependence: how does it work? Addiction 1995;90(9):1179-88.

Littleton 2003

Littleton J, Zieglgansberger W. Pharmacological mechanisms of naltrexone and acamprosate in the prevention of relapse in alcohol dependence. American Journal of Addiction 2003;12 Supplement 1:3-11.

Mann 2004

Mann K, Lehert P, Morgan M Y. The efficacy of acamprosate in the maintenance of abstinence in alcohol-dependent individuals: results of a meta-analysis. Alcoholism: Clinical and Experimental Research 2004;28(1):51-63.

Mann 2008

Mann K, Kiefer F, Spanagel R, Littleton J. Acamprosate: recent findings and future research directions. Alcoholism: Clinical and Experimental Research 2008;32(7):1105-10.

Mantel 1959

Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. Journal of the National Cancer Institute 1959;22(4):719-48.

Marlatt 1985

Marlatt GA, Gordon J. Relapse prevention. New York: Guilford Press, 1985.

McGeehan 2003

McGeehan AJ, Olive MF. The anti-relapse compound acamprosate inhibits the development of a conditioned place preference to ethanol and cocaine but not morphine. British Journal of Pharmacology 2003;138(1):9-12.

McQueen 2009

McQueen J, Howe TE, Allan L, Mains D. Brief interventions for heavy alcohol users admitted to general hospital wards. Cochrane Database of Systematic Reviews 2009, Issue 8. 10.1002/14651858.CD005191.pub2.

Mller 1994

Miller WR, Zweben A, DiClemente CC, Rychtarik RG. Motivational Enhancement Therapy manual: A clinical research guide for therapists treating individuals with alcohol abuse and dependence. Rockville, MD: National Institute on Alcohol Abuse and Alcoholism, 1994.

Moher 2001

Moher D, Jones A, Lepage L, CONSORT Group (Consolitdated Standards for Reporting of Trials). The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001;285(15):1992-5.

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman D G. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097.

Moncrieff 2004

Moncrieff J, Wessely S, Hardy R. Active placebos versus antidepressants for depression. Cochrane Database of Systematic Reviews 2004, Issue 1. 10.1002/14651858.

Moos 2006

Moos RH, Moos BS. Rates and predictors of relapse after natural and treated remission from alcohol use disorders. Addiction 2006;101(2):212-22.

Naassila 1998

Naassila M, Hammoumi S, Legrand E, Durbin P, Daoust M. Mechanism of action of acamprosate. Part I. Characterization of spermidine-sensitive acamprosate binding site in rat brain. Alcoholism: Clinical and Experimental Research 1998;22(4):802-9.

Newell 1992

Newell DJ. Intention-to-treat analysis: implications for quantitative and qualitative research. International Journal of Epidemiology 1992;21(5):837-41.

Nickerson 1998

Nickerson RS. Confirmation Bias: A Ubiquitous Phenomenon. Review of General Psychology 1998;2:175-7.

Nowinski 1995

Nowinski J, Baker S, Carroll, K. Twelve Step Facilitation Therapy manual. A clinical research guide for therapists treating individuals with alcohol abuse and dependence. Rockville, MD: Project MATCH Monograph Series Volume I. U.S. Department of Health and Human Services, 1995.

Olive 2002

Olive MF, Nannini MA, Ou CJ, Koenig HN, Hodge CW. Effects of acute acamprosate and homotaurine on ethanol intake and ethanol-stimulated mesolimbic dopamine release. European Journal of Pharmacology 2002;437(1-2):55-61.

Pettinati 2004

Pettinati HM, Weiss RD, Miller WR, Donovan D, Ernst DB, Rounsaville BJ. Medical Management Treatment Manual. A Clinical Research Guide for MedicallyTrained Clinicians Providing Pharmacotherapy as Part of the Treatment for AlcoholDependence. Vol 2 edition. Vol. 2. No (NIH) 04-5289: COMBINE Monograph Series, 2004.

Pildal 2007

Pildal J, Hrobjartsson A, Jorgensen K J, Hilden J, Altman D G, Gotzsche P C. Impact of allocation concealment on conclusions drawn from meta-analyses of randomized trials. International Journal of Epidemiology 2007;36(4):847-57.

Pocock 1987

Pocock S J, Hughes M D, Lee R J. Statistical problems in the reporting of clinical trials. A survey of three medical journals. New England Journal of Medicine 1987;317(7):426-32.

Project Match Research Group 1997

Project Match Research Group. Matching alcoholism treatment to client heterogeneity: Project Match posttreatment drinking outcomes. Journal of Studies on Alcoholism 1997;58:7-29.

Rabkin 1992

Rabkin J G, Markowitz J S, Ocepek-Welikson K, Wager S S. General versus systematic inquiry about emergent clinical events with SAFTEE: implications for clinical research. Journal of Clinical Psychopharmacology 1992;12(1):3-10.

Rehm 2009

Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. Lancet 2009;373(9682):2223-33.

Riley 2007

Riley RD, Simmonds MC, Look MP. Evidence synthesis combining individual patient data and aggregate data: a systematic review identified current practice and possible methods. Journal of Clinical Epidemiology 2007;60(5):431-49.

Rosner 2008

Rösner S, Leucht S, Lehert P, Soyka M. Acamprosate supports abstinence, naltrexone prevents excessive drinking: evidence from a meta-analysis with unreported outcomes. Journal of Psychopharmacology 2008;22(1):11-23.

Rucker 2008

Rücker G, Schwarzer G, Carpenter J R, Schumacher M. Undue reliance on I(2) in assessing heterogeneity may mislead. BMC Medical Research Methodology 2008;8:79.

Schoechlin 2000

Schoechlin C, Engel RR. Meta-analysis of pharmacotherapeutic trials. In: Zernig G, Saria A, Kurz M, O'Malley S, editors(s). Handbook of Alcoholism. Innsbruck: Innsbruck University Press, 2000:339-351.

Schulz 1995

Schulz KF. Subverting randomisation in controlled trials. JAMA 1995;274(18):1456-8.

Selzer 1971

Selzer ML. The Michigan Alcoholism Screening Test (MAST): The quest for a new diagnostic instrument. American Journal of Psychiatry 1971;127:1653-8.

Skinner 1982

Skinner HA, Allen BA. Alcohol dependence syndrome: measurement and validation. Journal of Abnormal Psychology 1982;91:199-209.

Skinner 1984

Skinner HA, Horn JL. Alcohol Dependence Scale: Users Guide. Toronto: Addiction Research Foundation, 1984.

Slattery 2003

Slattery J, Chick J. Prevention of Relapse in Alcohol Dependence. Health Technology Assesment Report 2003;3.

Sobell 1988

Sobell LC, Sobell MB, Riley DM, Schuller R, Pavan DS, Cancilla A, et al. The reliability of alcohol abusers' self-reports of drinking and life events that occurred in the distant past. Journal of Studies on Alcohol 1988;49(3):225-32.

Sobell 1992

Sobell LC, Toneatto T, Sobell MB, Leo GI, Johnson L. Alcohol abusers' perceptions of the accuracy of their self-reports of drinking: implications for treatment. Addictive Behaviors 1992;17(5):507-11.

Spanagel 1996

Spanagel R, Holter S M, Allingham K, Landgraf R, Zieglgansberger W. Acamprosate and alcohol: I. Effects on alcohol intake following alcohol deprivation in the rat. European Journal of Pharmacology 1996;305(1-3):39-44.

Spanagel 1997

Spanagel R, Zieglgansberger W. Anti-craving compounds for ethanol: new pharmacological tools to study addictive processes. Trends in Pharmacological Sciences 1997;18(2):54-9.

Spanagel 2003

Spanagel R, Mann K. Acamprosate--new preclinical research aspects. MMW, Fortschritte der Medizin 2003;145 Supplement(3):61-4.

Srisurapanont 2005

Srisurapanont M, Jarusuraisin N. Opioid antagonists for alcohol dependence. Cochrane Database of Systematic Reviews 2005, Issue 1.10.1002/14651858.

Tannock 1996

Tannock I F. False-positive results in clinical trials: multiple significance tests and the problem of unreported comparisons. Journal of the National Cancer Institute 1996;88(3-4):206-7.

The Nordic Cochrane Centre 2008

Review Manager (RevMan). 5.0 [Computer program]. The Nordic Cochrane Centre. Copenhagen: The Nordic Cochrane Centre, 2008.

Turner 2000

Turner R M, Omar R Z, Yang M, Goldstein H, Thompson S G. A multilevel model framework for meta-analysis of clinical trials with binary outcomes. Statistics in Medicine 2000;19(24):3417-32.

Verheul 2005

Verheul R, Lehert P, Geerlings P J, Koeter MW, van den Brink W. Predictors of acamprosate efficacy: results from a pooled analysis of seven European trials including 1485 alcohol-dependent patients. Psychopharmacology (Berl) 2005;178(2-3):167-73.

WHO 2002

WHO. The World Health Report: Reducing risk, promoting healthy life. The World Health Report 2002.

Williamson 2005

Williamson PR, Gamble C, Altman DG, Hutton JL. Outcome selection bias in meta-analysis. Statistical Methods in Medical Research 2005;14(5):515-24.

Wood 2008

Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. BMJ 2008;336(7644):601-5.

Zeise 1993

Zeise M L, Kasparov S, Capogna M, Zieglgansberger W. Acamprosate (calciumacetylhomotaurinate) decreases postsynaptic potentials in the rat neocortex: possible involvement of excitatory amino acid receptors. European Jorunal of Pharmacology 1993;231(1):47-52.

Zornoza 2003

Zornoza T, Cano M J, Polache A, Granero L. Pharmacology of acamprosate: an overview. CNS Drug Reviews 2003;9(4):359-74.

Other published versions of this review

Classification pending references

Data and analyses

1 Acamprosate versus placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Return to any drinking	24	6172	Risk Ratio (M-H , Random , 95% CI)	0.86 [0.81, 0.91]
1.2 Cumulative abstinence duration	19	5224	Mean Difference (IV , Random , 95% CI)	10.94 [5.08, 16.81]
1.3 Return to heavy drinking	6	2132	Risk Ratio (M-H , Random , 95% CI)	0.99 [0.94, 1.04]
1.4 Gamma-glutamyl transpeptidase	7	1650	Mean Difference (IV , Random , 95% CI)	-11.91 [-24.12, 0.30]
1.5 Side effect: Diarrhea	16	8972	Risk Difference (M-H , Fixed , 95% CI)	0.11 [0.10, 0.13]
1.6 Side effect: Abdominal pain	3	947	Risk Difference (M-H , Random , 95% CI)	0.00 [-0.04, 0.05]
1.7 Side effect: Constipation	3	941	Risk Difference (M-H , Random , 95% CI)	-0.04 [-0.11, 0.03]
1.8 Side effect: Nausea	5	1447	Risk Difference (M-H , Random , 95% CI)	0.02 [-0.01, 0.05]
1.9 Side effect: Vomiting	3	1782	Risk Difference (M-H , Fixed , 95% CI)	0.02 [-0.00, 0.04]
1.10 Side effect: Further gastrointestinal symptoms	8	2303	Risk Difference (M-H , Random , 95% CI)	0.04 [-0.01, 0.08]
1.11 Side effect: Headache	6	1444	Risk Difference (M-H , Random , 95% CI)	-0.00 [-0.05, 0.05]
1.12 Side effect: Pruritus	4	695	Risk Difference (M-H , Random , 95% CI)	0.02 [-0.02, 0.05]
1.13 Side effect: Vertigo	1	569	Risk Difference (M-H , Random , 95% CI)	-0.05 [-0.09, -0.01]

1.14 Other side effects	8		Risk Difference (M-H , Random , 95% CI)	Subtotals only
1.14.1 Chest pain	1	569	Risk Difference (M-H , Random , 95% CI)	0.03 [-0.01, 0.06]
1.14.2 Confusion	1	569	Risk Difference (M-H , Random , 95% CI)	0.03 [-0.00, 0.05]
1.14.3 Daytime sleepiness	1	569	Risk Difference (M-H , Random , 95% CI)	-0.02 [-0.07, 0.03]
1.14.4 Decreased appetite	2	1181	Risk Difference (M-H , Random , 95% CI)	0.03 [-0.02, 0.08]
1.14.5 Decreased libido	1	569	Risk Difference (M-H , Random , 95% CI)	0.03 [-0.03, 0.09]
1.14.6 Depression	1	116	Risk Difference (M-H , Random , 95% CI)	0.00 [-0.05, 0.05]
1.14.7 Drowsiness	2	644	Risk Difference (M-H , Random , 95% CI)	0.02 [-0.02, 0.06]
1.14.8 Dry mouth	2	685	Risk Difference (M-H , Random , 95% CI)	-0.04 [-0.08, NaN]
1.14.9 Dyspepsia	1	601	Risk Difference (M-H , Random , 95% CI)	0.03 [-0.00, 0.06]
1.14.10 Dyspnoea	1	569	Risk Difference (M-H , Random , 95% CI)	0.03 [-0.03, 0.09]
1.14.11 Excitation	1	569	Risk Difference (M-H , Random , 95% CI)	0.05 [-0.02, 0.11]
1.14.12 Fatigue	2	685	Risk Difference (M-H , Random , 95% CI)	-0.04 [-0.09, 0.01]
1.14.13 Fainting sensation	1	569	Risk Difference (M-H , Random , 95% CI)	-0.01 [-0.04, 0.03]
1.14.14 Increased libido	2	757	Risk Difference (M-H , Random , 95% CI)	0.01 [-0.02, 0.05]
1.14.15 Insomnia	2	685	Risk Difference (M-H , Random , 95% CI)	0.04 [-0.01, 0.09]
1.14.16 Muscular pain	1	569	Risk Difference (M-H , Random , 95% CI)	-0.04 [-0.09, NaN]
1.14.17 Noctural wakening	1	569	Risk Difference (M-H , Random , 95% CI)	-0.02 [-0.09, 0.05]
1.14.18 Palpitation	1	569	Risk Difference (M-H , Random , 95% CI)	-0.00 [-0.05, 0.04]
1.14.19 Poor concentration	1	569	Risk Difference (M-H , Random , 95% CI)	-0.04 [-0.08, -0.00]
1.14.20 Poor memory	2	651	Risk Difference (M-H , Random , 95% CI)	-0.01 [-0.05, 0.03]
1.14.21 Sexual dysfunction	2	639	Risk Difference (M-H , Random , 95% CI)	0.02 [-0.02, 0.06]
1.14.22 Skin rush	1	569	Risk Difference (M-H , Random , 95% CI)	0.04 [-0.01, 0.09]
1.14.23 Somnolence	2	728	Risk Difference (M-H , Random , 95% CI)	0.03 [-0.11, 0.17]
1.14.24 Strangury	1	75	Risk Difference (M-H , Random , 95% CI)	-0.04 [-0.17, 0.09]
1.14.25 Sweating	1	569	Risk Difference (M-H , Random , 95% CI)	-0.02 [-0.08, 0.04]
1.14.26 Vertigo	1	569	Risk Difference (M-H , Random , 95% CI)	-0.05 [-0.09, -0.01]
1.15 Drop out due to adverse events	19	5763	Risk Ratio (M-H , Random , 95% CI)	1.35 [1.01, 1.80]
1.16 Drop out	22	6111	Risk Ratio (M-H , Random , 95% CI)	0.91 [0.83, 0.99]
1.17 Post-treatment: Return to any drinking	7	1986	Risk Ratio (M-H , Random , 95% CI)	0.91 [0.87, 0.96]
1.18 Post-treatment: Continuous abstinence	9	3069	Mean Difference (IV , Random , 95% CI)	8.92 [5.08, 12.77]

1.19 Sensitivity analysis: Return to heavy drinking	6	2132	Risk Ratio (M-H , Fixed , 95% CI)	0.97 [0.92, 1.03]

2 Acamprosate versus naltrexone

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Return to any drinking	3	800	Risk Ratio (M-H , Random , 95% CI)	1.03 [0.96, 1.10]
2.2 Cumulative abstinence duration	2	720	Mean Difference (IV , Random , 95% CI)	2.98 [-7.45, 13.42]
2.3 Return to heavy drinking	3	800	Risk Ratio (M-H , Random , 95% CI)	1.04 [0.95, 1.15]
2.4 Gamma-glutamyl transpeptidase	1	80	Mean Difference (IV , Random , 95% CI)	9.70 [5.18, 14.22]
2.5 Side effect: Diarrhea	3	800	Risk Difference (M-H , Random , 95% CI)	0.27 [0.21, 0.33]
2.6 Side effect: Nausea	3	800	Risk Difference (M-H , Random , 95% CI)	-0.08 [-0.13, -0.03]
2.7 Other side effects	2		Risk Difference (M-H , Random , 95% CI)	Subtotals only
2.7.1 Decreased appetite	1	612	Risk Difference (M-H , Random , 95% CI)	-0.02 [-0.08, 0.05]
2.7.2 Depression	1	108	Risk Difference (M-H , Random , 95% CI)	-0.04 [-0.11, 0.03]
2.7.3 Dry mouth	1	108	Risk Difference (M-H , Random , 95% CI)	-0.04 [-0.10, 0.02]
2.7.4 Fatigue	1	108	Risk Difference (M-H , Random , 95% CI)	-0.13 [-0.26, -0.01]
2.7.5 Headache	1	108	Risk Difference (M-H , Random , 95% CI)	-0.06 [-0.15, 0.03]
2.7.6 Insomnia	1	108	Risk Difference (M-H , Random , 95% CI)	-0.02 [-0.11, 0.07]
2.7.7 Somnolence	2	720	Risk Difference (M-H , Random , 95% CI)	-0.07 [-0.13, -0.01]
2.7.8 Vomiting	1	612	Risk Difference (M-H , Random , 95% CI)	-0.06 [-0.11, -0.01]
2.8 Drop outs due to adverse events	3	800	Risk Ratio (M-H , Random , 95% CI)	0.76 [0.37, 1.58]
2.9 Drop outs	3	800	Risk Ratio (M-H , Random , 95% CI)	1.09 [0.91, 1.31]

3 Acamprosate + naltrexone versus placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
3.1 Return to any drinking	2	694	Risk Ratio (M-H , Random , 95% CI)	0.70 [0.35, 1.39]
3.2 Cumulative abstinence duration	1	614	Mean Difference (IV , Random , 95% CI)	2.20 [-1.90, 6.30]
3.3 Return to heavy drinking	2	694	Risk Ratio (M-H , Random , 95% CI)	0.71 [0.38, 1.35]
3.4 Gamma-glutamyl transpeptidase	1	80	Mean Difference (IV , Random , 95% CI)	-8.70 [-24.86, 7.46]
3.5 Side effect: Diarrhoea	2	694	Risk Difference (M-H , Random , 95% CI)	0.20 [0.13, 0.27]

3.6 Other side effects	2		Risk Difference (M-H , Random , 95% CI)	Subtotals only
3.6.1 Decreased appetite	1	614	Risk Difference (M-H , Random , 95% CI)	0.11 [0.05, 0.17]
3.6.2 Nausea	2	694	Risk Difference (M-H , Random , 95% CI)	0.20 [0.14, 0.26]
3.6.3 Somnolence	1	614	Risk Difference (M-H , Random , 95% CI)	0.07 [-0.00, 0.14]
3.6.4 Vomiting	1	614	Risk Difference (M-H , Random , 95% CI)	0.09 [0.03, 0.14]
3.7 Drop out due to adverse events	2	694	Risk Ratio (M-H , Random , 95% CI)	3.75 [1.33, 10.55]
3.8 Drop out	2	694	Risk Ratio (M-H , Random , 95% CI)	0.83 [0.28, 2.49]

4 Acamprosate + naltrexone versus acamprosate

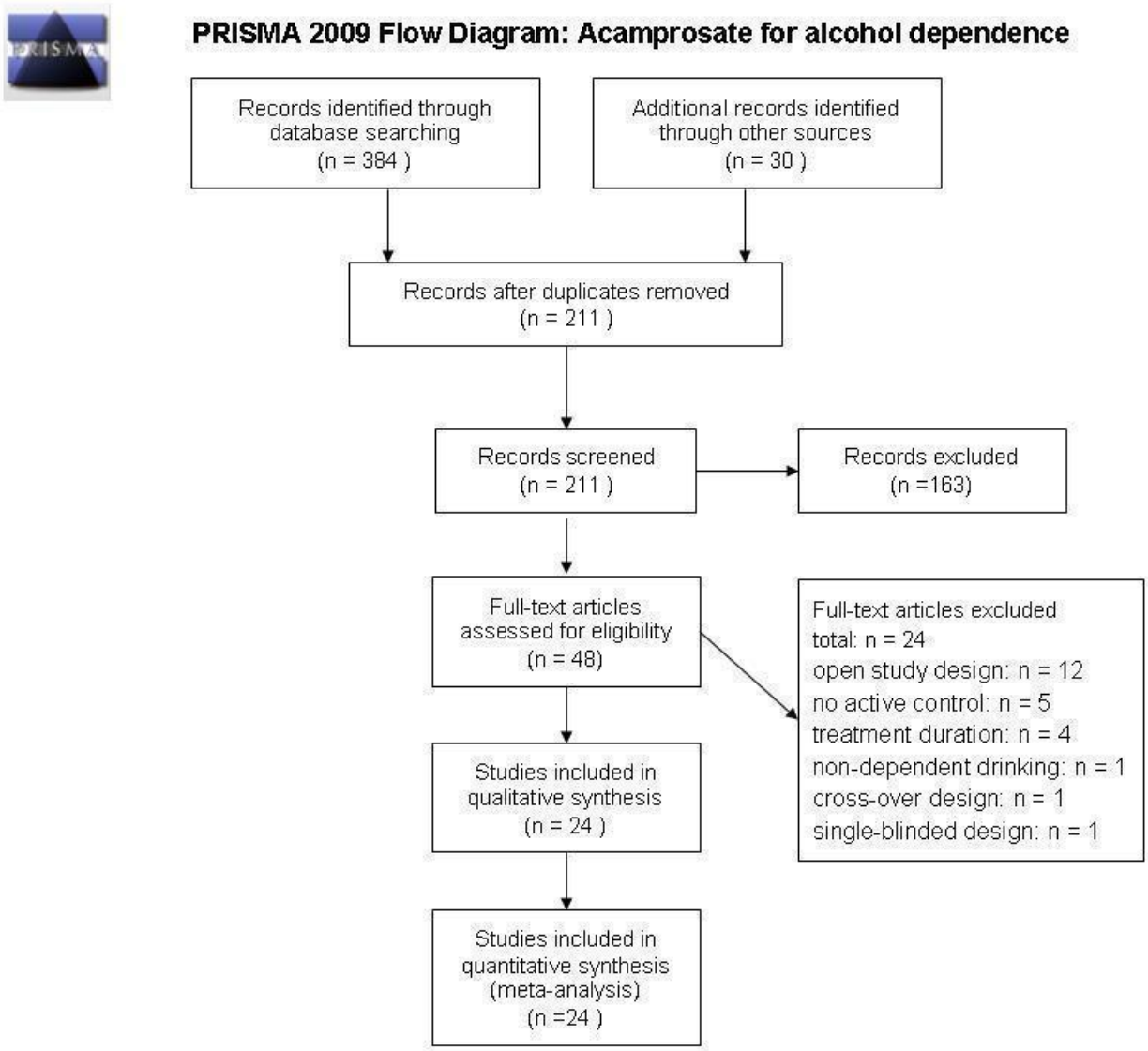
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
4.1 Return to any drinking	2	688	Risk Ratio (M-H , Random , 95% CI)	0.80 [0.49, 1.30]
4.2 Cumulative abstinence duration	1	608	Mean Difference (IV , Random , 95% CI)	2.10 [-2.03, 6.23]
4.3 Return to heavy drinking	2	688	Risk Ratio (M-H , Random , 95% CI)	0.81 [0.50, 1.34]
4.4 Gamma-glutamyl transpeptidase	1	80	Mean Difference (IV , Random , 95% CI)	1.00 [-8.65, 10.65]
4.5 Side effect: Diarrhea	2	694	Risk Difference (M-H , Random , 95% CI)	0.08 [-0.27, 0.43]
4.6 Other side effects	2		Risk Difference (M-H , Random , 95% CI)	Subtotals only
4.6.1 Decreased appetite	1	608	Risk Difference (M-H , Random , 95% CI)	0.06 [-0.01, 0.12]
4.6.2 Nausea	2	688	Risk Difference (M-H , Random , 95% CI)	0.18 [0.11, 0.24]
4.6.3 Somnolence	1	608	Risk Difference (M-H , Random , 95% CI)	-0.01 [-0.09, 0.06]
4.6.4 Vomiting	1	608	Risk Difference (M-H , Random , 95% CI)	0.08 [0.03, 0.13]
4.7 Drop out due to adverse events	2	688	Risk Ratio (M-H , Random , 95% CI)	1.41 [0.68, 2.90]
4.8 Drop out	2	688	Risk Ratio (M-H , Random , 95% CI)	0.84 [0.49, 1.44]

5 Risk of bias related to founding source

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
5.1 Funding source	24	6172	Risk Ratio (M-H , Random , 95% CI)	0.86 [0.81, 0.91]
5.1.1 Fully industry sponsored	11	2858	Risk Ratio (M-H , Random , 95% CI)	0.88 [0.80, 0.97]
5.1.2 Partially industry sponsored	6	1765	Risk Ratio (M-H , Random , 95% CI)	0.84 [0.78, 0.89]
5.1.3 Non profit sponsored	7	1549	Risk Ratio (M-H , Random , 95% CI)	0.88 [0.81, 0.96]

Figures

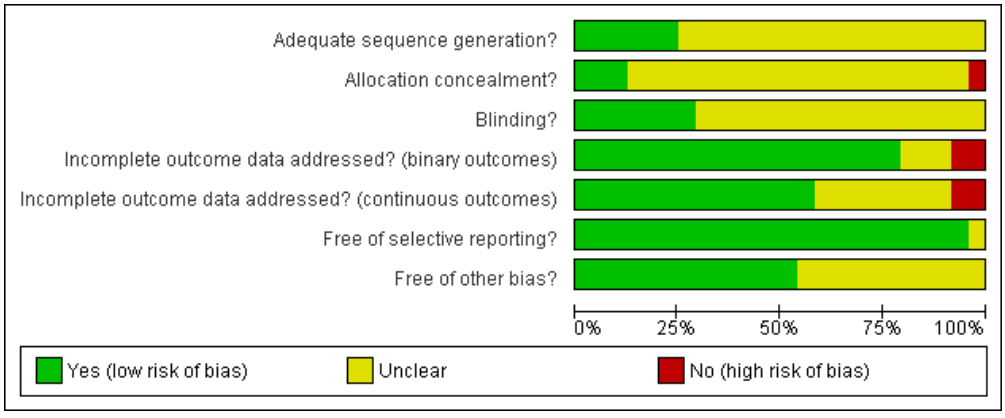
Figure 1



Caption

Flow chart of studies

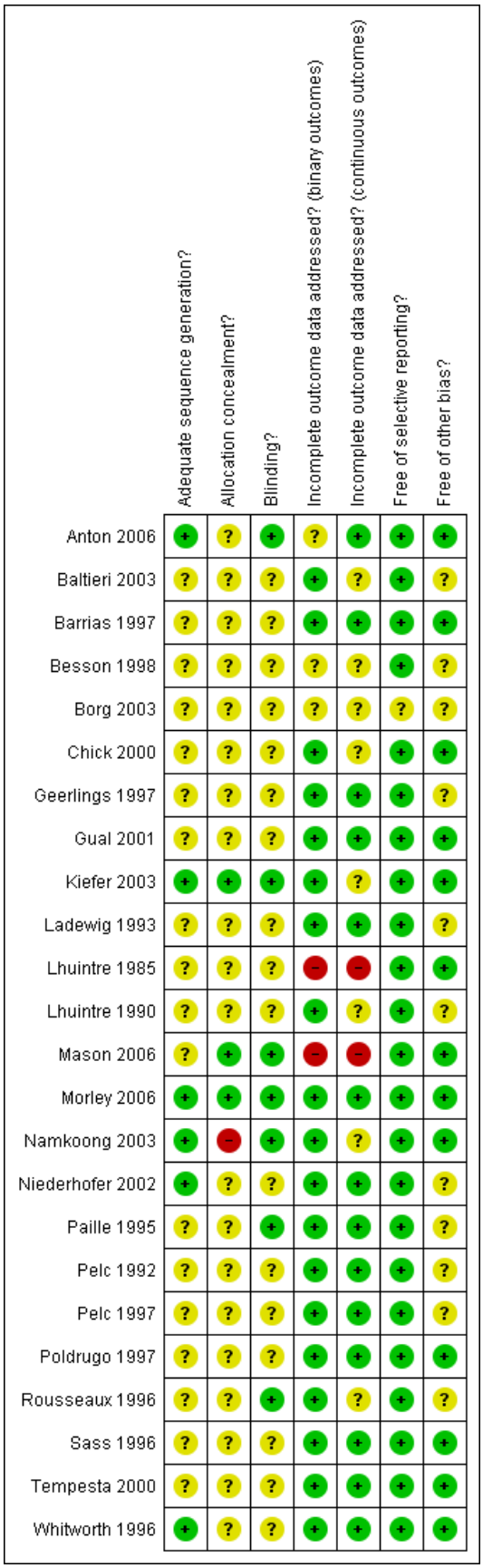
Figure 2



Caption

Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

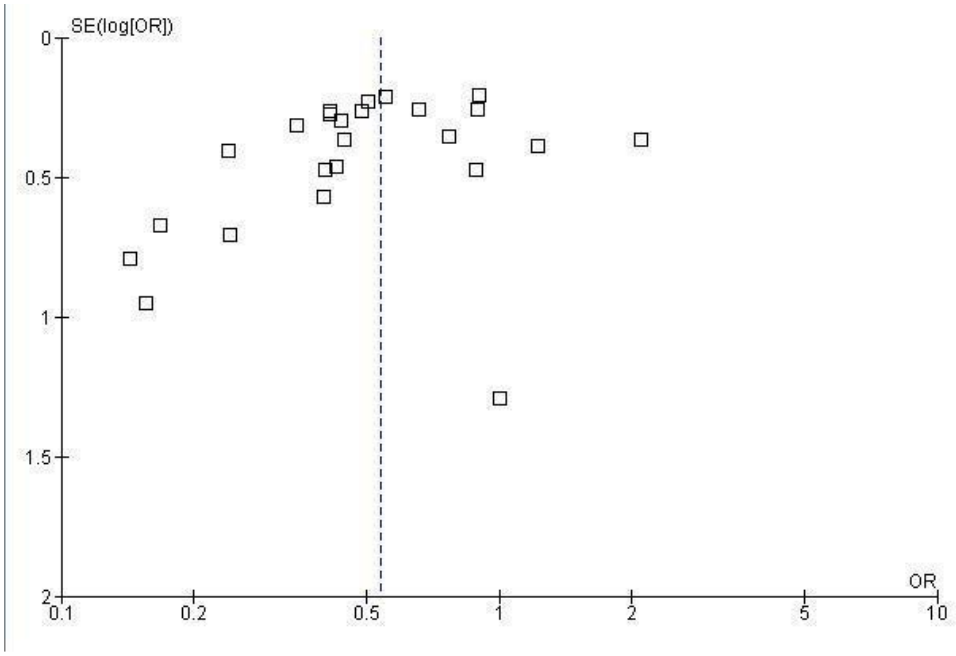
Figure 3



Caption

Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

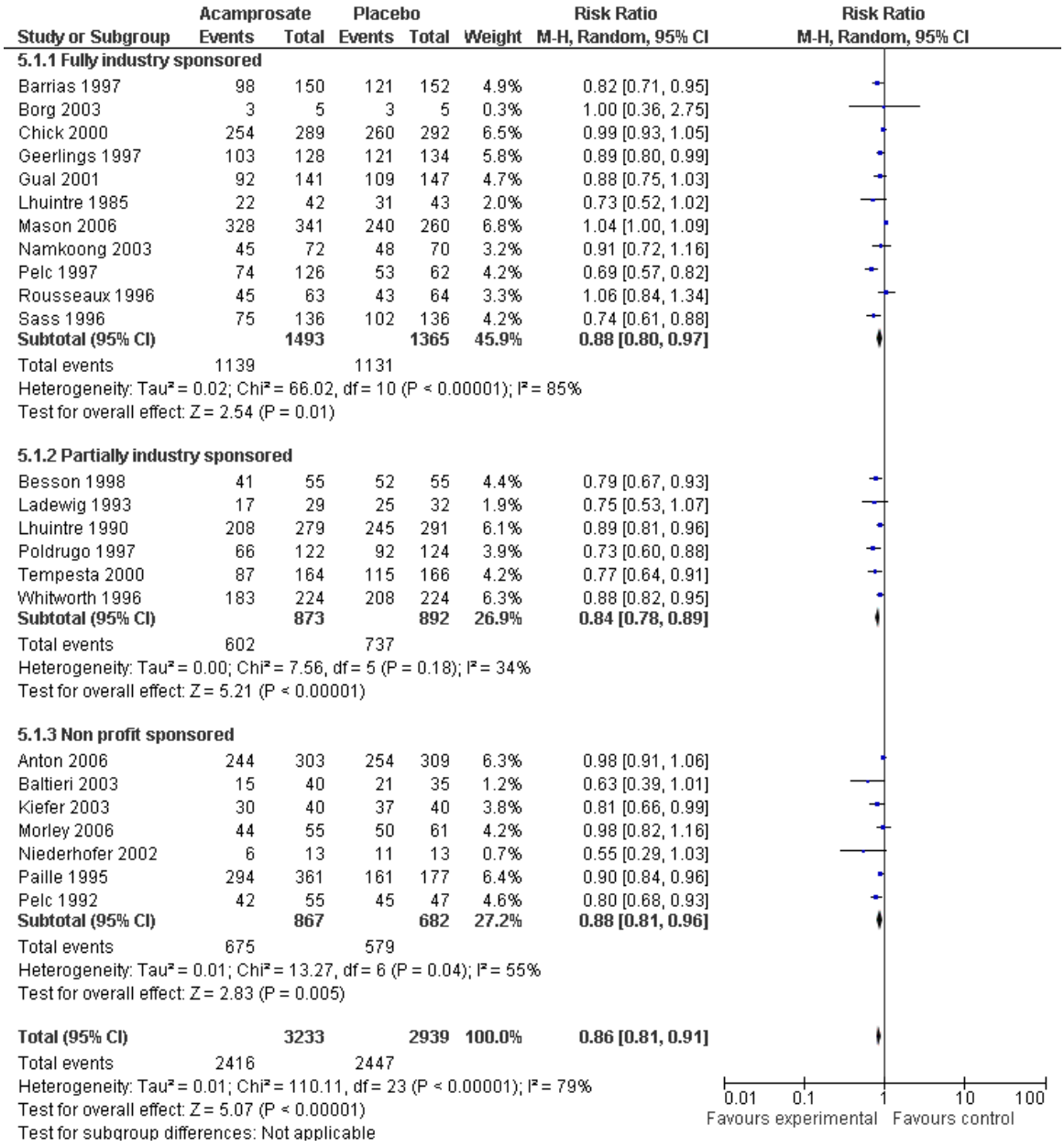
Figure 4



Caption

Risk of publication bias

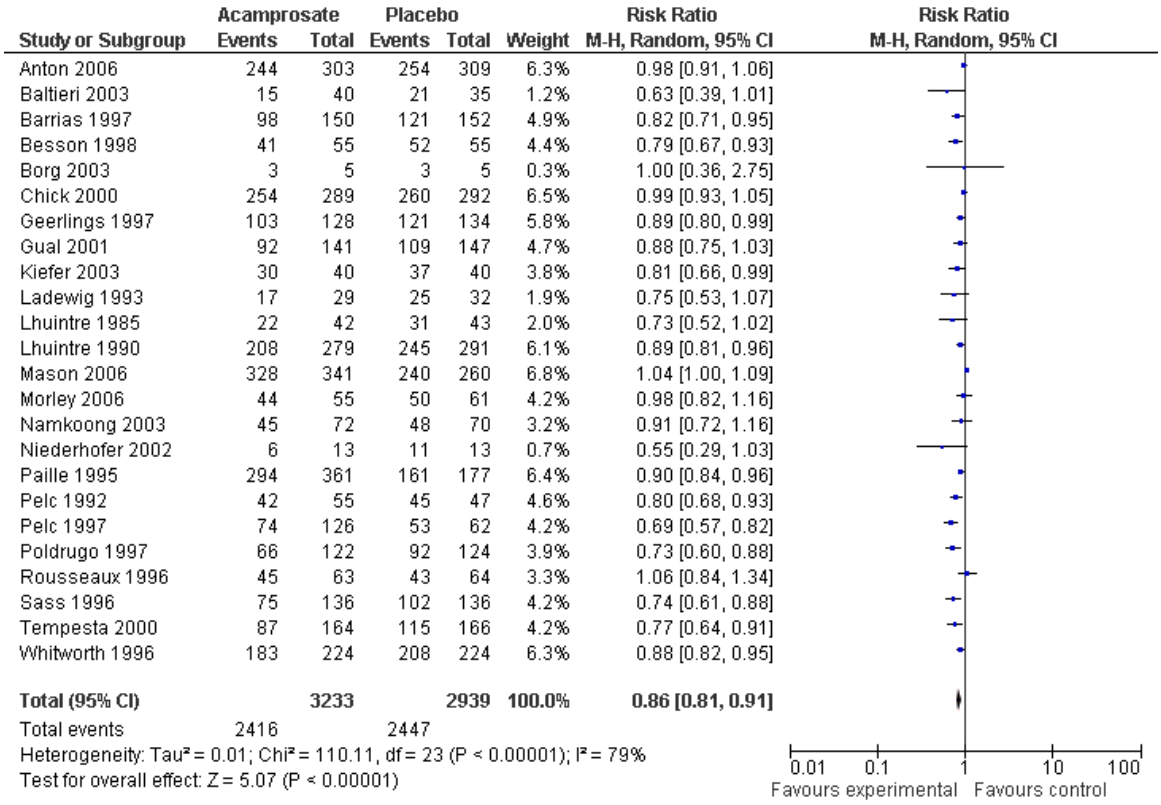
Figure 5 (Analysis 5.1)



Caption

Forest plot of comparison: 5 Sensitivity analysis of risk of bias, outcome: 5.2 Funding source.

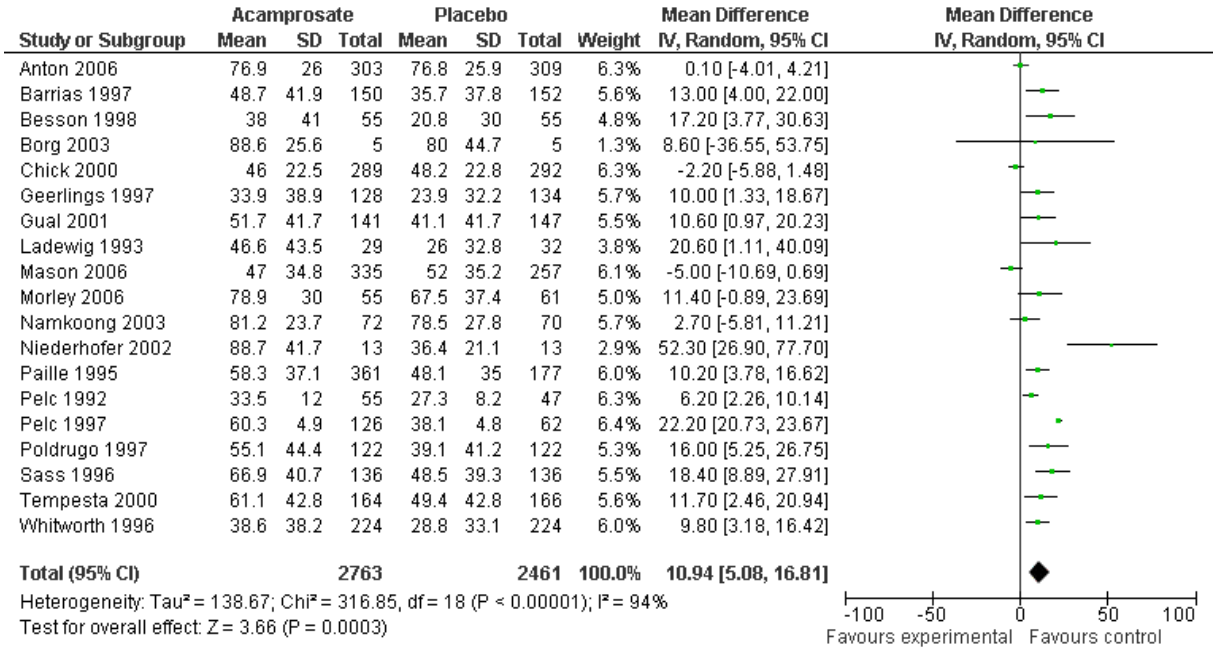
Figure 6 (Analysis 1.1)



Caption

Forest plot of comparison: 1 ACAM versus PBO, outcome: 1.1 Return to any drinking.

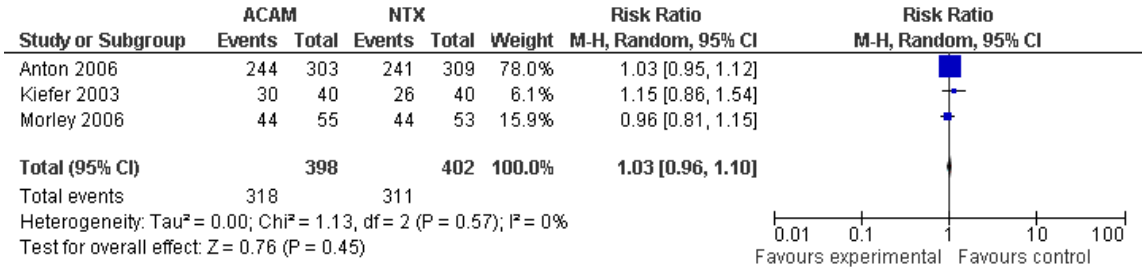
Figure 7 (Analysis 1.2)



Caption

Forest plot of comparison: 1 ACAM versus PBO, outcome: 1.2 Cumulative abstinence duration.

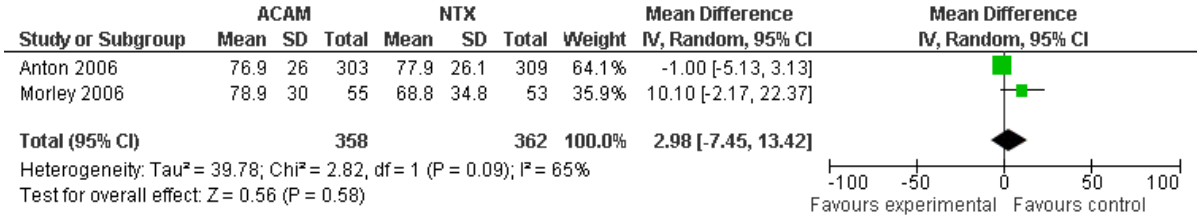
Figure 8 (Analysis 2.1)



Caption

Forest plot of comparison: 2 ACAM versus NTX, outcome: 2.1 Return to any drinking.

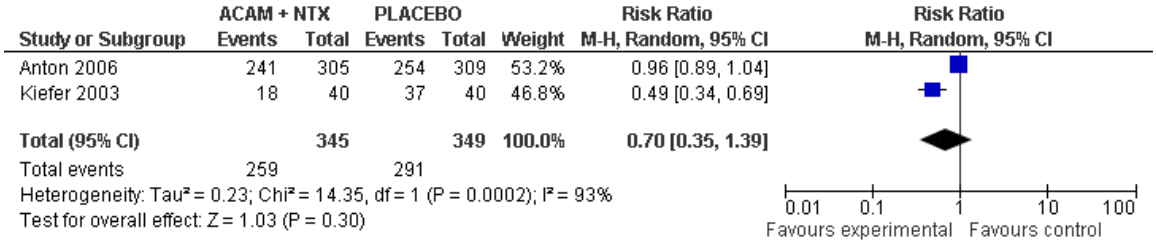
Figure 9 (Analysis 2.2)



Caption

Forest plot of comparison: 2 Acamprosate versus naltrexone, outcome: 2.2 Cumulative abstinence duration .

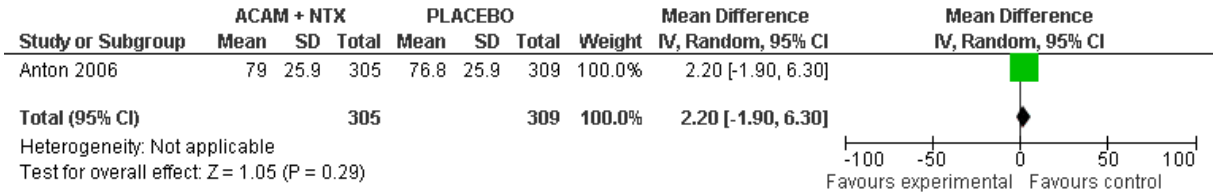
Figure 10 (Analysis 3.1)



Caption

Forest plot of comparison: 3 ACAM + NTX versus PBO, outcome: 3.1 Return to any drinking.

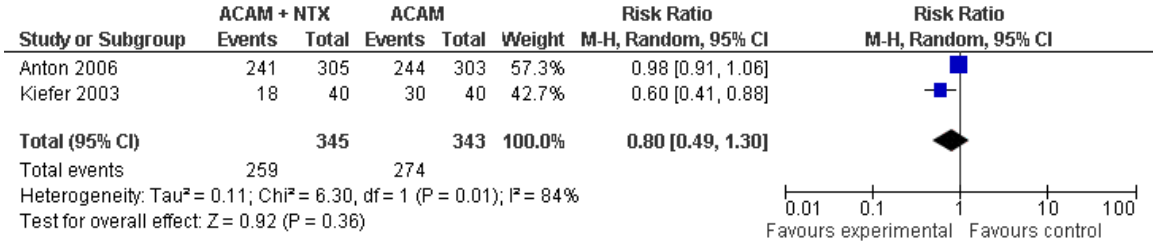
Figure 11 (Analysis 3.2)



Caption

Forest plot of comparison: 3 ACAM + NTX versus PBO, outcome: 3.2 CAD.

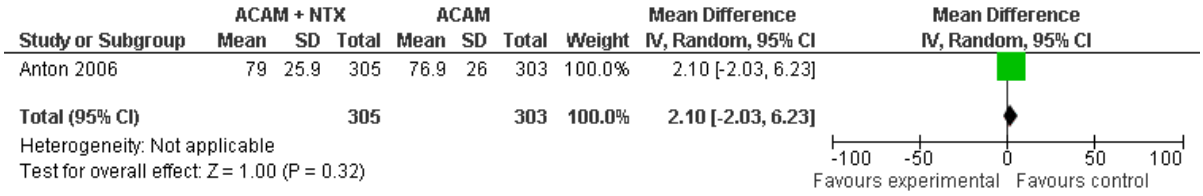
Figure 12 (Analysis 4.1)



Caption

Forest plot of comparison: 4 ACAM + NTX versus ACAM, outcome: 4.1 Return to any drinking.

Figure 13 (Analysis 4.2)



Caption

Forest plot of comparison: 4 ACAM + NTX versus ACAM, outcome: 4.2 CAD.

Sources of support

Internal sources

- Ludwig Maximilian University of Munich, Germany
  provision of infrastructure and related services
- Technical University of Munich, Germany
  provision of infrastructure and related services

External sources

- Federal Ministry of Education and Research, Germany
  financial support / salary

Feedback

Appendices

1 Abbreviations

Term (abbreviation)

Acamprosate (ACAM)

Acceptable Quality Level (AQL)

Alcoholics Anonymous (AA)

Carbohydrate-deficient transferrin (CDT)

Case report form (CRF)

Cognitive Behavioral Intervention (CBI)

Clinical Trials Registry Platform Search Portal (ClinicalTrials.gov)

Cochrane Drugs and Alcohol Group (CDAG)

Confidence interval (CI)

Cumulative abstinence duration (CAD)

Diagnostic and Statistical Manual of Mental Disorders (DSM)

Food and Drug Administration (FDA)

Gamma-glutamyltransferase (GGT)

Good Clinical Practice (GCP)

Individual patient database (IPD)

Intention-to-treat (ITT)

International Statistical Classification of Diseases (ICD)

International Unit (IU)

Mean corpuscular volume (MCV)

Mean difference (MD)

Meta-analysis based on literature (MAL)

*Meta*Register of Controlled Trials (*m*RCT)

Motivational Enhancement (ME)

Naltrexone (NTX)

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

N-methyl-D-aspartic acid (NMDA)

Number needed to treat for an additional beneficial outcome (NNTB)

Number needed to treat for an additional harmful outcome (NNTH)

Placebo (PBO)

Randomized controlled trial (RCT)

Risk benefit (RB)

Risk difference (RD)

Risk ratio (RR)

Systematic Assessment for Treatment Emergent Effects (SAFTEE)

Standard deviation (SD)

Standard error (SE)

Standard drink unit (SDU)

2 Search strategies

Search strategy for CENTRAL

1. Alcohol-Related Disorders[mesh]
2. ((alcohol) NEAR/2 (dependen* or disorder* or drink* or misuse or abuse* or consumption))
3. alcoholism [mesh]
4. alcohol*
5. exp drinking behaviour [mesh]
6. 1 or 2 or 3 or 4 or 5
7. acamprosate or Campral
8. alcohol deterrents [mesh]
9. 7 or 8
0. 6 AND 9

Search strategy for PubMEd

1. Alcohol-Related Disorders[mesh]
2. ((alcohol) AND (dependen* or disorder* or drink* or misuse or abuse* or consumption))
3. alcoholism [mesh]
4. alcohol*
5. exp drinking behaviour [mesh]
6. 1 or 2 or 3 or 4 or 5
7. Acamprosate [substance name]
8. acamprosate [tiab]
9. Campral [tiab]
0. alcohol deterrents [mesh]
1. 7 or 8 or 9 or 10
2. randomized controlled trial[pt]
3. controlled clinical trial[pt]
4. random*[tiab]
5. placebo[tiab]
6. drug therapy[mesh]
7. trial[tiab]
8. groups[tiab]
9. 12 or 13 or 14 or 15 or 16 or 17 or 18
0. animals [mesh]
1. humans [mesh]
2. animals NOT (20 and 21)
3. 19 NOT 22
4. 6 AND 11 AND 23

Search strategy for EMBASE (Host: OVID)

1. exp Alcohol-Related Disorders
2. exp drinking behaviour
3. ((alcohol) and (abuse* OR dependen* OR disorder*or drink* or consumption))
4. alcoholism.ti,ab
5. 1 or 2 or 3 or 4
6. exp acamprosate
7. acamprosate.ti,ab
8. campral.ti,ab
9. Aotal.ti,ab

0. N-acetylhomotaurin*.ti,ab
1. 6 or 7 or 8 or 9 or 10
2. random*.ti,ab
3. placebo. ti,ab
4. (control* or prospective* or volunteer*).ti,ab
5. (single or double or treble or triple) and (blind* or mask*)).ti,ab
6. crossover*.ti,ab
7. exp randomized controlled trial/
8. clinical-trial/
9. exp double blind procedure/
10. exp single blind procedure/
11. exp crossover procedure/
12. exp Latin square design/
13. exp placebos/
14. exp multicenter study/
15. OR 12/24
16. 5 AND 11 AND 25
17. limit 26 to human

Search strategy for CINAHL (Host: EBSCO)

1. MESH alcohol-related disorders
2. TX (((alcohol) and (abuse* OR dependen* OR disorder*or drink* or consumption))
3. TX alcoholism
4. or 2 or 3
5. MH Alcohol Deterrents
6. TX acamprosate
7. TX campral
8. 5 or 6 or 7
9. MH Random Assignment/
0. MH Clinical Trials/
1. TW random*
2. TW placebo*
3. TW group*
4. TW (single or double or triple or treble) and (mask* or blind*)
5. MH crossover design
6. TW (crossover* or allocate* or assign*)
7. OR 9/16
8. 4 AND 8 AND 17