Opioid antagonists for alcohol dependence

Review information

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Abstract

Background

Alcohol dependence belongs to the globally leading health risk factors. Therapeutic success of psychosocial programs for relapse prevention is moderate and could be increased by an adjuvant treatment with the opioid antagonists naltrexone and nalmefene.

Objectives

To determine the effectiveness and tolerability of opioid antagonists in the treatment of alcohol dependence.

Search strategy

We searched the Cochrane Drugs and Alcohol Group (CDAG) Specialized Register, PubMed, EMBASE and CINAHL in January 2010 and inquired manufacturers and researchers for unpublished trials.

Selection criteria

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

Data collection and analysis

Two authors independently extracted outcome data. Trial quality was assessed by one author and cross-checked by a second author.

Main results

Based on a total of 50 RCTs with 7793 patients, naltrexone reduced the risk of heavy drinking to 83% of the risk in the placebo group RR 0.83 (95% CI 0.76 to 0.90) and decreased drinking days by about 4%, MD -3.89 (95% CI -5.75 to -2.04). Significant effects were also demonstrated for the secondary outcomes of the review including heavy drinking days, MD - 3.25 (95% CI -5.51 to -0.99), consumed amount of alcohol, MD - 10.83 (95% CI -19.69 to -1.97) and gamma-glutamyltransferase, MD - 10.37 (95% CI -18.99 to -1.75), while effects on return to any drinking, RR 0.96 (95 CI 0.92 to 1.00) missed statistical significance. Side effects of naltrexone were mainly gastrointestinal problems (e.g. nausea: RD 0.10; 95% CI 0.07 to 0.13) and sedative effects (e.g. daytime sleepiness: RD 0.09; 95% CI 0.05 to 0.14). Based on a limited study sample, effects of injectable naltrexone and nalmefene missed statistical significance. Effects of industry-sponsored studies, RR 0.90 (95% CI 0.78 to 1.05) did not significantly differ from those of non-profit funded trials, RR 0.84 (95% CI 0.77 to 0.91) and the linear regression test did not indicate publication bias (P = 0.765).

Authors' conclusions

Naltrexone appears to be an effective and safe strategy in alcoholism treatment. Even though the sizes of treatment effects might appear moderate in their magnitudes, these 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

Naltrexone and nalmefene for alcohol dependent patients

Alcohol dependence is a chronic disease, which can develop when alcohol is heavily used over longer periods of time. Alcohol affects various brain regions, including the opioid receptor system, which mediates euphoric and pleasurable effects of alcohol. By blocking alcohol effects at these receptors, the opioid antagonists naltrexone and nalmefene can reduce alcohol "liking" and "craving" and thus support alcohol dependent patients in cutting down their drinking. 50 studies with 7793 participants were included in the review, in most studies treatment was provided over a period of three months. The review shows that more patients who took naltrexone were able to reduce the amount and frequency of drinking than those who took an identical appearing, but inert substance (placebo). On average, one out of nine patients was helped by naltrexone. Naltrexone does not have serious side effects, but gastrointestinal symptoms like nausea, stomach pain and loss of appetite are common. Some patients also get tired from naltrexone. For injectable formulations of naltrexone, which can be advantageous for patients who have problems with taking their medication on schedule, and the second opioid antagonist nalmefene, the database is still too sparse to allow final conclusions. Nevertheless, the available studies indicate that these drugs might have comparable effects on drinking than oral naltrexone has. Naltrexone does not cause dependency and unlike disulfiram, another medicine that is sometimes used to treat alcohol dependence, it does not make patients feel sick if they drink alcohol while taking it.

Background

Description of the condition

Alcohol dependence and alcohol related impairments belong to the most widespread psychiatric disorders (Alonso 2004). The one year prevalence of alcohol-use disorders is estimated at 5.2% in the American Region, 5.5% in European countries and at over 10% in Eastern European Regions (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 risk factors, underscoring the need for effective strategies to reduce excessive drinking and to maintain abstinence in patients who are dependent on alcohol.

Description of the intervention

The treatment of alcohol dependence was exclusively dominated by psychosocial 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, which were not confirmed by multicenter trials. Two substances were repeatedly shown to be effective: The glutamate-antagonist *acamprosate* and the opioid antagonist *naltrexone.*

Naltrexone is a competitive antagonists for mu-opioid receptors (Preston 1993), originally used for the treatment of opioid dependence to prevent a relapse to opioid use after heroin detoxification and to treat accidental heroin overdose. In animal models of alcohol dependence, naltrexone was shown to decrease the alcohol intake under free-choice conditions (e.g. Altshuler 1980; Ulm 1995) and to prevent the development of a conditioned place preference for alcohol (Matsuzawa 1999; Middaugh 2000), indicating that the opioid antagonist does not only block the immediate release of endorphins and dopamine, but also influences conditioned processes induced by drinking-associated stimuli, known as "conditioned high" (Childress 1986).

Effects of naltrexone on drinking were less consistent in animal studies, which tested the effectiveness of naltrexone to suppress the "alcohol deprivation effect" - a phenomena that describes the temporary increase in voluntary alcohol intake, observed during a reinstated access to alcohol after a period of deprivation. While in the trial of Heyser 2003, naltrexone was shown to diminish this effect, some evidence indicates that naltrexone given during abstinence even increased subsequent drinking (Sinclair 2001). Holter 1999 found that the effects are mediated by the treatment regimen, with low dose and intermittent treatment causing a reduction in ethanol intake, while chronic treatment can increase the ethanol preference during and after alcohol deprivation.

Until today, various clinical studies have been conducted, with the majority of trials demonstrating the superiority of opioid antagonists compared to placebo. Nevertheless, patients have been shown to strongly differ in their responsiveness to naltrexone; to explain these differences, a polymorphism in the mu-opioid receptor gene (OPRM1) has been identified as a predictor of response (Oslin 2003; Anton 2008), while a further analysis of clinical data could not find such an association (Gelernter 2007). Since its approval by the U.S. Food and Drug Administration (FDA) as an adjuvant therapy for the treatment of alcohol-dependent patients in 1994, naltrexone has been introduced to the market in many countries all over the world. In April 2006, the FDA approved a new extended-release injectable formulation of naltrexone for the treatment of alcohol dependence, while nalmefene, a newer opioid antagonist, is tested, but not yet licensed for this indication. Nalmefene has a comparable chemical structure to naltrexone, while proposed to offer a number of potential advantages (Mason 1999), including a more effective binding to central opiate receptors (DeHaven-Hudkins 1990; Emmerson 1994; Ingman 2005), a higher bioavailability (Dixon 1987; Gal 1986) and the absence of a dose-dependent association with liver toxicity (Mason 1999).

How the intervention might work

Alcohol affects various transmitter systems in the brain, including the endogenous opioid receptors, which are assumed to mediate pleasant and euphoric effects of drinking (Froehlich 1993; O'Malley 2003; Gianoulakis 2004). As naltrexone and nalmefene competitively bind to these receptors, they block the endogenous opioids at these sites (Clintron 1995) and thus diminish the pleasant and euphoric effects of drinking. This explains why patients given naltrexone in combination with alcohol reported a reduced "high" compared to former drinking (Volpicelli 1995). As changes in the opioid system also have a modulator influence on the mesolimbic dopamine system, especially on dopamine neurons in the ventral tegmental area and their projections to the nucleus accumbens in the ventral striatum - the predominant pathway involved in reinforcement and motivation (Adcock 2006) - naltrexone is also assumed to mediate motivational processes including reward anticipation and reinforcement.

Why it is important to do this review

Naltrexone has already been subject to various meta-analyses, which indicate small to moderate, but significant effects of the substance in preventing a relapse to heavy drinking in alcohol dependent patients (Schoechlin 2000 ; Kranzler 2001; Hopkins 2002; Berglund 2003; Streeton 2001; Srisurapanont 2000; Slattery 2003; Bouza 2004; Srisurapanont 2005a; Srisurapanont 2005b; Roozen 2006; Rosner 2008). Since the last update of the Cochrane review "Opioid antagonists for alcohol dependence" (Srisurapanont 2000), based on 29 RCTs (Srisurapanont 2005a), the primary database for opioid antagonists has been considerably extended, with some of the newer trials partly differing 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 is likely to increase the precision of estimated effects and 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 and to estimate the risk of over- or underestimating the effectiveness of opioid antagonists with the available database. Furthermore, a meta-analytic evaluation of the side effect profile of naltrexone and nalmefene and their post-treatment effectiveness appears to be overdue.

Objectives

To determine the effects of opioid antagonists on drinking in alcohol dependent patients in comparison to

placebo and other pharmacological agents in RCTs. Further objectives of the review are to determine

- the stability of treatment effects (post-treatment); and
- the side effect profile.

Methods

Criteria for considering studies for this review

Types of studies

All double-blind randomised controlled trials (RCTs) which compare the effects of opioid antagonists (monotherapy and combined therapy) with placebo or active control in 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 (> 90%).

Types of interventions

- Opioid antagonists versus placebo control group
- opioid antagonists versus active control group.

A minimum of four weeks daily treatment was required to ensure an adequate implementation of the intervention. To allow clinically relevant conclusions on treatment stability, post-treatment evaluations had to include at least 12 weeks of observation. Any dose, any mode of administration and any combination of therapies was considered.

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. 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

- Return to heavy drinking;
- return to any drinking;
- drinking days.

Return to *heavy drinking* is a binary variable containing the information whether a patient returned to drinking over a certain cut-off value as determined in the primary analysis (≥5 (4) standard drink units (SDUs) for men (women) in most trials). Return to *any drinking* with its complementary event "continuous abstinence" is a binary variable containing the information whether a patient returned to drinking after detoxification, or whether a patient remained completely abstinent throughout the entire course of the study. *Drinking days* are defined as the ratio of the total sum of drinking days (including low and heavy drinking days) related to the entire duration of the study, multiplied with the factor 100.

Secondary outcomes

- heavy drinking days;
- consumed amount per drinking day;
- gamma-glutamyl transpeptidase (GGT); and
- side effects

Heavy drinking days are defined as the ratio of the total sum of days with heavy drinking (as predetermined by the definition of heavy drinking in the primary analysis), related to the entire duration of the study, multiplied with the factor 100. The *consumed amount per drinking day was* calculated by relating the amount of alcohol (transformed into grams alcohol) to drinking days or drinking occasions, implying the exclusion of abstinent days from the analyses. *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 documented in at least three trials or for more than 200 patients and with a significant group difference in the meta-analysis, 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 2010) which contains the Cochrane Drugs and Alcohol Group's Trials Register;
- MEDLINE (from 1966 to January 2010);
- EMBASE (from 1988 to January 2010);
- CINAHL (from 1982 to January 2010).

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, subset, age as well as 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 1.

We searched for ongoing clinical trials and unpublished studies via Internet searches 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 manufacturers 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 of 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 second 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).

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 the 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 in 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 author, followed by consensus discussion and arbitration; and
3. contact of the study investigators to obtain the information of interest.

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

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). *The equivalence of baseline characteristics* was considered as further bias risks in the rating of the 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 criteria considered as constitutive for the rating of bias risks are outlined in the appendix (Appendix 3).

The results of the quality assessment with the risk of bias tables are used for a qualitative description of bias risks and considered in the discussion and the authors' conclusions. The risk of publication bias is graphically illustrated and quantified with a linear regression test (see Assessment of reporting biases), while the risk of funding bias is further explored by sensitivity analyses (see Sensitivity analysis).

Measures of treatment effect

Treatment effects for dichotomous effectiveness outcomes were measured with the 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. As Risk Differences (RD) can be calculated even when there are no events in either group, RD were used to assess the risk of side effects. Treatment effects on continuous outcomes (drinking days, heavy drinking days, consumed amount, gamma-glutamyl transpeptidase) were measured by mean differences (MD) of standardized units. All treatment effects were calculated within a 95% Confidence Interval (CI). If effects on binary outcomes reached statistical significance, the Number Needed to Treat for an Additional Beneficial Outcome (NNTB) for effectiveness outcomes and the Number Needed to Treat for an Additional Harmful Outcome (NNTH) for side effects were calculated. A P value of 0.05 and below was chosen to indicate statistical significance of effects.

Unit of analysis issues

As all identified studies eligible for the review are based on a parallel group designs and as for all repeated measurements, only one time-point (study endpoint) was included in the evaluation of effectiveness, the units of allocation invariably correspond with the unit of analysis.

Dealing with missing data

For the analyses of binary outcome data (return to heavy drinking, return to any drinking), all randomized patients were included in the statistical analyses, with drop-outs or lost to follow up being assigned to the relapse category. For analyses of continuous effectiveness outcomes (drinking days, heavy drinking days, consumed amount per drinking day, GGT), means and standard deviations were included as provided by the study publications irrespective of the handling of missing data in the primary analysis.

Assessment of heterogeneity

Inconsistency across studies was quantified with the I^2-statistic (Higgins 2003), using a variability of 50% as a 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 quantified with a linear regression test (Egger 1997), determining the linear regression coefficient between the log Odds Ratio (OR) and its standard error for "return to any drinking". The risk of outcome reporting bias (Chan 2004; Pocock 1987; Tannock 1996; 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 Mantal-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.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were conducted for trials with extended release naltrexone.

As a preliminary exploration of heterogeneity indicted 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 a meta-regression at a later stage.

Sensitivity analysis

Sensitivity analyses were conducted to determine the influence of the following variables on the primary outcome "return to any drinking":

- the underlying statistical model, by comparing effect sizes for low heterogeneity outcomes ($I^2 < 30\%$) based on random effects models versus fixed effect models;
- the funding source, by comparing effect sizes between trials that were sponsored by the pharmaceutical industry versus those that were investigator-driven and of non-profit funding.

Results

Description of studies

Results of the search

The study search for the review yielded 681 potentially relevant references, of which 621 were identified through bibliographic databases and 60 through other sources (personal communication: n = 3, database of ongoing trials: n = 57). 463 references were identified as duplicates and removed. From the remaining 218 screened records, 124 were excluded on the base of the information provided in the abstracts. Full-text articles were obtained for the 94 records, on whose base a further 44 studies were excluded. 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 50 RCTs (naltrexone: n = 47; nalmefene; n = 3) with 7793 patients was included in the review. Of the 7793 patients, 3881 have received treatment with naltrexone, 286 treatment with nalmefene and 3626 treatment with either placebo or active control.

Comparisons

44 of the 50 RCTs included in the review were based on a 2-arm design, comparing naltrexone with placebo (n = 40), nalmefene with placebo (n = 3) or naltrexone with the new generation antipsychotic drug aripiprazole (Martinotti 2008). In all 2-arm design trials, naltrexone and nalmefene were tested as monotherapy, with the exception of two trials which tested naltrexone combined with the 5HT-antagonist ondansetron (Johnson 2000) and the selective serotonin reuptake inhibitor sertraline (O'Malley 2008) against placebo.

Three trials used three treatment arms, either comparing naltrexone and placebo with the glutamate antagonist acamprosate (Morley 2006), with the serotonin-antagonist nalmefene (Kranzler 2000) or the anticonvulsant drug topiramate (Baltieri 2008). A further three trials were based on a four-armed design, testing naltrexone monotherapy, acamprosate monotherapy, placebo and a combined treatment with naltrexone and acamprosate (Anton 2006; Kiefer 2003) as well as naltrexone monotherapy, disulfiram monotherapy, placebo and combined naltrexone and disulfiram (Pettinati 2008b).

Publication types

47 of the 50 RCTs were published as journal articles, one study at a time as a congress abstract (Auriacombe 2000) or in book format (Ziółkowski 2000), while one study was only available as unpublished dissertation (de Goes e Castro 2004).

Patients

For the inclusion in the clinical trials, a diagnosis of alcohol dependence or abuse and a minimum age of 18 years was required. Patients in the included RCTs fulfilled the criteria of alcohol dependence or alcohol abuse as diagnosed with either DSM-III-R, DSM-IV or ICD-10. Mixed samples with both, patients with alcohol dependence and alcohol abuse, were included in six studies (Chick 2000; Gastpar 2002; Hersh 1998; Monti 2001; Morley 2006; Petrakis 2004); in none of these studies, alcohol abusers exceeded 10% of the entire sample. The mean age of the patient sample varied between 40 and 50 years in most studies (n = 43). 40 of the 50 RCTs were based on mixed gender samples, with men constituting the majority. Nine trials exclusively included male patients (Ahmadi 2002; Baltieri 2008; Ahmadi 2002; Baltieri 2008; Huang 2005; Lee 2001; Morris 2001; Oslin 1997; Petrakis 2004; Volpicelli 1992; Ziółkowski 2000), while one study evaluated the effectiveness of naltrexone in alcohol-dependent women (O'Malley 2007).

Patients with concurrent major psychiatric disorders or a psychiatric condition requiring the concurrent use of psychotropic medication were excluded in most studies (n = 48). Three studies did not explicitly state psychiatric comorbidity as a criteria of exclusion (Ahmadi 2002; Killeeen 2004; Oslin 2005) and three further studies even defined concurrent psychiatric disorders as a criteria of inclusion (Brown 2009; Petrakis 2004; Petrakis 2005). Petrakis 2004 included patients with concurrent schizophrenia and schizoaffective disorders, Brown 2009 patients with concurrent bipolar disorders and Petrakis 2005 examined naltrexone's effectiveness in a patient sample with axis I-diagnosis.

Like psychiatric comorbidity, a concurrent drug use (other than alcohol or nicotine) led to the exclusion of patients in most trials (n = 42). In contrast, Brown 2009, Petrakis 2005 and Martinotti 2008 did not exclude users of illegal drugs and in the studies of Hersh 1998, Pettinati 2008a; Pettinati 2008b and Schmitz 2004; Schmitz 2009, a concurrent cocaine diagnosis was constitutive for patient inclusion.

Treatment setting and study design

14 of the 50 RCTs included in the review used a multi-centre trials design (Anton 2004; Anton 2006; Balldin 2003; Chick 2000; Garbutt 2005; Gastpar 2002; Guardia 2002; Johnson 2004; Krystal 2001; Kranzler 2004; Latt 2002; Morley 2006; O'Malley 2008; Petrakis 2005). Sample sizes varied from 20 patients (Galarza 1997; Johnson 2000; Kranzler 1998) to over 600 patients (Anton 2006; Garbutt 2005; Krystal 2001), whereby most studies (n = 28) included between 80 and 200 patients. With a total of 1383 patients, the COMBINE-study (Anton 2006) was the largest trial included in the review.

Industry sponsorship was reported in 11 study publications (Anton 2006; Balldin 2003; Chick 2000; Galarza 1997; Garbutt 2005; Gastpar 2002; Guardia 2002; Kranzler 2004; Latt 2002; Mason 1994; Oslin 1997), four studies did not provide information on the funding sources (Ahmadi 2002; Auriacombe 2000; Huang 2005; de Goes e Castro 2004), while the remaining 39 RCTs reported a sponsoring by non-profit organizations.

Most studies were conducted in the United States (n = 37), eight studies in Europe (Auriacombe 2000; Balldin 2003; Chick 2000; Heinälä 2001; Kiefer 2003; Gastpar 2002; Guardia 2002; Ziółkowski 2000Ziółkowski 2000) and three studies at a time in Australia (Morris 2001; Morley 2006; Latt 2002), Asia (Ahmadi 2002; Lee 2001; Huang 2005) and Latin America (Baltieri 2008; Galarza 1997; de Goes e Castro 2004).

Before treatment, patients were detoxified in most trials, whereby at least 3 to 7 days, but not more than 30 days of abstinence were required to enter randomization. Detoxification was not necessarily required in seven RCTs (Brown 2009; Garbutt 2005; Heinälä 2001; Johnson 2000; Oslin 2005; Schmitz 2004; Schmitz 2009) and in three of these trials (Brown 2009; Garbutt 2005; Heinälä 2001), the entire patient sample was actively drinking when the treatment started.

Seven trials started with a placebo run-in week (Balldin 2003; Heinälä 2001; Hersh 1998; Kranzler 2000; Mason 1994; Monterosso 2001; Volpicelli 1992; Volpicelli 1997), one trial (Kranzler 1998) with a two-week run-in period with naltrexone, followed by a two-week washout period without medication.

In the course of the trial, drinking-related outcomes were repeatedly measured. In the majority of studies (n = 39), drinking was assessed with the Time Line Follow-Back method (Sobell 1988; Sobell 1992), which is a semi-structured interview that uses calendar format to record the quantity and frequency of drinking. Further instruments used to assess drinking were alcohol use questionnaires (de Goes e Castro 2004; Volpicelli 1992; Volpicelli 1997), daily monitoring cards (Baltieri 2008), drinking diaries (Heinälä 2001; Kiefer 2003), quantity-frequency assessments (Guardia 2002) and a patients` self-evaluation interview (Martinotti 2008; Latt 2002).

To systematically assess side effects, checklists (Kiefer 2003; Hersh 1998; Johnson 2000; Johnson 2004; Latt 2002), an open ended inquiry (Morley 2006), a rating scale (Balldin 2003) and the Systematic Assessment for Treatment Emergent Effects (SAFTEE; Levine 1986; Rabkin 1992) were used (Anton 2006; Kranzler 1998; Pettinati 2008a; Pettinati 2008b). Petrakis 2004 and Petrakis 2005 applied the Hopkins Symptom Checklist (HSCL; Derogatis 1974), Baltieri 2008 the Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale (Lingjaerde 1987) and Martinotti 2008 the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar; Sullivan 1989) for the assessment of side effects.

The post-treatment drinking status was assessed at intervals of 3 months (Kiefer 2004; Anton 2001), 6 months (Krystal 2001; O'Malley 1996), 8 months (Ziółkowski 2000), 12 months (Anton 2006; Monti 2001), and 17 months (O'Malley 2008) after treatment was discontinued.

To measure compliance, riboflavin was used in five RCTs (Monti 2001; Anton 1999; Schmitz 2004; Hersh 1998; Kranzler 2000), while the most common method to monitor medication compliance was pill count (Anton 2004; Anton 2006; Balldin 2003; Baltieri 2008; Brown 2009; Chick 2000; Gastpar 2002; Guardia 2002; Johnson 2000; Kiefer 2003; Latt 2002; Lee 2001; Mason 1999; Morley 2006; Monti 2001; Monterosso 2001; Morris 2001; Oslin 2005; Oslin 2008; Petrakis 2004; Pettinati 2008a; Pettinati 2008b; Schmitz 2009;Volpicelli 1997). Seven further RCTS (Anton 2005; Killeeen 2004; Krystal 2001; Mason 1999; O'Malley 2007; O'Malley 2008; Petrakis 2005) used electronic systems (e.g. Microelective Events Monitoring System (MEMS); Electronic Microchip System (EMS)) to assess compliance, which uses medication caps containing microelectronics to record each time and date the bottle is opened and closed. Five studies report that pill counts and cap openings have been verified by the measurement of plasma naltrexone levels (Kranzler 1998) or 6 beta naltrexol blood levels (Chick 2000; Gastpar 2002; Kranzler 1998; Krystal 2001).

Treatment

In 4 RCTs of the 47 RCTS with naltrexone included in the review, an injectable extended-release formulation was used (Garbutt 2005; Johnson 2004; Kranzler 1998; Kranzler 2004). Injectable naltrexone was administered at four-week intervals at doses between 150 mg (Kranzler 2004) and 400 mg (Johnson 2004). When naltrexone was administered orally, a daily dose of 50 mg was used in most trials, while in the trials of Anton 2006, Monterosso 2001, Oslin 2008, Pettinati 2008b and Schmitz 2009, the daily dose was 100 mg dose, in Pettinati 2008a 150 mg. For nalmefene, which is exclusively available as oral formulation, different dose regimes were tested from 5 mg (Anton 2004) to 80 mg (Mason 1999).

Treatment duration varied from four weeks (Galarza 1997; Kranzler 1998) up to 52 weeks (Auriacombe 2000), while a duration of three months was most common (n = 34). In the study of Krystal 2001, different treatment durations (3 months versus 12 months) were tested within one trial. Treatment was exclusively provided in outpatient settings. In two studies (Lee 2001; Ziółkowski 2000), treatment started for four weeks on an inpatient base, before it was continued as outpatient treatment. Psychosocial treatment was provided in all but two trials (Mason 1994; Morley 2006), whereby cognitive behavioral therapies (n = 17) and motivational therapies (n = 10) were most common.

Outcomes

The most frequently considered outcome was “return to heavy drinking”, reported for 32 RCTs, followed by "return to a any drinking" and "drinking days", available for 29 respectively 28 RCTs. The secondary outcomes of the review, "drinks per drinking day", “heavy drinking days” and GGT values were less frequently provided; anyhow, information on these outcomes was available for 18 (drinks per drinking day), 17 (heavy drinking days) and 16 trials (GGT). Besides the outcome information available from the trial publications, information on "return to any drinking” was subsequently provided by the investigators for seven RCTs (Anton 2006; Balldin 2003;

Brown 2009; Guardia 2002; Killeeen 2004; Krystal 2001; Ziółkowski 2000), on GGT values for three RCTs (Killeeen 2004; Morris 2001; Morley 2006), on drinking days for two RCTs (Brown 2009; Morris 2001) and on "heavy drinking days" (Morley 2006) and "consumed amount per drinking day" (Brown 2009) for one trial at a time. Post-treatment results for "return to heavy drinking" (Anton 2001; Anton 2006; Kiefer 2004; Monti 2001; O'Malley 1992O'Malley 1992), "return to any drinking" (O'Malley 1996; Ziółkowski 2000) and "drinking days" (Anton 2006) at post-treatment, were exclusively extracted from trial publications.

A cut-off value for heavy drinking of five (four) standard drink units (SDU) for men (women) was chosen in most studies, while Killeeen 2004; Krystal 2001; Mason 1999 and Morley 2006 considered six drinks as a critical threshold value for heavy drinking in men. Ahmadi 2002, Heinälä 2001, Huang 2005, Kiefer 2003, Mason 1999, Oslin 1997, Volpicelli 1992 and Volpicelli 1997 additionally assigned patients to the heavy drinking category if drinking occurred on five or more days or occasions a week or if the blood alcohol concentration (BAC) was higher than 100mg/dl. In the Brazilian trials, alcohol consumption was defined as heavy drinking if more than 90 grams alcohol were consumed per week (Baltieri 2008) or if drinking was above 9 SDUs per day (de Goes e Castro 2004); in the latter trial, moderate drinking (defined as drinking 5 to 9 SDU per day), was subsequently assigned to the "heavy drinking"-category for the meta-analysis to adapt the definition to the majority of trials.

Excluded studies

44 trials were excluded on the basis of their full-text versions. Reasons for exclusion was an open label study design in 17 studies (Buri 2007; Caputo 2003, Caputo 2007, Carroll 1993, Croop 1997, De Sousa 2004, Deas 2005, Galloway 2005, Hermos 2004, Kranzler 2008, Laaksonen 2008, Landabaso 1999, Martinotti 2007, Nava 2006, Oslin 1999, Rubio 2002, Stella 2008), a single-blind design in three further studies (Ponce 2005, Rubio 2001, Rubio 2005) and targeted treatment in one trial (Karhuvaara 2007). Ten studies were excluded as they did not meet the sample requirement "alcohol dependence", including hazardous drinkers (Davidson 2004; Palfai 1999), heavy drinkers (Ray 2007; Tidey 2008), problem drinkers (Kranzler 1997; Hernandez-Avila 2006; Kranzler 2004b) and healthy persons (Dunbar 2006; Mason 2002) or patients with hepatic impairments (Turncliff 2005) to test pharmacokinetic or -dynamic properties of naltrexone. A further eight studies were excluded as they did not comply with the minimum study duration of 30 days, of which three clinical trials only covered three weeks of treatment (Johnson 2003; Knox 1999; Ooteman 2007) and five laboratory studies one week of treatment (Drobes 2000; Drobes 2004; Kranzler 2004a; Modesto-Lowe 1997; Myrick 2008). Other reasons for exclusion were the lack of a control group (Davidson 2007a; Farren 2009; Tucker 2004) and a multiphase design, which started with open label naltrexone in both, intervention and control groups (Davidson 2007b; O'Malley 2003). Post-treatment results from two studies were excluded because of the low post-treatment duration (Kranzler 1998) and the non-randomised allocation (Latt 2002).

Risk of bias in included studies

Allocation

Sequence generation

For 14 of the 50 RCTs (Anton 2006; Balldin 2003; Baltieri 2008; Brown 2009; Garbutt 2005; Kiefer 2003; Killeeen 2004; de Goes e Castro 2004; Latt 2002; Martinotti 2008; Morley 2006; Schmitz 2009; Volpicelli 1997; Ziółkowski 2000), the methods used for sequence generation were specified in the trial publications and considered as adequate. Seven trials (Baltieri 2008; Brown 2009; Kiefer 2003; Latt 2002; Morley 2006; Volpicelli 1997; Ziółkowski 2000) used computer-generated randomization lists, some trials random number tables (Balldin 2003; de Goes e Castro 2004), urn drawing (Killeeen 2004; Schmitz 2009), an interactive voice response system (Anton 2006; Martinotti 2008) and coin tossing (Garbutt 2005). For the remaining 36 RCTs, methods used for sequence generation were not specified.

Allocation concealment

Randomization was described as centralized and conducted by an independent support unit remote from patient recruitment centres in five trials (Anton 2006; Balldin 2003; Kiefer 2003; Kranzler 2004; Morley 2006), in eight trials drug containers were described as being prepared by an independent pharmacy (Balldin 2003; Baltieri 2008 ; Galarza 1997; Kiefer 2003; Kranzler 1998; Latt 2002; Morley 2006; Petrakis 2005). Three of these trials additionally reported that allocation codes were provided in sealed envelopes (Balldin 2003; Kiefer 2003; Morley 2006). 3 of 50 RCTs (Balldin 2003; Kiefer 2003; Morley 2006) fulfilled both criteria (centralized randomisation and drug preparation, sealed envelopes) considered as relevant for an adequate allocation concealment.

Blinding

In all but three trial publications (Ahmadi 2002; Auriacombe 2000; Galarza 1997) placebo and active medication were reported to have identical appearance. In studies with an active control group, blinding was ensured through a double-dummy design signifying that an identically matched placebo was available for each drug, and that participants in each group took the same number of pills per day (Anton 2006; Johnson 2000; Kiefer 2003; Morley 2006; O'Malley 2008; Pettinati 2008b). From the 50 RCTs included in the review, 21 RCTs (Anton 2006; Balldin 2003; Baltieri 2008; Garbutt 2005; Hersh 1998; Huang 2005; Kiefer 2003; Kranzler 1998; Kranzler 2000; Kranzler 2004; Latt 2002; Mason 1999; Monti 2001; Morley 2006; Morris 2001; O'Malley 1992; O'Malley 2007; O'Malley 2008; Oslin 2008; Petrakis 2005; Ziółkowski 2000) fulfilled both criteria of adequate blinding (blinding of patients and research stuff, identically matched placebo). From those, six trials (Baltieri 2008; Kiefer 2003;

Kranzler 1998; Kranzler 2000; Mason 1999; Morley 2006) additionally tested and confirmed the integrity of blinding by inquiries on patients and therapists. 31 RCTs (Anton 2006; Balldin 2003; Baltieri 2008; Chick 2000; Garbutt 2005; Gastpar 2002; Guardia 2002; Hersh 1998; Huang 2005; Johnson 2000; Johnson 2004; Kiefer 2003; Killeeen 2004; Kranzler 1998; Latt 2002; Lee 2001; Martinotti 2008; Mason 1994; Mason 1999; Monterosso 2001 ; Monti 2001; Morley 2006; Morris 2001; O'Malley 1992; O'Malley 2007; O'Malley 2008; Oslin 1997; Oslin 2008; Petrakis 2004; Petrakis 2005; Ziółkowski 2000) have used objective outcomes for a validity check of patient-reported drinking outcomes.

Incomplete outcome data

Binary outcomes

The handling of missing binary data was considered as adequate for 11 RCTs (Balldin 2003; Baltieri 2008; Chick 2000; Kiefer 2003; Mason 1999; Morley 2006; O'Malley 2008; Oslin 2008; Pettinati 2008a; Pettinati 2008b; Ziółkowski 2000) of the 40 RCTs, which provided dichotomous outcomes (return to any drinking, return to heavy drinking) for the review: In these trials, all randomized patients or at least those who received treatment, were included in the data analysis (ITT principle) and assigned to the relapse category.

The problem of incomplete binary outcome data was considered as inadequately addressed in four trials, which either excluded patients who dropped out early (Gastpar 2002; Krystal 2001; Lee 2001) or which only considered those patients who attended at least one week of treatment (O'Malley 1992). For the remaining 25 trials with binary outcomes, the bias risks associated with missing data remained unclear.

Continuous outcomes

For 12 of the 26 RCTs, which provided "drinking days" as a study outcome, the handling of missing data was considered as adequate, meaning that all randomized patients or those who received on treatment dose were included in the analysis, while missing information on drinking frequency did either not occur (Kranzler 2000, Mason 1999) or was adequately replaced: The latter included substitutions with “worst case” scenarios, rating the complete interval from the last attendance of a patient who dropped out from a trial as non-abstinent (Anton 2006; Baltieri 2008; Kranzler 2000; Morley 2006; O'Malley 2007, O'Malley 2008), the imputation with the mean of nearby subgroup values (Balldin 2003) and the application of a pattern mixture strategy that was applied to assess the sensitivity of the results to the underlying assumptions of handling missing data (Oslin 2008; Pettinati 2008a; Pettinati 2008b).

The problem of missing continuous data was considered as inadequately addressed in five trials, which either excluded patients who dropped out early (Gastpar 2002; Krystal 2001; Lee 2001) or which only considered those patients who attended at least one week of treatment (Mason 1994; O'Malley 1992). For the remaining trials, the handling of missing continuous outcome data remained unclear.

Selective reporting

With the concordance between outcomes listed in the study protocol or the methods section of the trial publication, 48 of the 50 RCTs fulfilled the criteria of non-selective outcome reporting. One trial (Ahmadi 2002) has explicitly listed an outcome in the method section, that was not presented in the result section, one study that was only available as a congress abstract (Auriacombe 2000), outcomes were not explicitly stated.

Other potential sources of bias

45 of the 50 RCTs included in the review (Anton 1999; Anton 2004; Anton 2005; Anton 2006; Balldin 2003; Baltieri 2008; Brown 2009; Chick 2000; Gastpar 2002; Guardia 2002; Hersh 1998; Johnson 2004; Killeeen 2004; Kranzler 2004; Krystal 2001; Mason 1994; Mason 1999; Morley 2006; Morris 2001; O'Malley 2007; Oslin 2008; Petrakis 2004; Pettinati 2008a; Pettinati 2008b; Schmitz 2004; Schmitz 2009; Volpicelli 1997) were considered as "free" of other potential sources of bias, ensuring the equivalence of baseline characteristics (age, gender, baseline drinking, drinking or treatment history). In four trials (Kiefer 2003; Monterosso 2001; Morley 2006; Oslin 2005), baseline imbalance was identified for selected patient characteristics and controlled in the statistical analyses of treatment effects.

See Figure 10, Figure 11

General susceptibility to bias effects

In 30 of the 50 RCTs, general susceptibility to bias was reduced by the inclusion of objective measures, which were assessed for a validity check of self-reported drinking outcomes. Most trials therefore used breath alcohol concentrations (Garbutt 2005; Gastpar 2002; Guardia 2002; Hersh 1998; Huang 2005; Johnson 2000; Kiefer 2003; Killeeen 2004; Kranzler 1998; Kranzler 2000; Kranzler 2004; Latt 2002; Mason 1994; Mason 1999; Monti 2001; Morris 2001; O'Malley 2007; Petrakis 2004; Petrakis 2005; Pettinati 2008b), 11 RCTs collateral reports (Baltieri 2008; Gastpar 2002; Guardia 2002; Kranzler 2000; Lee 2001; Martinotti 2008; Mason 1999; Monterosso 2001; Monti 2001; O'Malley 1992; O'Malley 2007), 5 RCTs either blood alcohol (Martinotti 2008; Oslin 1997) or urine alcohol concentrations (Chick 2000; Guardia 2002; Morley 2006), 3 RCTs (Johnson 2004; Lee 2001; O'Malley 2008) GGT values and one trial (Anton 2006) carbohydrate-deficient transferrin (CDT) values.

Publication bias

The plotting of the log odds ratio against its standard error showed a slight asymmetry with a gap in the bottom

corner of the graph (Figure 9), while the linear regression test (Egger 1997) did not indicate a considerable risk of publication bias, neither for the non-weighted regression (R^2 = 0.20; P = 0.229; SE = 1.440; n = 29) nor for the weighted regression (R^2 = 0.52; P = 0.765; SE = 1.221; n = 29).

Effects of interventions

01 Naltrexone versus placebo

Treatment phase

Naltrexone was shown to significantly reduce the risk to return to heavy drinking to 83%, RR 0.83 (95% CI 0.76 to 0.90) of the risk in the placebo group see Analysis 1.1 or Figure 2, while its effect on return to any drinking missed statistical significance, RR 0.96 (95% CI 0.92 to 1.00) see Analysis 1.2 or Figure 3. The corresponding NNTB for preventing heavy drinking was 9.09 (95% CI 6.66 to 14.28). Drinking days were decreased by about 4% with naltrexone compared to placebo MD -3.89 (95% CI -5.75 to -2.04) see Analysis 1.3 or Figure 4).

The superiority of naltrexone compared to placebo has also been shown for the secondary outcomes of the review. Naltrexone was associated with a reduction of heavy drinking days by about 3% MD -3.25 (95% CI -5.51 to -0.99) see Analysis 1.4 or Figure 5, a decrease of the consumed amount of alcohol on drinking days by about 11 grams MD - 10.83 (95% CI -19.69 to -1.97) see Analysis 1.5 or Figure 6 and a reduction of GGT values by about 10 units per liter MD - 10.37 (95% CI -18.99 to -1.75) see Analysis 1.6 or Figure 7.

The risk difference to be affected by any side effect was 0.05 (95% CI 0.01 to 0.09), see Analysis 1.7, Among a total of 79 single side effects reported in the included studies, 45 were considered in more than one study allowing a statistical synthesis of results. Seexteen out of these 45 showed result statistically significant in favour of placebo. These include gastrointestinal symptoms like abdominal pain RD 0.08 (95% CI 0.04 to 0.11), see Analysis 1.8; decreased appetite RD 0.07 (95% CI 0.03 to 0.11), see Analysis 1.18, nausea RD 0.10 (95% CI 0.07 to 0.13), see Analysis 1.39, and vomiting RD 0.07 (95% CI 0.04 to 0.09), see Analysis 1.52 as well as symptoms associated with a decreased central nervous arousal like daytime sleepiness RD 0.09; 95% CI 0.05 to 0.14, see Analysis 1.17, drowsiness RD 0.10 (95% CI 0.00 to 0.19), see Analysis 1.23, fatigue RD 0.05 (95% CI 0.01 to 0.09), see Analysis 1.26, insomnia RD 0.03 (95% CI 0.00 to 0.06), see Analysis 1.31, lethargy RD 0.13 (95% CI 0.04 to 0.23), see Analysis 1.35, somnolence RD 0.10 (95% CI 0.05 to 0.14); see Analysis 1.49, and weakness RD 0.17 (95% CI 0.05 to 0.29) see Analysis 1.53. Further side effects that appeared more often under naltrexone than placebo were blurred vision RD 0.13 (95% CI 0.04 to 0.21), see Analysis 1.13, decreased libido RD 0.08 (95% CI 0.01 to 0.16), see Analysis 1.19, depression RD 0.04 (95% CI 0.00 to 0.08) see Analysis 1.20, dizziness RD 0.06 (95% CI 0.04 to 0.08), see Analysis 1.22 and nightmares RD 0.10 (95% CI 0.04 to 0.16), see Analysis 1.41. The remaining 29 side effects considered, did not show statistically significant differences see Analysis 1.9; Analysis 1.10; Analysis 1.11; Analysis 1.12; Analysis 1.14; Analysis 1.15; Analysis 1.16; Analysis 1.21; Analysis 1.24; Analysis 1.25; Analysis 1.27; Analysis 1.28; Analysis 1.29; Analysis 1.30; Analysis 1.32; Analysis 1.33; Analysis 1.34; Analysis 1.36; Analysis 1.37; Analysis 1.38; Analysis 1.40; Analysis 1.42; Analysis 1.43; Analysis 1.44; Analysis 1.45; Analysis 1.47; Analysis 1.48; Analysis 1.50; Analysis 1.51. Also the risk difference for experiencing serious side effects did not differ between groups RD -0.02 (CI -0.05 to 0.00), see Analysis 1.46. Side effects lead more often to an early termination in the naltrexone than in the placebo group: Compared to placebo, the risk of dropping out due to adverse events was 60% higher in intervention groups RR 1.60; (95% CI 1.15 to 2.23), see Analysis 1.54. The risk of dropping out irrespective of reasons was 8% lower in the naltrexone group than in the placebo group RR 0.92 (95% CI 0.83 to 1.01), see Analysis 1.55.

Post-treatment results

Three to twelve months after treatment was discontinued, patients who were in the naltrexone group had a 14% lower risk to return to heavy drinking RR 0.86 (95% CI 0.75 to 0.99), see Analysis 1.56 and a 6% lower risk to return to any drinking RR = 0.94 (95% CI 0.79 to 1.11), see Analysis 1.57 than those who were in the placebo group.

Sensitivity analyses

If data synthesis for "return to any drinking" (I^2 = 28%) was based on a fixed-effect model, a significant effect was obtained RR 0.95 (95% CI 0.92 to 0.98) see Analysis 1.58, meaning that the effectiveness conclusions concerning the outcome vary with the statistical model chosen for its calculation.

Synthesis of effects according to their sponsoring indicated a higher magnitude of effects for non-profit sponsored, investigator-driven trials RR 0.84 (95% CI 0.77 to 0.91) than for industry-sponsored studies (RR = 0.90; 95% CI 0.78 to 1.05) see Analysis 1.59 or Figure 8.

02 Subgroup analyses: Injectable naltrexone

Subgroup analyses of extended-release formulations of naltrexone compared to placebo (Garbutt 2005; Johnson 2004; Kranzler 1998; Kranzler 2004) indicate that injected naltrexone reduced the risk of any drinking after detoxification to 92% of the placebo group RR = 0.92 (95% CI 0.84 to 1.00), see Analysis 2.1, the percentage of drinking days by about 9% MD - 8.54 (95% CI -15.77 to -1.31), see Analysis 2.2 and the percentage of heavy drinking days by about 3% MD = -3.05 (95% CI -8.46 to 2.35), see Analysis 2.3.

Extended-release naltrexone caused significantly more often daytime sleepiness than placebo RD 0.22 (95% CI

0.02 to 0.42) see Analysis 2.5, decreased appetite RD 0.08 (95% CI 0.04 to 0.11), see Analysis 2.6, dizziness RD 0.08 (95% CI 0.04 to 0.12), see Analysis 2.7, fatigue RD 0.06 (95% CI 0.01 to 0.10), see Analysis 2.8 and vomiting RD 0.06 (95% CI 0.02 to 0.11), see Analysis 2.15. Other seven adverse events considered did not show statistically significant differences, see Analysis 2.4; Analysis 2.9; Analysis 2.10; Analysis 2.11; Analysis 2.12; Analysis 2.13; Analysis 2.14. Early drop-out due to side effects were more frequent in the extended-release naltrexone group than in the placebo group RR 1.57 (95% CI 0.92 to 2.69), see Analysis 2.16, while the risk of dropping out irrespective of reasons slightly differed between injectable naltrexone and placebo RR 0.98 (95% CI 0.68 to 1.40), see Analysis 2.17.

03 Naltrexone versus acamprosate

Summary statistics based on the three clinical trials (Anton 2006; Kiefer 2003; Morley 2006), which include naltrexone and acamprosate, did not indicate a significant difference between both substances in any of the primary outcomes. For the risk to return to heavy drinking RR 0.96 (CI 0.87 to 1.06), see Analysis 3.1, the risk to return to any drinking RR 0.97 (CI 0.91 to 1.04) see Analysis 3.2 a non-significant trend favouring naltrexone compared to acamprosate was found. In contrast, drinking days were non-significantly higher under naltrexone compared to acamprosate MD 3.06 (95% CI -7.42 to 13.53), see Analysis 3.3.

Naltrexone was associated with a higher risk of nausea RD 0.08 (95% CI 0.03 to 0.13) see Analysis 3.5 and somnolence RD 0.07 (95% CI 0.01 to 0.13), see Analysis 3.6 compared to acamprosate, while acamprosate caused more often diarrhoea RD -0.27 (95% CI -0.34 to -0.20), see Analysis 3.4. Naltrexone had a 31% higher risk of terminating the study early because of adverse events than acamprosate RR 1.31 (95% CI 0.63 to 2.73), see Analysis 3.7. In contrast, the risk of dropping out from a study irrespective of drop-out reasons was 8% lower in the naltrexone than in the acamprosate RR 0.92 (95% CI 0.77 to 1.10), see Analysis 3.8.

04 Naltrexone versus apripiprazole, nefazodone or topiramate

Summarized effects for naltrexone versus the new generation antipsychotic aripiprazole (Martinotti 2008), the antidepressant nefazodone (Kranzler 2000) and the anticonvulsant topiramate (Baltieri 2008), based on one study at a time, showed a non-significant superiority of active control compared to naltrexone. Patients in the naltrexone group had a non-significantly higher risk of heavy drinking (aripiprazole: RR = 1.32; 95% CI 0.73 to 2.39; nefazodone: RR = 1.08; 95% CI 0.73 to 1.59) and of any drinking (aripiprazole: RR = 1.04; 95% CI 0.68 to 1.59; nefazodone: RR = 1.04; 95% CI 0.82 to 1.32; topiramate: RR = 1.33; 95% CI 0.98 to 1.80) than in the active control group.

Naltrexone was also non-significantly associated with more drinking days (aripiprazole: MD = 4.30; 95% CI -15.73 to 24.33; nefazodone: MD = 4.40; 95% CI -4.99 to 13.79; topiramate: MD = 13.30; 95% CI -2.01 to 28.61) and heavy drinking days (aripiprazole: MD = 3.00; 95% CI -3.89 to 9.8; nefazodone: MD = 1.30; 95% CI -6.69 to 9.29; topiramate: MD = 13.4; 95% CI -2.27 to 29.07). In contrast, GGT values were lower in the naltrexone group compared to nefazodone (MD = -4.7; 95% CI -27.11 to 17.71) and topiramate (MD = -5.00; 95% CI -35.49 to 25.49), but this trend was again not statistically significant.

The only side-effects, which significantly differed between groups was decreased appetite and insomnia, which were documented more frequently in the naltrexone than in the nefazodone group (decreased appetite: RD = 0.22; 95% CI 0.07 to 0.38; NNTH = 4.54; insomnia: RD = 0.23; 95% C 0.06 to 0.41; NH = 4.35). Drop-out risks were 4%, 51% and 12% higher under naltrexone than aripiprazole (RR = 1.04; 95% CI 0.42 to 2.57), nefazodone (RR = 1.51; 95% CI 0.90 to 2.53) and topiramate (RR = 1.12; 95% CI 0.68 to 1.83).

Naltrexone + acamprosate versus placebo

The combination of naltrexone and acamprosate, tested in two RCTs (Anton 2006; Kiefer 2003), was shown to reduce the risk to return to heavy drinking and to any drinking by about 30% (heavy drinking: RR = 0.71; 95% CI 0.38 to 1.35; any drinking: RR = 0.70; 95% CI 0.35 to 1.39) compared to placebo; drinking days were lowered by two percent (MD = -2.20; 95% CI -6.30 to 1.90) and GGT values by about nine units per liter (MD = -8.70; 95% CI -24.86 to 7.46). None of the effects reached statistical significance. Compared to placebo, the combined therapy with naltrexone and acamprosate caused significantly more often decreased appetite (RD = 0.11; 95% CI 0.05 to 0.17; NNTH = 9.09), diarrhea (RD = 0.20; 95% CI 0.13 to 0.27; NNTH = 5), nausea (RD = 0.20; 95% CI 0.14 to 0.26; NNTH = 5) and vomiting (RD = 0.09; 95% CI 0.03 to 0.14; NNTH = 11.1). The risk to drop-out due to adverse events was higher in the combined therapy group than in the placebo group (RR = 3.75; 95% CI 1.33 to 10.55), while the risk of dropping out irrespective of reasons was higher in the placebo group (RR = 0.83; 95% CI 0.28 to 2.49).

Naltrexone + acamprosate versus naltrexone

When compared to naltrexone alone, effects of combined treatment with naltrexone and acamprosate turned out be lower in their magnitude than compared to placebo for most outcomes: The risk reduction for return to heavy drinking was 3% (RR = 0.97; 95% CI 0.75 to 1.26), for any drinking 12% (RR = 0.88; 0.61 to 1.28), while drinking days were decreased by about 1% (MD = -1.10; 95% CI -5.21 to 3.01). None of the primary outcomes reached statistical significance. A significant effect was demonstrated for the GGT, assessed in one trial only, which was lower in the naltrexone than in the combined treatment group (MD = 10.7; 95% CI 1.87 to 19.93). The combination of acamprosate and naltrexone induced significantly more often diarrhea (RD = 0.37; 95% CI 0.10 to 0.65; NNTH = 2.70) and nausea (RD = 0.09; 95% CI 0.02 to 0.16; NNTH = 11.1) than naltrexone alone. The risk of dropping out because of side effects (RR = 1.07; 95% CI 0.55 to 2.08) and the risk of terminating the study

early irrespective of reasons (RR = 1.03; 95% CI 0.95 to 1.43) were non-significantly higher in the combined treatment group than in the naltrexone group.

Naltrexone + ondansetrone / sertraline versus placebo

Combinations of naltrexone with either the 5HT-antagonist ondansetrone (Johnson 2000) or the selective serotonin reuptake inhibitor sertraline (O'Malley 2008) have both been shown to significantly reduce drinking days and consumed amount per drinking day: In the trial with ondansetron (Johnson 2000), patients drank alcohol on about 25% days less than those treated with placebo (MD = -23.80; 95% CI -58.13 to 10.53); in the trial with sertraline (O'Malley 2008), the effect was lower (MD = -10.6; 95% CI -12.06 to -9.14), but reached statistical significance. The same applies to consumed amount per drinking day, which reduced at about 50 grams in the ondansetron trial (MD = -50.70; 95% CI -81.53 to -19.87) and 28 grams in the sertraline trial (MD = -10.6; 95% CI -12.06 to -9.14) in comparison to placebo. For the combination with sertraline, a significant effect was also demonstrated on heavy drinking days (MD = -8.20; 95% CI -9.61 to -6.79). Effects on dichotomous outcomes (return to heavy drinking: RR = 0.79; 95% CI 0.59 to 1.05; return to any drinking: RR = 0.79; 95% CI 0.61 to 1.02) and the GGT values (MD = -7.30; 95% CI 33.79 to 19.19) in the sertraline trial slightly missed statistical significance. At the same time, sertraline was associated significantly more often with sleepiness (RR = 0.40; 95% CI 0.18 to 0.62), nausea (RR = 0.29; 95% CI 0.06 to 0.51) and dizziness (RR = 0.25; 95% CI 0.03 to 0.47).

Nalmefene versus placebo

Treatment phase

By including data from 3 RCTs (Anton 2004; Mason 1994; Mason 1999) with 396 patients, nalmefene was shown to reduce the risk to return to heavy drinking to 85% (RR = 0.85; 95% CI 0.67 to 1.08) of the risk in the placebo group and to lower the risk to return to any drinking after detoxification to 92% (RR = 0.92; 95% CI 0.70 to 1.20). Nalmefene was furthermore associated with a 5% reduction of heavy drinking days (MD = -4.70; 95% CI -12.38 to 2.98) and a decrease of the amount of alcohol consumed per drinking day at about 4 grams (MD = -4.16; 95% CI -32.69 to 24.37). None of the effects reached statistical significance.

Adverse effects associated with the use of nalmefene were nausea (RD = 0.20; 95% CI 0.14 to 0.26), insomnia (RD = 0.12; 95% CI 0.05 to 0.19) and dizziness (RD = 0.15; 95% CI 0.05 to 0.25). Patients in the nalmefene group had a 43% higher risk to drop out due to adverse events than patients in the placebo group (RR = 1.43; 95% CI 0.22 to 9.24), while the risk to drop out irrespective of the reasons for termination, was lower (RR = 0.92; 95% CI 0.68 to 1.25) than in the placebo group. None of the effects on effectiveness outcomes and drop-out rates reached statistical significance.

Heterogeneity

With the exception of the effect variance for "return to any drinking", which was predominantly explained by sampling error (I^2 = 28%; Figure 3), with proportions of between-study heterogeneity over 60%, I^2 statistics indicated a substantial level of heterogeneity (Deeks 2008). High levels of heterogeneity for the continuous outcomes drinking days (I^2 = 94%; Figure 4), heavy drinking days (I^2 = 81%; Figure 5), consumed amount per drinking day (I^2 = 66%; Figure 6) and GGT (I^2 = 61%; Figure 7) were confirmed by τ^2statistics (drinking days: τ^2 = 9.59; heavy drinking days: τ^2 = 10.71; consumed amount per drinking day; τ^2 = 178.98; GGT: τ^2 = 139.02), while the τ^2statistics indicate moderate heterogeneity for the binary outcome "return to heavy drinking" (τ^2 = 0.02; Figure 2).

Discussion

Summary of main results

A total of 50 RCTs with 7793 patients was included in the review. Two of the three primary outcomes of the review clearly support the effectiveness of naltrexone in the treatment of alcohol dependence: Added to psychosocial treatment strategies, the opioid antagonist was shown to reduce the risk to return to heavy drinking to 83% of the placebo risk and to decrease drinking days by about 4%. For the third primary outcome of the review, return to any drinking, effects slightly missed statistical significance RR 0.96 (95% CI 0.92 to 1.00), if based on a random effects model.

Statistical significance was obtained for all secondary outcomes of the review: Compared to placebo, heavy drinking days were reduced by about 3% with naltrexone, the consumed amount of alcohol per drinking days was lowered by almost 11 grams and gamma-glutamyltransferase (GGT) values were decreased by 10 units per liter . Post-treatment evaluations, provided from a subset of six RCTs, indicate that the therapeutic effects of naltrexone fade after treatment is discontinued; anyhow, 3 to 12 months after the end of the treatment period, effects on heavy drinking still reach statistical significance .

Naltrexone intake was associated with different side effects, mainly assignable to the following two categories: 1. gastrointestinal symptoms like abdominal pain, decreased appetite, nausea and vomiting and 2. symptoms of sedation reported as daytime sleepiness, drowsiness, fatigue, lethargy, insomnia, somnolence and weakness. Further side effects were blurred vision, decreased libido, depression, dizziness and nightmares. In none of the trials, analyses of side effect indicated serious safety concerns. Anyhow, in one out of 50 patients, the adverse

events induced by naltrexone lead to the discontinuation of treatment, indicating that most alcohol dependent patients accept side effects as a tolerable part of the treatment.

Treatment effects of extended-release naltrexone and of nalmefene, the second opioid antagonist tested in review, were shown to be comparable in their magnitude with those of oral naltrexone. However, for both drugs, extended-release naltrexone and nalmefene, statistical significance was missed. Besides a more pronounced sedative component for injectable naltrexone, the tolerability of extended-release naltrexone and nalmefene appears comparable to that of oral naltrexone.

Meta-analytic integrations of head-to-head comparisons between naltrexone and acamprosate did not indicate a significant superiority of one or the other drug, but the corresponding study base of three RCTs is still 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. Further head-to-head comparisons of naltrexone with the antipsychotic aripiprazole, the antidepressant nefazodone and the anticonvulsant topiramate, based on one RCT in each case, showed a non-significant trend in favour of the active control groups. Future research on these substance will show, if the demonstrated effects will withstand further testing.

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 and 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

Analyses of return to heavy drinking, return to any drinking and drinking frequency (drinking days) refer to databases with 28, 27 and 26 RCTs, indicating outcome completeness rates of 56%, 54% and 52%. For secondary and post-treatment outcomes, completeness rates are considerably lower: outcome data on drinking amount and GGT are available from 16 RCTs (32%), heavy drinking days from 15 RCTS (30%) and post-treatment results from 6 RCTs (12%).

Applicability of the results

With the trials included in the review, treatment durations, types of psychosocial interventions and intensity of co-treatments are represented with a high variability. Additionally, inclusion criteria were defined in a non-restrictive way, meaning that samples reflect a mix of different patient characteristics. In contrast, some features of the study design, including the dosing of naltrexone as well as the settings of treatment, did not considerably vary between studies: With few exceptions, patients were detoxified before treatment, dosing of oral naltrexone was 50 mg per day and treatment was realized in outpatient programs. Thus, the generalizability of the demonstrated results might be restricted, if the frame conditions in clinical practice differ from those applied in research. Further limitations in the representativity of the sample might arise from the proceeding to screen out patients with concurrent psychiatric diagnoses from trials.

Quality of the evidence

Various features of the study design, which have been implemented in the naltrexone and nalmefene trials included in the review, ensure a high methodological quality of the primary database: To prevent selection bias, patients were randomly assigned to treatment groups, to mask treatment allocation, active medication and placebo with identical appearance were used 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.

If treatment groups differed in baseline characteristics, differences were controlled in the statistical analyses of treatment effects. Group differences in the attendance to treatment as assessed with drop-out and compliance rates, were rarely demonstrated and are likely to be rather generated by chance than by systematic factors associated with performance bias. Sensitivity analysis did not suggest a difference between the results of industry sponsored trials and investigator-driven research and the testing of publication bias with the Egger's linear regression (Egger 1997) did not indicate that non-significant trials have been omitted from publication. The side effects caused by naltrexone can potentially reveal a patient's affiliation to the verum or placebo group - a methodological limitation that was discussed to have caused an overestimation of effects for antidepressants (Moncrieff 2004); nevertheless, as none of the trials which tested blinding integrity found evidence that treatment allocation was unmasked, the associated risk of bias appears to be rather low.

Nevertheless, some uncertainties persist. As specific 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. For example, most analyses were conducted in accordance with the ITT principle, considered as the "gold standard" in data-analyses of RCTs (Newell 1992), but it has not consistently been reported, how lost to follow-ups were handled in the data analyses. Additionally, poor reporting concerned the methods used for generating random sequences, the exact 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).

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 and research before.

Agreements and disagreements with other studies or reviews

Basically, the present Cochrane review confirms most effectiveness and safety conclusions drawn from previous reviews and meta-analyses (Schoechlin 2000; Kranzler 2001; Hopkins 2002; Berglund 2003; Streeton 2001; Srisurapanont 2000; Slattery 2003; Bouza 2004; Srisurapanont 2005a; Srisurapanont 2005b; Roozen 2006; Rosner 2008). With RR = 0.64 (95% CI 0.51 to 0.82) for return to heavy drinking, based on 7 RCTs with 822 patients, and RR = 0.91 (95% CI 0.81 to 1.02) for return to any drinking, based on 10 RCTs with 1014 patients, the results of the latest available update of the Cochrane review (Srisurapanont 2005a; Srisurapanont 2005b) have already indicated the significance of effects for the prevention of heavy drinking, but not for any drinking. Likewise, a meta-analysis of the Spanish Agency for Health Technology Assessment (Bouza 2004) reported significant effects on heavy drinking rates (NNTB = 9; 95% CI 6.o to 14.0), while abstinence rates have not significantly been modified by naltrexone. With RR = 0.96 (95% CI 0.92 to 1.01) for "return to any drinking", RR = 0.83 (95% CI 0.76 to 0.90) for "return to heavy drinking" and an associated NNTB of 9.09 (95% CI 6.67 to 14.28), the magnitude of treatment effects estimated by the present Cochrane review is marginally below the results of previous reviews - a fact that can be ascribed to the inclusion of newer studies with negative results.

Authors' conclusions

Implications for practice

Based on comprehensive evidence from 50 RCTs with 7793 patients, the review demonstrates the effectiveness and safety of naltrexone for the treatment of alcohol dependence. The opioid antagonist was shown to reduce the risk to return to heavy drinking to 83% of the placebo risk, to decrease drinking days by about 4% and heavy drinking days by about 3%, meaning that the drug on average avoids one additional day with heavy drinking per month. On days, on which alcohol is consumed, patients treated with naltrexone manage to refrain from about one drink they would have had under placebo. Referred to a population of alcohol dependent patients, naltrexone can be expected to prevent heavy drinking in one out of nine patients, who would otherwise have returned to a heavy drinking pattern. In contrast, statistical significance was missed for return to any drinking; the dependency of the effectiveness conclusions on the assumptions of the underlying statistical model, as indicated by the sensitivity analysis, underscores preliminary nature of this finding.

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 impede the demonstration of therapeutic effects in clinical trials. For patients, who take naltrexone regularly, therapeutic benefits are likely to exceed those demonstrated in clinical trials. Secondly, it should be kept in mind that naltrexone was added to psychosocial and psychotherapeutic interventions in most trials. Thus, strictly speaking, effect sizes rather reflect the additional benefit of adding naltrexone to psychosocial treatments than its benefit compared to placebo - a fact which often remained unconsidered in the interpretation of results. Nevertheless, despite these obstacles and restrictions, demonstrated treatment effects for naltrexone are comparable in their magnitude with those obtained in other areas of psychiatric research (Adams 2007; Arroll 2009; Citrome 2008).

All in all, opioid antagonists are not magic bullets 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 available evidence, naltrexone 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 randomised 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.

The reporting of clinical trials with opioid antagonists 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 methodological 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 naltrexone and acamprosate are needed to determine the relative effectiveness of both substances. 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. In addition, direct comparisons between oral versus injectable naltrexone would help to further specify the advantages and disadvantages of different forms of application. The identification of patient characteristics which determine a patient's responsiveness to the available 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.

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* 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.

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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

MANIT SRISURAPANONT:

- protocol elaboration
- interpretation and discussion of results

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 SanofiAventis, BMS, EliLilly, Janssen/Johnson and Johnson, Lundbeck and Pfizer

Vecchi, S.: No conflict of interest known

Srisurapanont, M.: No conflict of interest known

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 and Simona Vecchi Lehert have not been considered as authors in the protocol as their contribution turned out in the course of the review process.

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. 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.

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 option to conduct a sensitivity analysis to examine the influence of the funding source on the study outcomes was not concerned in the protocol and subsequently added to the review.

Published notes

Characteristics of studies

Characteristics of included studies

Ahmadi 2002

Methods	**Title: A double-blind, placebo-controlled study of naltrexone in the treatment of alcohol dependence** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks; **principle of analysis:** not reported; **setting:** outpatient; **study sites:** 1; **country:** Iran
Participants	**Diagnosis:** alcohol dependence (DSM-IV); **required abstinence:** 3 to 30 days; **baseline characteristics:** 100% male; mean age: 43.0 (SD = 9.2); 87% married; 83.6% employed; **pre-baseline drinking:** no indicators reported; **exclusionary psychiatric conditions:** 1. a concurrent drug abuse or dependence (other than alcohol or nicotine); 2. a concurrent use of opioids, disulfiram or neuroleptic drugs
Interventions	1. 50 mg naltrexone (n = 58) 2. placebo (n = 58) **Psychosocial treatment:** cognitive-behavioral techniques: a) analyses of drinking behavior cues; b) coping skills to avoid or manage high-risk situations; c) individual counselling sessions
Outcomes	1. Time to first relapse* (survival analysis) 2. side effects * relapse: drinking ≥ 5 SDU per drinking occasion or drinking on ≥ 5 days a week
Financial support	No information provided
Data assessment methods	**Assessment of drinking:** TLFB interview (Sobell 1988; Sobell 1992; weekly); **assessment of side-effects:** systematic enquiry; no further information provided; **assessment of compliance:** pill count
Treatment adherence	**Drop-out rates:** naltrexone: 21% (n = 12); placebo: 57% (n = 33); **lost to follow-up rates:** *not reported;* **compliance rates:** not reported; group differences in compliance rates: *not reported*
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Patients were stratified to dose and duration of drinking alcohol; no further details provided
Allocation concealment?	Unclear	No information provided
Blinding? all outcomes	Unclear	**Persons blinded:** double-blind, including patients and research staff; **placebo appearance:** not reported
Blinding? patient-reported outcomes	Unclear	GGT, urine analysis and urine toxicology screens were assessed; unclear if used to validate patient-reported drinking outcomes
Blinding? objective outcomes	Unclear	No objective outcomes reported in the trial publication
Incomplete outcome data addressed? Binary outcomes	Unclear	**Principle of analysis:** not reported; **handling of missing data:** not reported
Incomplete outcome data addressed? Continuous outcomes	Unclear	No continuous outcomes considered in the study
Free of selective reporting?	No	**Outcome reporting:** abstinence is listed as a primary study outcome in the method section, but it is not reported in the results section
Free of other bias?	Unclear	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: *not reported*; drinking history or treatment history: *not reported*
Susceptibility to bias reduced?	Unclear	**Validation of patient-reported outcomes:** GGT, urine analysis and urine toxicology screens were assessed; unclear if used to validate patient-reported outcomes; **laboratory assessment of drop-outs:** not reported

Anton 1999

Methods	**Title: Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks (treatment); 14 weeks (post-treatment); **principle of analysis:** ITT (modified); **setting:** outpatient; **study sites:** 1; **country:** USA
Participants	**Diagnosis:** alcohol dependence (DSM-III-R); **required abstinence**: ≥ 5 days; **baseline characteristics:** 69% male; mean age: 42.5 (SD = 9.2); 68% married; 82% employed full time; **pre-baseline drinking:** 82% (SD = 21) drinking days; 11.8 (SD = 4.9) drinks per drinking day; ADS score (Skinner 1982; Skinner 1984): 17 (SD = 16.5); **exclusionary psychiatric conditions:** 1. a concurrent drug abuse or dependence (other than nicotine or alcohol); 2. a lifetime diagnosis of opioid dependence; 3. a concurrent major psychiatric disorder; 4. a concurrent use of psychotropic or anti seizure medications or disulfiram
Interventions	1. 50 mg naltrexone (n = 68) 2. placebo (n = 63) **Psychosocial treatment:** CBT (cognitive behavioral therapy); **applied manual:** Kadden 1992 as applied in Project MATCH (Project Match Research Group 1997)
Outcomes	1. Time to first relapse* (survival curve) 2. return to any drinking 3. days abstinent 4. drinks per drinking day 5. craving 6. gamma-glutamyltransferase (GGT) 7. carbohydrate-deficient transferrin (CDT) 8. side effects * relapse / heavy drinking: drinking ≥5 (4) SDU for men (women)
Financial support	National Institute on Alcohol Abuse and Alcoholism (NIAAA)
Data assessment methods	**Assessment of drinking:** TLFB interview (Sobell 1988; Sobell 1992; weekly; post-treatment: week 4, 14); **assessment of side-effects:** week 1, 2, 3, 4, 8, 12; **assessment of compliance:** urinary riboflavin detection
Treatment adherence	**Treatment phase / drop-out rates:** naltrexone: 13% (n = 9); placebo: 22% (n = 14); **lost to follow-up rates:** naltrexone: 1.5% (n = 1); placebo: 1.5% (n = 1); **post-treatment phase / lost to follow-up rates:** naltrexone: 3% (n = 2); placebo: 8% (n = 5); **compliance rates** (patients with > 75% compliance): naltrexone: 69%; placebo: 67%
Notes	Posttreatment results published in Anton 2001

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	No information provided
Blinding? all outcomes	Unclear	**Persons blinded:** no detailed information provided; **placebo appearance:** identical to active medication
Blinding? patient-reported outcomes	Unclear	GGT, CDT were assessed; unclear if used to validate patient-reported outcomes; collateral reports (post-treatment phase)
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Unclear	**Principle of analysis:** ITT modified version; patients who did receive one treatment dose (n = 1) were excluded from the primary analysis; **handling of missing data:** not reported; it was supposed for the meta-analysis that lost to follow-ups have been categorized as relapsers in the survival analyses
Incomplete outcome data addressed? Continuous outcomes	Unclear	**Principle of analysis:** ITT modified version; patients who did receive one treatment dose (n = 1) were excluded from the primary analysis; **handling of missing data:** not reported
Free of selective reporting?	Yes	**Outcome reporting:** primary outcomes were explicitly stated in the methods section and adequately reported in the results section
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: *not reported*
Susceptibility to bias reduced?	Unclear	**Validation of patient-reported outcomes:** GGT, CDT were assessed; unclear if used to validate patient-reported outcomes; collateral reports (post-treatment phase); **laboratory assessment of drop-outs:** not reported (treatment phase); yes (post-treatment phase)

Anton 2004

Methods	**Title: A multi-site dose ranging study of nalmefene in the treatment of alcohol dependence** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks; **principle of analysis:** ITT; **setting:** outpatient; **study sites:** 13; **country:** USA
Participants	**Diagnosis:** alcohol dependence (DSM-IV); **required abstinence**: 3 to 14 days; **baseline characteristics**: 70% male; mean age: 45.0 (SD = 10.5) years; 48% married; **pre-baseline drinking:** 80% days drinking; 8.5 (SD = 5.1) drinks per drinking day; ADS score (Skinner 1982; Skinner 1984): 16 (SD = 7); **exclusionary 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 medication (except stable antidepressant treatment), disulfiram or opioids or a recent treatment with naltrexone or investigational drugs
Interventions	1. 5 mg nalmefene (n = 68) 2. 20 mg nalmefene (n = 66) 3. 40 mg nalmefene (n = 68) 4. placebo (n = 68) **Psychosocial treatment:** motivational enhancement (ME); **applied manual:** Motivating for Alcohol Reduction and Medication Management (MARMM), which is a modified version of motivational enhancement therapy (MET) as applied as applied in Project MATCH (Project Match Research Group 1997); **aim:** flexible
Outcomes	1. Time to first relapse* (survival curve) 2. heavy drinking days 3. craving 4. gamma-glutamyltransferase (GGT) 5. carbohydrate-deficient transferrin (CDT) 6. side effects *relapse / heavy drinking: drinking ≥ 5 (4) SDU for men (women)
Financial support	BioTie Therapies Corporation (Espoo, Finland)
Data assessment methods	**Assessment of drinking:** TLFB interview (Sobell 1988; Sobell 1992; week 1, 3, 6, 9, 12); **assessment of side-effects:** adverse event recording (week 1, 3, 6, 9, 12); **assessment of compliance:** pill count
Treatment adherence	**Drop-out rates:** nalmefene: 24.5% (n = 50); placebo: 28% (n = 19); **lost to follow-up rates:** nalmefene: 12.7% (n = 26); placebo: 16% (n = 11); **compliance rates** (% of prescribed medication taken): 90%; no group specific values provided
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	No information provided
Blinding? all outcomes	Unclear	**Persons blinded:** double-blind, no detailed information provided; **placebo appearance:** identical to active medication
Blinding? patient-reported outcomes	Unclear	GGT, CDT were assessed (week 6, 12); unclear if used to validate patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Unclear	**Principle of analysis:** ITT; **handling of missing data:** not reported; it was supposed for the meta-analysis that lost to follow-ups have been categorized as relapsers in the survival analyses
Incomplete outcome data addressed? Continuous outcomes	Unclear	**Principle of analysis:** ITT; **handling of missing data:** not reported
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported in the results section
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: *not reported*
Susceptibility to bias reduced?	Unclear	**Validation of patient-reported outcomes:** GGT, CDT were assessed (week 6, 12); unclear if used to validate patient-reported outcomes; **laboratory assessment of drop-outs:** not reported

Anton 2005

Methods	**Title: Naltrexone combined with either cognitive behavioral or motivational enhancement therapy for alcohol dependence** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks; **principle of analysis:** ITT; **setting:** outpatient; **study sites:** 1; **country:** USA
Participants	**Diagnosis:** alcohol dependence (DSM-IV); **required abstinence:** ≥ 5 days; **baseline characteristics:** 76% male; mean age: 43.7 (SD = 9.5) years; 38.7% married; 85% employed full time; **pre-baseline drinking:** 74% (SD = 16.3) days drinking; 12.0 (SD = 6.1) drinks per drinking day; ADS score (Skinner 1982; Skinner 1984): 14.7 (SD = 7); **exclusionary psychiatric conditions:** 1. a concurrent drug abuse or dependence (other than alcohol, nicotine or marijuana); 2. a lifetime diagnosis of opioid abuse or dependence; 3. a concurrent major psychiatric disorder or current suicidal or homicidal ideation; 4. a concurrent use of psychotropic or antiseizure medications or disulfiram or any use of an opiate antagonist in the month before study entry
Interventions	1. 50 mg naltrexone + CBT (n = 39) 2. 50 mg naltrexone + ME (n = 41) 3. placebo + CBT (n = 41) 4. placebo + ME (n = 39) **Psychosocial treatment:** a) group 1. + 3: cognitive behavioral therapy (CBT); **applied manual:** Kadden 1992as applied in Project Match (Project Match Research Group 1997); b) group 2 + 4: motivational enhancement therapy (ME); applied manual: MIller 1994 as applied in Project Match (Project Match Research Group 1997)
Outcomes	1. Time to first relapse* (survival curve) 2. return to heavy drinking* 3. days abstinent 4. drinks per drinking day 5. time to first /second /third /fourth event 6. craving 7. gamma-glutamyltransferase (GGT) 8. carbohydrate-deficient transferrin (CDT) 9. side effects * relapse / heavy drinking: drinking ≥ 5 (4) SDU for men (women)
Financial support	National Institute on Alcohol Abuse and Alcoholism (NIAAA)
Data assessment methods	**Assessment of drinking:** TLFB interview (Sobell 1988; Sobell 1992; week 2, 6, 12); **assessment of side-effects:** (week 2, 6, and 12); **assessment of compliance:** Microelective Events Monitoring System (MEMS); urinary riboflavin detection (weeks 2, 6, and 12)
Treatment adherence	**Drop-out rates:** naltrexone: 20% (n = 16); placebo: 17% (n = 14); group difference in drop-out rates: not significant; group difference in reasons for drop-out: not significant; **lost to follow-up rates:** not reported; **compliance rates** (% of electronic pill bottle cap openings): naltrexone: 85%; placebo: 80%
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	No information provided
Blinding? all outcomes	Unclear	**Persons blinded:** no detailed information provided; **placebo appearance:** identical to active medication
Blinding? patient-reported outcomes	Unclear	GGT, CDT were assessed; unclear if used to validate patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Unclear	**Principle of analysis:** ITT; **handling of missing data:** not reported; it was supposed for the meta-analysis that lost to follow-ups have been categorized as relapses for in the survival analyses
Incomplete outcome data addressed? Continuous outcomes	Unclear	**Principle of analysis:** ITT; **handling of missing data:** not reported
Free of selective reporting?	Yes	**Outcome reporting:** primary outcomes were explicitly stated in the methods section and adequately reported in the results section
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: *not reported*
Susceptibility to bias reduced?	Unclear	**Validation of patient-reported outcomes:** GGT, CDT were assessed; unclear if used to validate patient-reported outcomes; **laboratory assessment of drop-outs:** not reported

Anton 2006

Methods	**Title: Combined pharmacotherapies and behavioral interventions for alcohol dependence (COMBINE study)** **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 (other than alcohol, nicotine, cannabis or habitual caffeine use); 2. opiate dependence or abuse (past 6 months) or chronic treatment with opiate-containing medications (past month); 3. a concurrent major psychiatric disorder irequiring medication; 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 behavioural intervention (CBI); **applied manual:** integrates aspects of cognitive behavioural 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)
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); **assessment of side-effects:** SAFTEE (Levine 1986, Rabkin 1992); **assessment of compliance:** pill count
Treatment adherence	**Treatment phase / drop-out rates:** naltrexone: 35% (n = 108); naltrexone + acamprosate: 40.7% (n = 124); acamprosate: 38.5% (n = 116); placebo: 28.5% (n = 88); **lost to follow-up rates**: naltrexone: 6.1% (n = 19); naltrexone + acamprosate: 6.2% (n = 19); acamprosate: 4.6% (n = 14); placebo: 5.8% (n = 18); **Posttreatment phase / drop-out rates:** naltrexone: 46.0% (n = 142); naltrexone + acamprosate: 53.1% (n = 162); acamprosate: 49.2 (n = 149); placebo: 38.2% (n = 118); **compliance rates** (% of prescribed medication taken): naltrexone: 85.4%; acamprosate: 84.2%
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? all outcomes	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)
Blinding? patient-reported outcomes	Yes	Knowledge of the allocated interventions was adequately prevented during the study (see "Blinding (all outcomes)") CDT (week 8, 16) was used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
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 (drinking days):** patients lost to follow-up were assumed to have relapsed to heavy drinking on the day after their last contact
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	**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
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** CDT (week 8, 16) used as a validity check for self-reported drinking; **laboratory assessment of drop-outs:** not reported

Auriacombe 2000

Methods	**Title: Naltrexone is ineffective to prevent relapse to alcohol in a realistic outpatient setting: a double-blind, one year controlled study** **Allocation:** random, unclear; **blinding:** double-blind; **principle of analysis:** not reported; **study duration:** 54 weeks; **setting:** outpatient; **study sites:** not reported; **country:** France
Participants	**Diagnosis:** alcohol dependence; **required abstinence:** no information available; **baseline characteristics:** no information available; **exclusionary of psychiatric conditions:**
Interventions	No information available
Outcomes	No information available
Financial support	No information available.
Data assessment methods	**Assessment of drinking:** no information available; **assessment of side-effects:** no information available; **assessment of compliance:** no information available.
Treatment adherence	**Drop-out rates:** no information available
Notes	Because of missing outcome data, the study was not included in the statistical analysis

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no information available
Allocation concealment?	Unclear	No information available
Blinding? all outcomes	Unclear	No information available
Blinding? patient-reported outcomes	Unclear	No information available
Blinding? objective outcomes	Unclear	No information available
Incomplete outcome data addressed? Binary outcomes	Unclear	No information available
Incomplete outcome data addressed? Continuous outcomes	Unclear	No information available
Free of selective reporting?	Unclear	No information available
Free of other bias?	Unclear	No information available
Susceptibility to bias reduced?	Unclear	No information available

Balldin 2003

Methods	**Title: 6-month controlled naltrexone study: combined effect with cognitive behavioral therapy in outpatient treatment of alcohol dependence** **Allocation:** random; **blinding:** double-blind; **study duration:** 24 weeks; **principle of analysis:** ITT; **setting:** outpatient; **study sites:** 10; **country:** Sweden
Participants	**Diagnosis:** alcohol dependence (DSM-IV); **required abstinence:** 14 to 28 days; **baseline characteristics:** 85% male; mean age: 49.7 (SD = 7.8) years; 56% married: 72% employed; **pre-baseline drinking:** 63.5% days drinking; 151 (SD = 79.1) grams alcohol per drinking day; ASI score (McLellan 1980): 0.55 (SD = 0.2); **exclusionary psychiatric conditions:** 1. a concurrent drug abuse or dependence (other than alcohol or nicotine); 2. a concurrent major psychiatric disorder including suicide liability, intense aggressive impulses, or brain damage; 3. a concurrent use of psychotropic medications as well as disulfiram, calcium carbamide, naltrexone, acamprosate, benzodiazepines, lithium or buspirone
Interventions	1. 50 mg naltrexone + CBT (n = 25) 2. 50 mg naltrexone + ME (n = 31) 3. placebo + CBT (n = 30) 4. placebo + ME (n = 32) **Trial started with a placebo run-in week** **Psychosocial treatment:** a) group 1 + 3: cognitive behavioral therapy; **applied manual:** Kadden 1992 as applied in Project Match (Project Match Research Group 1997); **aim:** flexible; b) group 2 + 4: motivational enhancement (ME) for sobriety without teaching specific coping skills; **aim:** abstinence
Outcomes	1. Time to first relapse* (survival curve) 2. heavy drinking* days 3. drinking days 4. amount per drinking day 5. gamma-glutamyltransferase (GGT) 6. carbohydrate-deficient transferrin (CDT) 7. aspartate aminotransferase (AST) 8. alanine aminotransferase (ALT) 9. craving 10. side effects *relapse / heavy drinking: drinking ≥5 (4) STD for men (women)
Financial support	DuPont Pharma (UK); Meda AB (Sweden)
Data assessment methods	**Assessment of drinking:** TLFB interview (Sobell 1988; Sobell 1992; week 2, 4, 6, 8, 10, 12, 16, 20, 24); **assessment of side-effects:** adverse clinical event forms; **assessment of compliance:** pill count
Treatment adherence	**Drop-out rates** (provided by the investigators): naltrexone: 19.6% (n = 11); placebo: 24.2% (n = 15); **lost to follow-up rates**: 9% of possible quantitative drinking data were not obtained; **compliance rates** (patients who took at least 80% of the prescribed medication): naltrexone: 80%; placebo: 85%
Notes	Abstinence rates and drop-out rates were subsequently provided by the investigator for the review

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	A randomisation list was used to assign the patient numbers to either of the two study medications
Allocation concealment?	Yes	The randomisation list was prepared by the manufacturer's clinical operations staff, who delivered the trial medications labelled with consecutive numbers. The statistician who performed the randomisation knew the block size but was blinded to the randomisation code for drug treatments. Every patient received the assigned number and type of psychological therapy in a sealed black envelope, which was opened by the patient at the study site together with one of the local research staff on the randomisation day
Blinding? all outcomes	Yes	**Persons blinded:** double-blind, including patients and research stuff; **placebo appearance:** identical to active medication
Blinding? patient-reported outcomes	Yes	Knowledge of the allocated interventions was adequately prevented during the study (see "Blinding (all outcomes)") ALT, AST, GGT (week 12, 24) and urine samples for serum levels of CDT (each study visit) were assessed; unclear if used to validate patient-reported drinking outcomes, but
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Yes	**Principle of analysis:** ITT; **handling of missing data:** individuals lost to follow-up were assumed to have failed
Incomplete outcome data addressed? Continuous outcomes	Yes	**Principle of analysis:** ITT; **handling of missing data:** imputations were made with the mean of nearby values in these subgroups
Free of selective reporting?	Yes	**Outcome reporting:** the publication provides all outcomes specified in the methods section
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes
Susceptibility to bias reduced?	Unclear	**Validation of patient-reported outcomes:** ALT, AST, GGT (week 12, 24) and urine samples for serum levels of CDT (each study visit) were assessed; unclear if used to validate patient-reported outcomes; **laboratory assessment of drop-outs:** drop-outs underwent a repeated physical examination and a laboratory evaluation

Baltieri 2008

Methods	**Title: Comparing topiramate with naltrexone in the treatment of alcohol dependence** **Allocation:** random; **blinding:** adequate; **study duration:** 12 weeks; **principle of analysis:** ITT; **setting:** outpatient; **study sites:** 1; **country:** Brazil
Participants	**Diagnosis:** alcohol dependence (ICD-10); **required abstinence:** 7 days (all patients received a 1-week detoxification prior to the initiation of double-blind treatment); **baseline characteristics:** 100% male; mean age: 44.3 (SD = 8.4) years; 51.6% married; **pre-baseline drinking:** 25 drinks with 12 grams (SD = 14.5) per drinking day (≈301 grams per day; SD = 174); SADQ score (Raistrick 1986): 28.8 (SD = 8.5); **exclusionary psychiatric conditions:** 1. a concurrent drug abuse or dependence (other than alcohol or nicotine); 2. a concurrent major psychiatric disorder that requires drug treatment; 3. previous treatment with naltrexone or topiramate (past 6 months)
Interventions	1. 50 mg of naltrexone (n = 49) 2. 300 mg topiramate (n = 52) 3. placebo (n = 54) **Psychosocial treatment:** cognitive behavioral therapy (CBT) with management of high-risk situations and negative mood, drink refusal skills + motivational enhancement (ME) for sobriety and medication compliance + attendance to AA groups
Outcomes	1. Time to first relapse (survival curve) 2. return to any drinking 3. cumulative abstinence duration (CAD) 4. heavy drinking* weeks (≥ 90 grams alcohol per week) 5. craving 6. gamma-glutamyltransferase (GGT) 7. side effects *relapse / heavy drinking: drinking ≥ 90 grams alcohol per week
Financial support	State of São Paulo Research Foundation (FAPESP)
Data assessment methods	**Assessment of drinking:** daily monitoring card; interview (week 1, 2, 3, 4, 6, 8, 10, 12); **assessment of side-effects:** Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale (Lingjaerde 1987); **assessment of compliance:** daily monitoring card, pill count, collateral reports (week 1, 2, 3, 4, 6, 8, 10, 12)
Treatment adherence	**Dropout rates:** naltrexone: 40.8% (n = 20); placebo: 57.4% (n = 31); topiramate: 36.5% (n = 19); **lost to follow-up rates:** naltrexone: 34.7% (n = 17); placebo: 44.4 % (n = 24); topiramate: 19.2% (n = 10); **compliance rates:** not reported
Notes	Information on the study design was subsequently provided by the investigator

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	The random sequence was generated by a computer random generator (information provided by the investigator)
Allocation concealment?	Unclear	Two pharmacists from the pharmacy sector at the psychiatric institute knew which medication corresponded to the specific code. The packages containing the capsules were distributed to patients by two blinded research assistants. Medications codes were revealed to researchers only after all patients had completed the study (information provided by the investigator)
Blinding? all outcomes	Yes	**Persons blinded:** double-blind, including patients, health care providers and outcome assessors; **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 validity of the double-blind procedure was examined and confirmed at the end of treatment (estimations of group allocation from patients and staff members)
Blinding? patient-reported outcomes	Yes	Knowledge of the allocated interventions was adequately prevented during the study (see "Blinding (all outcomes)") Collateral reports (week 1, 2, 3, 4, 6, 8, 10, 12) were used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Yes	**Principle of analysis**: ITT; **handling of missing data:** drop-outs were classified as treatment failures
Incomplete outcome data addressed? Continuous outcomes	Yes	**Principle of analysis**: ITT; **handling of missing data:** the entire week was considered a relapse period, if alcohol consumption at any day or sequence of days was reported
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** collateral reports (week 1, 2, 3, 4, 6, 8, 10, 12); **laboratory assessment of drop-outs:** not reported

Brown 2009

Methods	**Title: A randomized, double-blind, placebo-controlled pilot study of naltrexone in outpatients with bipolar disorder and alcohol dependence** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks; **principle of analysis**: ITT; **setting:** outpatient; **study sites:** 1; **country:** USA
Participants	**Diagnosis:** alcohol dependence (DSM-IV); **concurrent psychiatric diagnosis:** bipolar disorder (100%); **required abstinence:** no prior detoxification required; patients were actively drinking; **baseline characteristics:** 51.2% male; mean age: 41.1 (SD = 12.1) years; 72.1% with bipolar disorder type I; 27.9% with bipolar disorder type II; **pre-baseline drinking:** 72.1% (SD = 25.9) drinking days; 9.4 (SD = 6.4) drinks per drinking day; ASI score (McLellan 1980): 0.6 (SD = 0.3); **exclusionary psychiatric conditions:** 1. a concurrent drug dependence (other than alcohol or nicotine); 2. a lifetime diagnosis of opioid dependence or a concurrent use of opioids; 3. a current mood state of depression or mania or a risk of suicide; 4. a concurrent use of acamprosate or disulfiram or a prior therapy with naltrexone **Note:** Concurrent drug abuse was not a criteria of exclusion (e.g. cocaine 11.6%; cannabis abuse 11.6%)
Interventions	1. 50 mg naltrexone (n = 20) 2. placebo (n = 23) **Permitted psychiatric co-medications:** lithium, anticonvulsants (valproate), antipsychotics, antidepressants and sedatives; **psychosocial treatment:** cognitive behavioral therapy (CBT) designed for patients with bipolar disorder and substance use; **applied manual:** Schmitz 2002
Outcomes	1. Return to any drinking (interval abstinence) 2. days abstinent 3. heavy drinking days 4. drinks per drinking day 5. craving 6. GGT
Financial support	National Institute of Health (NIH)
Data assessment methods	**Assessment of drinking:** TLFB interview (Sobell 1988; Sobell 1992); **assessment of side-effects:** not reported; **assessment of compliance:** pill count
Treatment adherence	**Drop-out rates**: naltrexone: 30% (n = 6); placebo: 47.8% (n = 11); **lost to follow-up rates**: not reported; **compliance rates** (% of prescribed medication taken): naltrexone: 94.4% (SD = 6.1); placebo: 95.3% (SD = 7.4)
Notes	The study was not published at the completion date of the review; the submitted manuscript was obtained from the investigator; further information (rates of continuous abstinence, drinking days, consumed amount per drinking day) were subsequently provided by the investigator for the review

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Randomization was performed with computerized randomisation procedures (randomizer.org)
Allocation concealment?	Unclear	No information provided
Blinding? all outcomes	Unclear	**Persons blinded:** no detailed information provided; **placebo appearance:** identical to active medication
Blinding? patient-reported outcomes	Unclear	GGT was assessed; unclear if used to validate patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Unclear	**Principle of analysis:** ITT; **handling of missing data:** not reported; it was supposed for the meta-analysis that lost to follow-ups have been categorized as relapsers in the survival analyses.
Incomplete outcome data addressed? Continuous outcomes	No	**Principle of analysis:** ITT; **handling of missing data:** excluded from the analyses (information provided from the investigator)
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported in the results section
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: *not reported*
Susceptibility to bias reduced?	Unclear	**Validation of patient-reported outcomes:** GGT was assessed; unclear if used to validate patient-reported outcomes; **laboratory assessment of drop-outs:** not reported

Chick 2000

Methods	**Title: A multi-centre, randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of alcohol dependence or abuse.** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks; **principle of analysis**: ITT (modified); per-protocol analysis; **setting:** outpatient; **study sites:** 6; **country:** United Kingdom
Participants	**Diagnosis**: alcohol dependence (96.6%); alcohol abuse (3.4%); DSM-III-R; **required abstinence:** 5 to 30 days; **baseline characteristics:** 65% male; mean age: 43.5 (SD=9.0) years; 53% married: 24% full time employed; **pre-baseline drinking:** 24.4 (SD = 9.7) years of drinking; 10.2 (SD = 8.4) drinks per drinking day; 10 days of abstinence at beginning of treatment; **exclusionary psychiatric conditions:** 1. a concurrent drug abuse or dependence; 2. a concurrent major psychiatric disorder requiring medication; 3. concurrent use of opioids, disulfiram, acamprosate, antidepressants, antipsychotics, lithium, or benzodiazepines
Interventions	1. 50 mg naltrexone (n = 85) 2. placebo (n = 79) * patients excluded who did not receive at least one dose of study medication **Psychosocial treatment:** centre specific treatments; patients were free to attend alternative facilities including Alcoholics Anonymous (AA) or other support groups; **aim:** flexible
Outcomes	1. Time to first relapse* (survival curve) 2. return to any drinking 3. return to heavy drinking 4. days abstinent 5. drinks during last four study weeks 6. craving 7. GGT 8. CDT 9. side effects *relapse / heavy drinking: drinking ≥5 (4) SDU for men (women)
Financial support	DuPont pharmaceuticals
Data assessment methods	**Assessment of drinking:** TLFB interview (Sobell 1988; Sobell 1992; week 2, 4, 6, 8, 10, 12); **assessment of side-effects:** week 2, 4, 6, 8, 10, 12; **assessment of compliance:** pill count, 6-beta-naltrexol
Treatment adherence	**Drop-out rates**: naltrexone: 58.9% (n = 53); placebo: 57.6% (n = 49); **lost to follow-up rates**: naltrexone: 18.9% (n = 17); placebo: 18.8% (n = 16); **compliance rates** (study completers with 80% of prescribed medication taken): naltrexone: 39%; placebo: 41%
Notes	Subgroup analysis: compliant completers

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomization was stratified according to diagnosis based on DSM-II-R criteria; no further details provided
Allocation concealment?	Unclear	No information provided
Blinding? all outcomes	Unclear	**Persons blinded:** no detailed information provided; **placebo appearance:** identical to active medication
Blinding? patient-reported outcomes	Yes	Urine alcohol test (week 2, 4, 6, 8, 10, 12) was used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
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 (naltrexone: n = 5; placebo: n = 6) were excluded from the primary analysis (= treatment-received analysis); **handling of missing data:** individuals lost to follow-up were assumed to have failed and were assigned to the heavy drinking category
Incomplete outcome data addressed? Continuous outcomes	No	**Principle of analysis:** per-protocol analyses; **handling of missing data:** the endpoint was defined as the last observation available
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** urine alcohol test (week 2, 4, 6, 8, 10, 12); **laboratory assessment of drop-outs:** not reported

de Goes e Castro 2004

Methods	**Title: Double-blind, randomized clinical trial of naltrexone combined with brief intervention for the treatment of alcohol dependence** **Allocation**: random; **blinding:** double-blind; **study duration:** 12 weeks; **principle of analysis**: ITT; **setting:** outpatient; **study sites:** 1; **country:** Brazil
Participants	**Diagnosis:** alcohol dependence; **required abstinence:** 5 to 30 days; **baseline characteristics:** 81.9% male; mean age: 45.9 (SD = 8.0) years; 57.7% married: 43.7% employed; **pre-baseline drinking:** not reported; SADQ score (Raistrick 1986): 21.4 (SD = 7.4); **exclusionary psychiatric conditions:** 1. a drug abuse (past 30 days); 2. a lifetime diagnosis of opioid dependence; 3. a concurrent major psychiatric disorder that required inpatient treatment; 4. a previous use of naltrexone, acamprosate or disulfiram or opioid analgesics (past 30 days)
Interventions	1. 50 mg naltrexone (n = 35) 2. Placebo (n = 36) **Psychosocial treatment:** eclectic therapy including cognitive behavioral therapy (CBT), motivational enhancement (ME) and a 12-step approach
Outcomes	1. Patients who return to heavy drinking* 2. drinking days 3. days with light drinking** 4. days with moderate drinking*** 5. heavy drinking days 6. craving 7. gamma-glutamyltransferase (GGT) 8. carbohydrate-deficient transferrin (CDT) 9. side-effects * relapse/heavy drinking: drinking ≥ 9 SDU; ** light drinking: drinking ≤ 4 SDU; moderate drinking: drinking 5 to 9 SDU; to comply with commonly used definitions of heavy drinking, moderate drinking was subsequently assigned to the "heavy drinking"-category
Financial support	Not reported
Data assessment methods	**Assessment of drinking:** alcohol use questionnaire (week 4, 8, 12); **assessment of side-effects:** checklist for side-effects; **assessment of compliance:** not reported
Treatment adherence	**Drop-out rates**: naltrexone: 51.4% (n = 18); placebo: 50% (n = 18); **lost to follow-up rates**: naltrexone: 5.7% (n = 2); placebo: 8.3% (n = 3); **compliance rates:** not reported
Notes	The study was reported in the format of an unpublished dissertation, conducted at the Department of Psychiatry, University of São Paulo Medical School; Brazil, advised by Prof. Ronaldo Laranjeira

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Seuquence was generated by a random number table
Allocation concealment?	Unclear	No information provided
Blinding? all outcomes	Unclear	**Persons blinded:** no detailed information provided; **placebo appearance**: identical to active placebo
Blinding? patient-reported outcomes	Unclear	GGT and CDT were assessed; unclear if used to validate patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Unclear	**Principle of analysis:** ITT; **handling of missing data:** lost to follow-ups were subsequently classified as relapsers in the meta-analysis
Incomplete outcome data addressed? Continuous outcomes	Unclear	**Principle of analysis:** available case analysis; **handling of missing data:** 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	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes
Susceptibility to bias reduced?	Unclear	**Validation of patient-reported outcomes:** not reported; **laboratory assessment of drop-outs:** not reported

Galarza 1997

Methods	**Title: The use of naltrexone to treat ambulatory patients with alcohol dependence** **Allocation:** random; **blinding:** double-blind; **study duration:** 4 weeks; **principle of analysis:** no information provided; **setting:** outpatient; **study sites**:1; **country:** Puerto Rico
Participants	**Diagnosis:** alcohol dependence (DSM-IV); **baseline characteristics:** 100% male; mean age: 55 (SD = 13) years; **pre-baseline drinking:** not reported; **exclusionary psychiatric conditions:** 1. a lifetime diagnosis of drug dependence (other than caffeine or nicotine); 2. a concurrent major psychiatric disorder
Interventions	1. Naltrexone* (n = 10) 2. placebo (n = 10) *treatment dose was not reported **Psychosocial treatment:** standard treatment; no further information provided
Outcomes	1. Depression 2. anxiety 3. somatization 4. craving 5. cognitive impairment No drinking outcomes provided
Financial support	No information provided
Data assessment methods	**Assessment of drinking:** TLFB interview (Sobell 1988; Sobell 1992; week 0, 12, 24, 48); **assessment of side-effects:** not reported; **assessment of compliance:** not reported
Treatment adherence	**Drop-out rates**: naltrexone: 50% (n = 5); placebo: 40% (n = 4); **lost to follow-up rates**: naltrexone: 30% (n = 3); placebo: 30% (n = 3); **compliance rates:** not reported
Notes	The trial did not provide any of the primary or secondary outcomes of the review; accordingly none of the outcomes from trial were included in the statistical analysis

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	The pharmacy department administered the medication or placebo to the patients according to the numbers assigned; all medication or placebo were pre-packed and pre-numbers by DuPont-Pharma
Blinding? all outcomes	Unclear	**Persons blinded:** double-blind, including patients and research staff; **placebo appearance:** no detailed information provided
Blinding? patient-reported outcomes	Unclear	No objective outcomes used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Unclear	No objective outcomes reported in the trial publication
Incomplete outcome data addressed? Binary outcomes	Unclear	No binary outcomes provided
Incomplete outcome data addressed? Continuous outcomes	Unclear	**Principle of analysis:** no information provided; **handling of missing data:** no information provided
Free of selective reporting?	Yes	**Outcome reporting:** primary outcomes were stated in the methods section and adequately reported in the results section
Free of other bias?	Unclear	**Baseline equivalence:** socio-demographic variables: *not reported;* drinking frequency and intensity: *not reported;* drinking history or treatment history: *not reported*
Susceptibility to bias reduced?	Unclear	**Validation of patient-reported outcomes:** not reported; **laboratory assessment of drop-outs:** not reported

Garbutt 2005

Methods	**Title: Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence** **Allocation:** random; **blinding:** double-blind; **study duration:** 24 weeks; **principle of analysis:** ITT (treatment- received analysis); **setting:** outpatient; **study sites:** 24; **country:** USA
Participants	**Diagnosis:** alcohol dependence (DSM-IV); **required abstinence:** no prior detoxification required; 91,2% of patients were actively drinking before at the beginning of the study; **baseline characteristics:** 68% male; mean age: 45 (SD = 10.7) years; 71% employed (≥20 hrs/wk); **pre-baseline drinking:** 65% (SD = 25.5) heavy drinking days; 43% of patients start with the treatment goal of abstinence; **exclusionary psychiatric conditions:** 1. a concurrent dependence on benzodiazepines, opiates, or cocaine (past year); 2. a lifetime diagnosis of opioid dependence; 3. a major depression; 4. a concurrent use of opiates, oral naltrexone, or disulfiram (past 2 weeks)
Interventions	1. 380 mg injectable naltrexone (n = 205) 2. 190 mg injectable naltrexone (n = 210) 3. injectable placebo (n = 209) Injections were administered at 4-week intervals. **Psychosocial treatment:** motivational enhancement (ME)+ bio-psychosocial feedback; **applied manual**: BRENDA intervention (Volpicelli 2001); **aim:** flexible
Outcomes	1. Heavy drinking* event rate 2. risky drinking** event rate 3. return to heavy drinking 4. median heavy drinking days 5. gamma-glutamyltransferase (GGT) 6. aspartate aminotransferase (AST) 7. alanine aminotransferase (ALT) 8. side effects *relapse / heavy drinking: drinking ≥5 (4) SDU for men (women); ** risky drinking: drinking ≥2 (1) SDU for men (women).
Financial support	Alkermes
Data assessment methods	**Assessment of drinking:** Computerized version of the TLFB interview (Sobell 1988; Sobell 1992); **assessment of side-effects:** coded according to Medical Dictionary for Regulatory Activities; **assessment of compliance:** assessed by the number of received injections
Treatment adherence	**Drop-out rates:** naltrexone: 39.8% (n = 165); placebo: 38.6% (n = 81); **lost to follow-up rates**: naltrexone: 13.3% (n = 55); placebo: 13.4% (n = 28); **compliance rates:** 64% of patients received all injections
Notes	Subgroup analysis: gender

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	The study used a dynamic randomisation procedure based on the coin principle
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Yes	**Persons blinded:** double-blind, including patients, all study personnel, besides staff who administered the injections (not involved in any of the safety or efficacy assessments or psychosocial treatments); **placebo appearance:** placebo appeared identical to active medication (injections were prepared in amber-coloured syringes to mask a slight colour difference between the active and placebo microspheres)
Blinding? patient-reported outcomes	Yes	Knowledge of the allocated interventions was adequately prevented during the study (see "Blinding (all outcomes)") Breathalyzer test (weekly) and collateral reports (monthly) were used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
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 = 3) were excluded from the primary analysis (= treatment-received analysis); **handling of missing data**: not reported; it was supposed for the meta-analysis that lost to follow-ups have been categorized as relapses
Incomplete outcome data addressed? Continuous outcomes	No	**Principle of analysis:** ITT modified version; patients who did not receive at least one dose of the study medication (n = 3) were excluded from the primary analysis (= treatment-received analysis); **handling of missing data:** no imputations were performed for days in which drinking data were unavailable
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: *not reported*
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** breathalyzer test (weekly; collateral reports (monthly); **laboratory assessment of drop-outs:** not reported

Gastpar 2002

Methods	**Title: Lack of efficacy of naltrexone in the prevention of alcohol relapse: Results from a German multicenter study** **Allocation:** random; **blinding:** double-blinded; **study duration:** 12 weeks; **principle of analysis:** available case analyses (subsequently transformed into ITT); **setting:** outpatient; **study sites:** 7; **country:** Germany
Participants	**Diagnosis:** alcohol dependence (97.7%), alcohol abuse (2.3%); DSM-III-R; **required abstinence:** 5 to 30 days; **baseline characteristics**: 72.5% male; mean age: 42.7 (SD = 9.7); **pre-baseline drinking**: 21.2 (SD = 9.6) years of drinking; 7.1 (SD = 5.5) drinks per drinking day; mean abstinence time at beginning: 19.5 (SD = 9.4) days; **exclusionary psychiatric conditions:** 1. a concurrent drug abuse or dependence (other than alcohol or nicotine); 2. a psychiatric condition requiring medication; 3. a concurrent use benzodiazepines, lithium, disulfiram, neuroleptics, or antidepressants
Interventions	1. 50 mg naltrexone (n = 80 + 4*) 2. placebo (n = 80 + 7*) ***** subsequently added to available case sample **Psychosocial treatment:** centre specific treatments; **aim:** abstinence
Outcomes	1. Time to first heavy drinking (survival curve) 2. time to first drink 3. consumed amount 4. craving 5. severity of alcohol problems 6. gamma-glutamyltransferase (GGT) 7. aspartate aminotransferase (AST) 8. alanine aminotransferase (ALT) 9. side effects *relapse / heavy drinking: drinking ≥5 (4) SDU for men (women)
Financial support	DuPont Pharmaceuticals, USA
Data assessment methods	**Assessment of drinking**: TLFB interview (Sobell 1988; Sobell 1992); **assessment of side-effects**: adverse clinical event data (no reference provided); **assessment of compliance:** pill count, 6-beta-naltrexol (no marker for placebo used)
Treatment adherence	**Drop-out-rates:** naltrexone: 33% (n = 28); placebo: 38% (n = 33); **lost to follow-up rates**: naltrexone: 5% (n = 4); placebo: 8% (n = 7); **compliance rates** (patients who took at least 80% of the medication): naltrexone: 80%; placebo: 80%
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Unclear	**Persons blinded:** double-blind; no detailed information; **placebo appearance:** no detailed information provided
Blinding? patient-reported outcomes	Yes	Breathalyzer test (weekly) were used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	No	**Principle of analysis:** available case analysis, subsequently transformed into ITT-analyses for the meta-analysis; **handling of missing data:** individuals lost to follow-up excluded from the analyses and subsequently included as re lapsers in the meta-analysis
Incomplete outcome data addressed? Continuous outcomes	No	**Principle of analysis:** available case analysis; **handling of missing data:** endpoint was defined as the last observation available during the treatment period
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section were adequately reported
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** breathalyzer test (weekly); collateral reports; **laboratory assessment of drop-outs:** not reported

Guardia 2002

Methods	**Titel: A double-blind, placebo-controlled study of naltrexone in the treatment of alcohol-dependence disorder** **Allocation:** random; **blinding:** double-blind; **duration:** 12 weeks; **principle of analysis:** ITT; **setting:** outpatient; **study sites:** 7; **country:** Spain
Participants	**Diagnosis:** alcohol dependence (DSM-IV); **required abstinence:** 5 to 30 days; **baseline characteristics:** 74.5% male; mean age: 41.0 (SD = 8.0); 58% married; 45% employed; **pre-baseline drinking:** 18.4 (SD = 9.2) years of drinking; 16.6 (SD = 8.2) drinks per day: 2.4 (SD = 2.6) past alcohol detoxifications; **exclusionary psychiatric conditions:** 1. a concurrent drug abuse or dependence (other than alcohol or nicotine); 2. severe psychiatric disorders. 3. a concurrent use of disulfiram, cyanamide, and acamprosate
Interventions	1. 50 mg naltrexone (n = 101) 2. placebo (n = 101) **Psychosocial treatment:** supportive group therapy; individual supportive counselling
Outcomes	1. Time to first relapse (survival curve) 2. time to first drink 3. days abstinent 4. drinks per drinking day 5. craving 6. gamma-glutamyltransferase (GGT) 7. aspartate aminotransferase (AST) 8. alanine aminotransferase (ALT) 9. carbohydrate-deficient transferrin (CDT) 10. side effects *relapse / heavy drinking: drinking ≥5 (4) SDU for men (women) per drinking occasion or drinking on ≥ 5 days a week.
Financial support	Pharmazam/Zambón S.A.
Data assessment methods	**Assessment of drinking:** quantity-frequency assessment (weekly); **assessment of side-effects:** not reported; **assessment of compliance:** pill count
Treatment adherence	**Drop-out-rates:** naltrexone: 39.6% (n = 40); placebo: 41.6% (n = 42); **lost to follow-up rates**: not reported; **compliance rates** (% of prescribed medication taken): naltrexone: 78%; placebo: 79%
Notes	Rates of continuous abstinence rates were subsequently provided by the investigators for the review

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	No information provided
Blinding? all outcomes	Unclear	**Persons blinded:** double-blind; no detailed information provided; **placebo appearance:** identical to active medication
Blinding? patient-reported outcomes	Yes	Urine alcohol tests, breathalyzer tests and collateral information were used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Unclear	**Principle of analysis**: ITT; **handling of missing data**: not reported; it was supposed for the meta-analysis that lost to follow-ups have been categorized as relapsers in the survival analyses
Incomplete outcome data addressed? Continuous outcomes	No	**Principle of analysis**: available case analysis; **handling of missing data:** missing data were not replaced
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section were adequately reported
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** urine alcohol tests, breathalyzer test, collateral information; l**aboratory assessment of drop-outs:** not reported

Heinälä 2001

Methods	**Title: Targeted use of naltrexone without prior detoxification in the treatment of alcohol dependence: A factorial double-blind, placebo-controlled trial** **Allocation:** random; **blinding**: double-blind; **study duration:** 12 weeks; **principle of analysis:** ITT; **setting**: outpatient; **study sites:** 1; **country:** Finland
Participants	**Diagnosis:** alcohol dependence; **required abstinence:** no prior detoxification; patients were actively drinking; **baseline characteristics:** 71.7% male; mean age: 45.5 (SD = 7.8) years; 72.7 % married: 75.2 % employed; **pre-baseline drinking:** 14 (SD = 11.6) past alcohol detoxifications; **exclusionary psychiatric conditions:** 1. a concurrent drug abuse or dependence; 2. a concurrent major psychiatric disorder
Interventions	1. 50 mg naltrexone + CBT (n = 34) 2. 50 mg naltrexone + ME (n = 29) 3. 50 mg placebo + CBT (n = 33) 4. 50 mg of placebo + ME (n = 25) **Psychosocial treatment:** a) group 1 and 3: cognitive behavioral therapy (CBT); focus of the program: controlled drinking; keeping a slip-up from developing into relapse); **aim:** harm reduction; b) group 2 + 4: motivation enhancement (ME) for complete abstinence; **aim:** abstinence. **Trial started with a placebo run-in week**
Outcomes	1. Time to first relapse (survival curve) 2. return to heavy drinking* 3. drinks per drinking day 4. craving 5. GGT 6. side effects * relapse: drinking ≥ 5 (4) SDU per drinking for men (women) or having ≥ 5 drinking occasions per week
Financial support	Finnish Alcohol Research Foundation; National Public Health Institute
Data assessment methods	**Assessment of drinking**: drinking diary (week 2, 4, 6, 8, 10, 12); **assessment of side-effects**: not reported; **assessment of compliance:** riboflavin
Treatment adherence	**Drop-out rates:** 16.5% (n = 20); no group specific values reported; **lost to follow-up rates:** not reported; group difference in lost to follow-up rates: not reported; **compliance rates** (% of riboflavin positive samples): not reported
Notes	The targeted medication period, which followed the regular medication interval, did not meet the inclusion criteria of the review and thus was not included in the data analysis

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Unclear	**Persons blinded:** no detailed information provided; **placebo appearance:** identical to active medication
Blinding? patient-reported outcomes	Unclear	GGT was assessed; unclear if used to validate patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Unclear	**Principle of analysis:** ITT; **handling of missing data:** not explicitly reported; it was assumed for the meta-analysis that lost to follow-ups have been classified as re lapsers
Incomplete outcome data addressed? Continuous outcomes	Unclear	**Principle of analysis:** ITT; **handling of missing data:** not reported
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: *not reported*
Susceptibility to bias reduced?	Unclear	**Validation of patient-reported outcomes:** GGT was assessed; unclear if used to validate patient-reported outcomes; **laboratory assessment of drop-outs:** not reported

Hersh 1998

Methods	**Title: Naltrexone treatment of comorbid alcohol and cocaine use disorders** **Allocation:** random; **blinding:** double-blind; **study duration:** 7 weeks; **principle of analysis:** ITT; **setting:** outpatient; **study sites:** 1; **country:** USA
Participants	**Diagnosis:** alcohol dependence (92.1%); alcohol abuse (7.9%); **concurrent psychiatric diagnosis:** cocaine dependence (95.3%); cocaine abuse (4.7%); **required abstinence**: no prior detoxification required; patients were actively consuming alcohol and cocaine; **baseline characteristics:** 92% male; mean age: 35.5 (SD = 6.0) years; 82 % employed; **pre-baseline drinking:** 50.9% (SD = 28.6) days drinking; 9.2 (SD = 5.1) drinks per drinking day; **exclusionary psychiatric conditions:** 1. a concurrent drug abuse or dependence on another psychoactive substance; and 2. a concurrent major psychiatric disorder were excluded
Interventions	1. 50 mg naltrexone (n = 31) 2. placebo (n = 33) **Psychosocial treatment:** cognitive behavioral therapy (CBT) and skills training; **applied manual:** Marlatt 1985; Chaney 1989 **Trial started with a placebo run-in week**
Outcomes	1. Time to first relapse (survival curve) 2. return to any drinking 3. return to heavy drinking* 4. days abstinent 5. drinks per drinking day 6. craving 7. gamma-glutamyltransferase (GGT) 8. side effects *relapse/heavy drinking: drinking ≥5 (4) STD for men (women)
Financial support	National Institute of Health (NIH)
Data assessment methods	**Assessment of drinking:** TLFB interview (Sobell 1988; Sobell 1992); **assessment of side-effects:** adverse event checklist; **assessment of compliance:** riboflavin
Treatment adherence	**Drop-out rates:** naltrexone: 35.5% (n = 11); placebo: 42.4% (n = 14); **lost to follow-up rates:** not reported; **compliance rates** (number of urine samples positive for riboflavin): naltrexone: 97.9%; placebo: 94.5%
Notes	Outcomes concerning the cocaine consumption were not included in the review

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Yes	**Persons blinded:** double-blind, including patients and research evaluators; **placebo appearance:** identical to active medication
Blinding? patient-reported outcomes	Yes	Knowledge of the allocated interventions was adequately prevented during the study (see "Blinding (all outcomes)") Breathalyzer test was used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
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	Unclear	**Principle of analysis:** ITT; **handling of missing data:** not reported
Free of selective reporting?	Yes	**Outcome reporting:** outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: *not reported*
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** breathalyzer test; **laboratory assessment of drop-outs:**not reported

Huang 2005

Methods	**Title: A double-blind, placebo-controlled study of naltrexone in the treatment of alcohol dependence in Taiwan** **Allocation:** random; **blinding:** double-blind; **study duration:** 14 weeks; **principle of analysis:** not reported; **setting:** outpatient; **study sites:** 1; **country:** Taiwan
Participants	**Diagnosis:** alcohol dependence (DSM-III-R); **required abstinence**: ≥ 14 days; **baseline characteristics:** 100% male; mean age: 40.5 (SD = 7.8) years; 65% married; 60% with an education < 9 years; **pre-baseline drinking:** age of first habitual alcohol use: 26.9 (SD = 6.9) years; **exclusionary psychiatric conditions:** 1. a concurrent drug abuse or dependence (other than alcohol or nicotine); 2. a concurrent major psychiatric disorder.
Interventions	1. 50 mg naltrexone (n = 20) 2. placebo (n = 20) **Psychosocial treatment:** individual supportive therapy for abstinence and motivation enhancement (ME) for medication compliance; **aim**: abstinence
Outcomes	1. Return to any drinking 2. return to heavy drinking* 3. gamma-glutamyltransferase (GGT) 4. aspartate aminotransferase (AST) 5. alanine aminotransferase (ALT) * relapse: drinking ≥ 5 (4) SDU per drinking for men (women) or having ≥ 5 drinking occasions per week or a blood alcohol concentration (BAC) ≥ 100mg/dl
Financial support	Not reported
Data assessment methods	**Assessment of drinking:** not reported; **assessment of side-effects:** not reported; **assessment of compliance:** not reported
Treatment adherence	**Drop-out rates**: naltrexone: 22.5% (n = 9); placebo: 17.5% (n = 7); **lost to follow-up rates**: not reported; **compliance rates**: not reported
Notes	Information on the study design was subsequently provided by the investigators for the review

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Yes	**Persons blinded:** double-blind, including patients and research staff; **placebo appearance**: identical to active medication
Blinding? patient-reported outcomes	Yes	Knowledge of the allocated interventions was adequately prevented during the study (see "Blinding (all outcomes)") Breathalyzer test (weekly) was used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Unclear	**Principle of analysis:** not reported; **handling of missing data:** not reported
Incomplete outcome data addressed? Continuous outcomes	Unclear	**Principle of analysis:** not reported; **handling of missing data:** not reported
Free of selective reporting?	Yes	**Outcome reporting:** primary outcomes were stated in the methods section and adequately reported in the results section
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: *not reported*
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** breathalyzer test (weekly); **laboratory assessment of drop-outs:** not reported

Johnson 2000

Methods	**Tilte: Combining ondansetron and naltrexone effectively treats biologically predisposed alcoholics: From hypotheses to preliminary clinical evidence** **Allocation:** random; **blinding:** double-blind; **study duration:** 8 weeks; **principle of analysis:** ITT; **setting:** outpatient; **study sites:** 1; **country:** USA
Participants	**Diagnosis:** alcohol dependence with early onset (< 25 years) **Required abstinence:** no prior detoxification required **Baseline characteristics:** gender: 75% male; mean age: 38 (SD = 7.9) years; **pre-baseline drinking:** 7.44 (SD = 3.5) drinks per day; MAST score: 32.9 (SD = 9.6) **Exclusionary psychiatric conditions:** 1. a concurrent drug abuse or dependence on narcotics, amphetamines, sedative hypnotics; or 2. a concurrent use of medications with a potential effect on alcohol consumption
Interventions	1. 50 mg naltrexone (25 mg twice a day) + 8 mg ondansetron (4 micrograms/kg twice a day) (n = 10) 2. placebo (n = 10) **Psychosocial treatment:** cognitive behavioral therapy (CBT) and coping skills training; **applied manuals:** Marlatt 1985; Monti 1989; **aim:** abstinence
Outcomes	1. Drinks per drinking day 2. days abstinent 3. side effects
Financial support	National Institute on Alcohol Abuse and Alcoholism (NIAAA)
Data assessment methods	**Assessment of drinking**: TLFB interview (weekly); **assessment of side-effects**: adverse event profile (weekly); **assessment of compliance:** pill count (weekly)
Treatment adherence	**Drop-out rates:** not reported; **lost to follow-up rates**: not reported; **compliance rates** (% of prescribed medication taken; pill count): naltrexone: 96.6%; placebo: 95%
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	Ondansetron and naltrexone as well as their matching placebos were dispensed in two separate bottles numbered sequentially and labelled with subject identification number, study and visit numbers, and the date; no further details provided
Blinding? all outcomes	Unclear	**Persons blinded:** double-blind; no detailed information provided; **placebo appearance:** identical to active medication; naltrexone, purchased as 25 mg tablets, were over-encapsulated in opaque size 1 gelatin capsules identical to those used for ondansetron; placebos were opaque gelatin capsules of the same size, shape, and color but contained only cornstarch
Blinding? patient-reported outcomes	Yes	Breathalyzer test was used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Unclear	No binary outcomes considered in the study
Incomplete outcome data addressed? Continuous outcomes	No	**Principle of analysis:** ITT; **handling of missing data:** endpoint was defined as the last visit of recorded drinking data in the study for each subject
Free of selective reporting?	Yes	**Outcome reporting:** primary outcomes were stated in the methods section and adequately reported in the results section
Free of other bias?	Unclear	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: *not reported*
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** breathalyzer test (weekly); **laboratory assessment of drop-outs:** not reported

Johnson 2004

Methods	**Title: A pilot evaluation of the safety and tolerability of repeat dose administration of long-acting injectable naltrexone (Vivitrex®) in patients with alcohol dependence** **Allocation:** random; **blinding:** double-blind; **study duration:** 16 weeks; **principle of analysis:** ITT; **setting:** outpatient; **study sites:** 4; **country:** USA, Europe
Participants	**Diagnosis:** alcohol dependence; **required abstinence**: ≥5 days; **baseline characteristics:** gender: 73.3% male; mean age: 42.5 (SD=9.2) years; **pre-baseline drinking:** 60.8% (SD = 34.4) days drinking: 7.9 (SD = 4.0) drinks per drinking day; ADS score (Skinner 1982; Skinner 1984): 17.8 (SD = 8.8); 56.7 % had a treatment goal of total abstinence; **exclusionary psychiatric conditions:** 1. an axis I diagnoses, including narcotic or benzodiazepine dependence; or 2. opiate use within 2 weeks of screening or 3. receiving pharmacological treatment for alcohol dependence
Interventions	1. 400 mg injectable naltrexone (n = 20) 2. injectable placebo (n = 5) Injections were administered on days 28, 56, and 84 **Psychosocial treatment:** motivational enhancement (ME)+ bio-psychosocial feedback; **applied manual** (in US centres): BRENDA (Volpicelli 2001)
Outcomes	1. Days abstinent 2. heavy drinking days* 3. drinks per drinking day 4. side effects *relapse/heavy drinking: drinking > 5 (4) STD for men (women)
Financial support	National Institute on Alcohol Abuse and Alcoholism (NIAAA)
Data assessment methods	**Assessment of drinking:** TLFB interview (Sobell 1988; Sobell 1992); **assessment of side-effects:** adverse event checklist
Treatment adherence	**Drop-out rates:** naltrexone: 32% (n = 8); placebo: 20% (n = 1); **lost to follow-up rates**: naltrexone: 16% (n = 4); placebo: 0%; **compliance rates** (number of received injections): naltrexone: 80%; placebo: 80%
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Eligible patients were randomised in a 5:1 ratio to either naltrexone or placebo; no further information provided
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Yes	**Persons blinded:** double-blind, including patients and research staff; **placebo appearance:** placebo had matching volume of microspheres
Blinding? patient-reported outcomes	Yes	Knowledge of the allocated interventions was adequately prevented during the study (see "Blinding (all outcomes)") GGT levels during the study were assessed as a marker of heavy drinking
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Unclear	No binary outcomes considered in the study
Incomplete outcome data addressed? Continuous outcomes	Unclear	**Principle of analysis:** ITT; **handling of missing data:** not reported
Free of selective reporting?	Yes	**Ooutcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: *not reported*
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** GGT levels during the study were assessed as a marker of heavy drinking; **laboratory assessment of drop-outs:** not reported

Kiefer 2003

Methods	**Title: Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism** **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. 50 mg naltrexone (n = 40) 2. 1998 mg acamprosate (n = 40) 3. 50 mg of naltrexone and 1998 mg of 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 (GT) 6. carbohydrate-deficient transferrin level (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
Financial support	University of Hamburg
Data assessment methods	**Assessment of drinking**: drinking diary (weekly); **assessment of side-effects:** adverse effect checklist, rating each adverse effect for its presumed association with the study medication; **assessment of compliance:** pill count
Treatment adherence	**Drop-out rates:** naltrexone: 45% (n = 18); naltrexone + acamprosate: 35.0% (n = 14); acamprosate: 57.5% (n = 23); placebo: 75% (n = 30); **lost to follow-up rates**: not reported; **compliance rates** (% of prescribed medication taken): 81.1%; no group specific values provided
Notes	Posttreatment results published in Kiefer 2004

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Randomization was organized with a computer-generated list
Allocation concealment?	Yes	Allocation codes were provided in sealed envelopes for each patient at the pharmacy of the university hospital, where formulation and blinding was conducted
Blinding? all outcomes	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
Blinding? patient-reported outcomes	Yes	Knowledge of the allocated interventions was adequately prevented during the study (see "Blinding (all outcomes)") Breathalyzer test, randomly registered, was used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
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:** not reported
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes (besides gender); drinking frequency: *not reported;* drinking intensity: yes*;* drinking history or treatment history: yes* (duration of alcohol problems); *baseline differences between groups (amount of alcohol consumed per day, history of drinking problems, GGT) were considered as covariate in the MANCOVA and were shown not have a significant influence on the treatment effects
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** breathalyzer test, randomly registered; **laboratory assessment of drop-outs:** not reported

Killeen 2004

Methods	**Title: Effectiveness of naltrexone in a community treatment program** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks (treatment); 48 weeks (post-treatment); **principle of analysis:** ITT modified; **setting:** outpatient; **study sites:** 1; **country:** USA
Participants	**Diagnosis:** alcohol dependence; **other psychiatric diagnosis**: axis 1 disorders: 51%; other substance abuse disorders: 35%; **required abstinence:** no prior detoxification required; 61.1% stopped drinking between study entry and treatment beginning; **baseline characteristics:** 63% male; mean age: 37.3 (SD=8.75) years; 28% married: 55% employed; **pre-baseline drinking:** 53% had previous treatments of alcohol dependence; **exclusionary psychiatric conditions:** 1. a current addiction to opiates; 2. having had 10 days of outpatient treatment in the past 3 months
Interventions	1. 50 mg of naltrexone (n = 54) 2. placebo (n = 43) 3. community program alone* (n = 48) ***** not included in the meta-analysis **Psychosocial treatment:** eclectic therapy including cognitive behavioral therapy (CBT) + 12-step facilitation ; patients were encouraged to attend Alcoholics Anonymous (AA) self-help groups
Outcomes	1. Return to heavy drinking* 2. days abstinent 3. heavy drinking days 4. drinks per day 5. drinks per drinking day 6. craving 7. gamma-glutamyltransferase (GGT) 8. side effects *relapse/heavy drinking: drinking ≥ 6 (4) STD for men (women)
Financial support	National Institute on Alcohol Abuse and Alcoholism (NIAAA)
Data assessment methods	**Assessment of drinking:** TLFB interview (week 0, 12, 24, 48); **assessment of side-effects:** symptom checklist (week 4,8,12); **assessment of compliance:** Microelective events monitoring system (MEMS); pill count (week 4, 8, 12)
Treatment adherence	**Drop-out rates**: naltrexone: 47% (n = 24); placebo: 33% (n = 12); **lost to follow-up rates**: naltrexone: 24% (n = 12); placebo: 33% (n = 12); **compliance rate** (% of MEMS cap openings): naltrexone: 51%; placebo: 61%
Notes	Rates of continuous abstinence and GGT values were subsequently provided by the investigator for the review Study arm "community program alone" did not meet the inclusion criteria of the review and not included in the meta-analysis

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Urn randomization
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Unclear	**Persons blinded:** double-blind, including outcome assessors, health care providers and patients; **placebo appearance:** no detailed information provided
Blinding? patient-reported outcomes	Yes	Breathalyzer test was used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Unclear	**Principle of analysis:** ITT modified version; patients who did not receive at least one treatment (naltrexone: n = 3; placebo: n = 7; usual treatment: n = 2) were excluded from the primary analysis, but subsequently considered in the meta-analysis; **handling of missing data:** not reported; it was assumed for the meta-analysis that lost to follow-ups have been classified as re lapsers
Incomplete outcome data addressed? Continuous outcomes	Unclear	**Principle of analysis:** ITT modified version; patients who did not receive at least one treatment (naltrexone: n = 3; placebo: n = 7; usual treatment: n = 2) were excluded from the primary analysis; **handling of missing data:** not reported
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: *not reported;* drinking history or treatment history: yes
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** breathalyzer test; **laboratory assessment of drop-outs:** not reported

Kranzler 1998

Methods	**Title: Sustained-Release Naltrexone for Alcoholism Treatment: A Preliminary Study** **Allocation:** random; **blinding:** double-blind; **study duration:** 4 weeks (treatment); 4 weeks (post-treatment); **principle of analysis**: ITT; **setting:** outpatient; **study sites:** 1; **country:** USA
Participants	**Diagnosis:** alcohol dependence; **required abstinence**: ≥ 3 days; **baseline characteristics:** 74.8% male; mean age: 47.3 (SD=8.2) years; 70% married: 70% employed; **pre-baseline drinking:** 20.7 (SD = 9.9) years of heavy drinking; 0.55 (SD = 0.6) previous alcohol detoxifications; ADS score (Skinner 1982; Skinner 1984): 13.6 (SD = 4.7); **exclusionary psychiatric conditions:** 1. a concurrent drug abuse or dependence (other than nicotine or alcohol); 2. a lifetime diagnosis of opioid dependence, psychoactive drug use in the preceding month; 3. a current major psychiatric disorder
Interventions	1. 206 mg injectable naltrexone (n = 15) 2. injectable placebo (n = 5) **Psychosocial treatment:** cognitive behavioral therapy (CBT) + skills training; **applied manual:** Marlatt 1985; Chaney 1989 **Trial started with two-week naltrexone (oral) run-in period, followed by a two-week, no-medication washout period**
Outcomes	1. Drinking days 2. heavy drinking days* 3. drinks per day 4. gamma-glutamyltransferase (GGT) 5. side effects * relapse/heavy drinking: drinking ≥ 5 (4) STD for men (women)
Financial support	National Institutes of Health Grants (General Clinical Research Center)
Data assessment methods	**Assessment of drinking:** TLFB interview; **assessment of side-effects:** SAFTEE (Levine 1986, Rabkin 1992)
Treatment adherence	**Drop-out rates**: not reported; **lost to follow-up rates**: not reported
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	A research pharmacist randomly assigned patients to a medication group, with double-blind conditions maintained throughout the study; no further details provided
Blinding? all outcomes	Yes	**Persons blinded:** double-blind; no detailed information provided; **placebo appearance:** identical to active medication The validity of the double-blind procedure was examined and confirmed at the end of treatment by estimations of group allocation from patients and staff members
Blinding? patient-reported outcomes	Yes	Knowledge of the allocated interventions was adequately prevented during the study (see "Blinding (all outcomes)") Breathalyzer test (weekly) was used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Unclear	No binary outcomes considered in the study
Incomplete outcome data addressed? Continuous outcomes	Unclear	**Principle of analysis:** ITT; **handling of missing data:** not reported
Free of selective reporting?	Yes	**Outcome reporting:** primary outcomes were stated in the methods section and adequately reported in the results section
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: *not reported;* drinking history or treatment history: yes
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** breathalyzer test (weekly); **laboratory assessment of drop-outs:** not reported

Kranzler 2000

Methods	**Title; Naltrexone vs. nefazodone for treatment of alcohol dependence (VA Cooperative Study # 425)** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks; **principle of analysis:** ITT; **setting:** outpatient; **study sites:** 1; **country:** USA
Participants	**Diagnosis:** alcohol dependence; **required abstinence:** 3 to 28 days; **baseline characteristics:** 77.6% male; mean age: 40.9 (SD=8.5) years; 44.8% married: 44.8% full time employed; **pre-baseline drinking:** 1.8 (SD = 2.9) previous alcohol treatments; MAST score: 26.5 (SD = 11.3); **exclusionary psychiatric conditions:** 1. a concurrent drug abuse or dependence (other than nicotine); 2. a lifetime diagnosis of opioid dependence; 3. concurrent suicidality, mania or psychosis Psychiatric disorders that did not require acute intervention, such as mild major depression, were not exclusionary
Interventions	1. 50 mg naltrexone (n = 61) 2. 400 mg of nefazodone (n = 59) 3. placebo (n = 63) **Trial started with a placebo run-in week** **Psychosocial treatment:** coping skills training; **applied manual:** McCrady 1985; Monti 1989
Outcomes	1. Time to first relapse (survival curve) 2. return to any drinking 3. return to heavy drinking* 4. days abstinent 5. heavy drinking days 6. average drinks per drinking occasion 7. time to first drink 8. craving 9. gamma-glutamyltransferase (GGT) 10. side effects * heavy drinking: drinking ≥ 5 (4) STD for men (women)
Financial support	National Institute of Health; General Clinical Research Center, University of Connecticut School of Medicine
Data assessment methods	**Assessment of drinking:** TLFB interview; **assessment of side-effects:** SAFTEE (Levine 1986, Rabkin 1992); **assessment of compliance:** riboflavin
Treatment adherence	**Drop-out rates**: naltrexone: 41% (n = 25); nefazodone: 27,1% (n = 17); placebo: 20.6% (n = 13); **lost to follow-up rates**: naltrexone: 1,6 % (n = 1); nefazodone: 0%; placebo: 0%; **compliance rates** (% of positive urine samples; riboflavin): naltrexone: 66.0%; nefazodone: 76.8%; placebo: 79.8%
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Yes	**Persons blinded:** double-blind, including patients and research staff; **placebo appearance:** double-dummy design (an identically matched placebo was available for each drug) The validity of the double-blind procedure was examined and confirmed at the end of treatment
Blinding? patient-reported outcomes	Yes	Knowledge of the allocated interventions was adequately prevented during the study (see "Blinding (all outcomes)") Breathalyzer test and collateral information were used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Unclear	**Principle of analysis:** ITT; **handling of missing data:** not explicitly reported; it was assumed for the meta-analysis that lost to follow-ups have been classified as re lapsers
Incomplete outcome data addressed? Continuous outcomes	Yes	**Principle of analysis:** ITT; **handling of missing data:** missings were excluded from analysis; because of the low lost to follow-up-rate (n = 1), the proceeding was considered as adequate
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: *not reported;* drinking history or treatment history: yes
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** collateral information, breathalyzer test; **laboratory assessment of drop-outs:** not reported

Kranzler 2004

Methods	**Title: Naltrexone Depot for Treatment of Alcohol Dependence** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks; **principle of analysis:** ITT; **setting:** outpatient; **study sites:** 29; **country:** USA
Participants	**Diagnosis:** alcohol dependence; **required abstinence:** ≥3 days (self-reported sobriety); **baseline characteristics:** gender: 77% male; mean age: 43.9 (SD = 9.1) years; **pre-baseline drinking:** 69.7% (SD = 24.7) heavy days drinking; 5 (SD = 3.7) previous alcohol detoxifications; ADS score: 18.4 (SD = 7.5); **exclusionary psychiatric conditions:** 1.a concurrent drug abuse or dependence (other than nicotine or alcohol); 2. a concurrent use of amphetamines, barbiturates, benzodiazepines, cocaine, or opiates; 3. a concurrent major psychiatric disorders4. the use of disulfiram, oral naltrexone, or antipsychotic medication (past 30 days)
Interventions	1. 150 mg injectable naltrexone (n = 167) 2. injectable placebo (n = 166) **Psychosocial treatment:** motivation enhancement (ME); **applied manual:** Motivating for Alcohol Reduction and Medication Management (MARMM), adapted from motivational enhancement (ME) Miller 1994 as applied in Project MATCH (Project Match Research Group 1997); patients were encouraged to attend Alcoholics Anonymous (AA) or another self-help recovery program. Trial started with a four day treatment with naltrexone (oral), followed by a non-medication wash-out
Outcomes	1. Time to first relapse (survival curve) 2. return to any drinking 3. return to heavy drinking* 4. days abstinent 5. heavy drinking days 6. time to first drink 7. gamma-glutamyltransferase (GGT) 8. side effects * heavy drinking: drinking ≥5 (4) STD for men (women)
Financial support	DrugAbuse Sciences, Inc. (Hayward, CA)
Data assessment methods	**Assessment of drinking:** TLFB; **assessment of side-effects:** not reported
Treatment adherence	**Drop-out rates**: naltrexone: 19.6% (n = 31); placebo: 24.8% (n = 39); group difference in drop-out rates: not significant; group difference in reasons for drop-out: not reported; **lost to follow-up rates**: not reported; **compliance rates:** between 70% and 90% of patients received week 4 and week 8 injections
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	Patients were assigned to sequential medication kits that had been centrally randomized; no further information provided
Blinding? all outcomes	Yes	**Persons blinded:** double-blind, including patients and research staff **Placebo appearance:** the placebo formulation contained microspheres and diluent, but no naltrexone
Blinding? patient-reported outcomes	Yes	Knowledge of the allocated interventions was adequately prevented during the study (see "Blinding (all outcomes)") Breathalyzer test was used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Unclear	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Unclear	**Principle of analysis:** ITT; **handling of missing data:** not explicitly reported; it was assumed for the meta-analysis that lost to follow-ups have been classified as re lapsers
Incomplete outcome data addressed? Continuous outcomes	Unclear	**Principle of analysis:** ITT; **handling of missing data:** not reported
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** breathalyzer test; **laboratory assessment of drop-outs:** not reported

Krystal 2001

Methods	**Tilte: Naltrexone in the treatment of alcohol dependence (VA Cooperative Study # 425)** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks, 12 months (treatment); 6 months (post-treatment); **principle of analysis:** available case analyses (subsequently transformed into ITT); **setting:** outpatient; **study sites:** 15; **country:** USA
Participants	**Diagnosis:** alcohol dependence; **required abstinence:** ≥ 5 days; **baseline characteristics:** 97.6% male; mean age: 48.5 (SD = 10) years; 36.9 % married or living with partner; **pre-baseline drinking:** 68.3% (SD = 29.0) drinking days: 14.1 (SD = 9.0) drinks per drinking day; **exclusionary psychiatric conditions:** 1. a concurrent drug abuse or dependence (other than alcohol, nicotine or occasional marijuana use); 2. a lifetime diagnosis of opioid or marijuana dependence; 3. a concurrent major psychiatric disorder requiring psychotropic medication
Interventions	1. 50 mg naltrexone (3 months) (n = 196 + 13*) 2. 50 mg naltrexone (12 months) (n = 190 + 19*) 3. placebo (12 months) (n = 195 + 14*) ***** subsequently added to available case sample **Psychosocial treatment:** individual 12-step facilitation counselling; patients were encouraged to attend Alcoholics Anonymous meetings; **aim:** abstinence Dosing: naltrexone was started with 25 mg once daily for 2 days, followed by 50 mg once daily
Outcomes	1. Time to first relapse 2. return to heavy drinking* 3. days abstinent 4. drinks per drinking day 5. side effects *heavy drinking: drinking ≥6 (4) STD for men (women)
Financial support	Department of Veterans Affairs
Data assessment methods	**Assessment of drinking:** TLFB interview (4-week intervals); **assessment of side-effects:** not reported; **assessment of compliance:** Microelective events monitoring system (MEMS); 6-beta-naltrexol levels
Treatment adherence	**Drop-out rates**: naltrexone: 1.7% (n = 7); placebo: 1.4% (n = 3); **lost to follow-up rates**: naltrexone: 10% (n = 40); placebo: 11% (n = 22); **compliance rates** (% of days taking medication (MEMS, 6-beta-naltrexol levels): naltrexone: 72%; placebo: 70%
Notes	Abstinence rates and drop-out rates were subsequently provided by the investigator for the review The short-term naltrexone group was switched in a double-blind fashion to matching placebo when naltrexone was discontinued at the 3 months visit; for the review, only the first three months of treatment were included with a pooled naltrexone group

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Unclear	**Persons blinded:** double-blind; no detailed information provided; **placebo appearance:** identical to active medication
Blinding? patient-reported outcomes	Unclear	No objective outcomes were used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Unclear	No objective outcomes reported in the trial publication
Incomplete outcome data addressed? Binary outcomes	No	**Principle of analysis:** available case analyses, subsequently transformed into ITT analyses for the meta-analyses; **handling of missing data:** individuals lost to follow-up were originally excluded from the analyses and subsequently considered as relapsers in the meta-analysis
Incomplete outcome data addressed? Continuous outcomes	No	**Principle of analysis:** available case analyses; **handling of missing data:** excluded from the analyses
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes
Susceptibility to bias reduced?	Unclear	**Validation of patient-reported outcomes:** not reported; **laboratory assessment of drop-outs:** not reported

Latt 2002

Methods	**Title: Naltrexone in alcohol dependence: a randomised controlled trial of effectiveness in a standard clinical setting** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks (treatment); 12 weeks (post-treatment)*; **principle of analysis:** ITT; **setting:** outpatient; **study sites:** 4; **country:** Australia * non-randomized sample
Participants	**Diagnosis:** alcohol dependence; **required abstinence:** not reported; mean abstinence was 11.7 days; **baseline characteristics:** 69.2% male; mean age: 44.8 (SD = 10.6); mean abstinence: 11.7 days (range: 7 to 51 days); **pre-baseline drinking:** 168.2 (SD = 80.4) grams per day; mean duration of alcohol dependence: 14.1 years; SDAQ-Score (Stockwell 1979). 23.5 (SD = 20); **exclusionary psychiatric conditions:** 1. a concurrent use of either illicit or prescribed opioids; 2. a concurrent major psychiatric disorder or an untreated major depression or a recent suicide attempt
Interventions	1. 50 mg naltrexone (n = 56) 2. placebo (n = 51) **Psychosocial treatment:** supportive behavioural therapy; AA attendance allowed
Outcomes	1. Time to first relapse (survival curve) 2. return to heavy drinking 3. drinks per day 4. drinking days 5. craving 6. gamma-glutamyltransferase (GGT) 7. aspartate aminotransferase (AST) 8. alanine aminotransferase (ALT) 9. mean corpuscular volume (MCV) 10. side-effects
Financial support	Du Pont Pharma; Northern Sydney Health, Orphan Australia; Kim and Kris Morris Trust Fund for Drug & Alcohol Services
Data assessment methods	**Assessment of drinking:** self-reported drinking quantity and frequency (week 1, 2, 3, 4, 6, 8, 12); **assessment of side-effects:** structured checklist; **assessment of compliance:** pill count
Treatment adherence	**Drop-out rates**: naltrexone: 41% (n = 23); placebo: 33,3% (n = 17); **lost to follow-up rates**: naltrexone: 32.1% (n = 18); placebo: 29.4% (n = 15); **compliance rates** (% of prescribed medication taken): not reported
Notes	Information on the study design was subsequently provided by the investigator The post-treatment evaluation did not meet the inclusion criteria of the review (non-randomised sample: patients who voluntarily chose to continue taking naltrexone) and was not included in the meta-analysis

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Patients were assigned by computer-generated random numbers to naltrexone or placebo (information provided by the investigator)
Allocation concealment?	Unclear	The chief pharmacist, who had no contact to the patients, packed up the active and placebo tablets (information provided by the investigator); no further information published
Blinding? all outcomes	Yes	**Persons blinded:** double-blind, including health care providers, outcome assessors and patients (information provided by the investigator); **placebo appearance:** identical to active medication (information provided by the investigator)
Blinding? patient-reported outcomes	Yes	Knowledge of the allocated interventions was adequately prevented during the study (see "Blinding (all outcomes)") Breathalyzer test was used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Unclear	**Principle of analysis**: ITT; **handling of missing data:** not explicitly reported; it was assumed for the meta-analysis that lost to follow-ups have been classified as relapsers
Incomplete outcome data addressed? Continuous outcomes	Unclear	**Principle of analysis:** ITT; **handling of missing data:** not reported
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Unclear	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** breathalyzer test, random; **laboratory assessment of drop-outs:** not reported

Lee 2001

Methods	**Title: Naltrexone in the treatment of male alcoholics- an effectiveness study in Singapore** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks (treatment); **principle of analysis:** available case analyses (subsequently transformed into ITT); **setting:** inpatient (4 weeks); outpatient (8 weeks); **study sites:** 1; **country:** Singapore
Participants	**Diagnosis:** alcohol dependence; **required abstinence:** not reported; mean abstinence duration: 7 days; **baseline characteristics:** gender: 100% male; mean age: 45.0 (SD = 9.5) years; 74% married: 41.5% employed; **pre-baseline drinking:** not reported; ADS Score: 17.0 (SD = 7.6); **exclusionary psychiatric conditions:** 1. a concurrent illicit drug abuse or dependence; 2. a concurrent major psychiatric disorder.
Interventions	1. 50 mg naltrexone (n = 24 + 11*) 2. placebo (n = 15 +3*) * subsequently added to available case sample **Psychosocial treatment:** 12-step primary rehabilitation programme; patients were free to attend Alcoholics Anonymous (AA) groups; **aim:** abstinence
Outcomes	1. return to any drinking 2. gamma-glutamyltransferase (GGT) 3. side effects
Financial support	Not supported by the pharmaceutical industry
Data assessment methods	**Assessment of drinking:** TLFB interview (week 1, 2, 3, 4, 6, 8, 10, 12); **assessment of side-effects:** comprehensive side-effects checklist (week 1, 2, 3, 4, 6, 8, 10, 12); **assessment of compliance:** pill count
Treatment adherence	**Drop-out rates**: naltrexone: 60% (n=21); placebo: 77.8% (n=14); group difference in drop-out rates: significant; group difference in reasons for drop-out: *not reported* (reasons for study drop-out were found to be mainly due to return to drinking); **lost to follow-up rates**: naltrexone: 31.4% (n = 11); placebo: 16.7% (n = 3); **compliance rates** (% of prescribed medication taken): *not reported*
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Unclear	**Persons blinded:** double-blind; no detailed information provided; **placebo appearance:** identical to active medication
Blinding? patient-reported outcomes	Yes	GGT and collateral information were used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	No	**Principle of analysis:** available case analyses, subsequently transformed into ITT analyses for the meta-analysis; **handling of lost to follow-up data:** individuals lost to follow-up excluded from the primary analyses and subsequently included as relapsers in the meta-analysis
Incomplete outcome data addressed? Continuous outcomes	No	**Principle of analysis:** ITT analyses; **handling of lost to follow-up data:** last observation carried forward
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Unclear	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: *not reported;* drinking history or treatment history: *not reported*
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** GGT, collateral information; **laboratory assessment of drop-outs:** not reported

Martinotti 2008

Methods	**Title: Aripiprazole in the treatment of patients with alcohol dependence: a double-blind, comparison trial versus naltrexone** **Allocation:** random; **blinding:** double-blind; **study duration:** 16 weeks; **principle of analysis:** ITT; **setting:** outpatient; **study sites:** 1; **country:** Italy
Participants	**Diagnosis:** alcohol dependence; **required abstinence:** 5 to 10 days; **baseline characteristics** 80% male; mean age: 40.3 (SD = 11.8) years; **pre-baseline drinking** 8.5 (SD = 3.5) drinks per day; 14.8 (SD = 6.7) years of alcohol disorder; **exclusionary psychiatric conditions:** 1. a concurrent severe mental disorder; 2. a regular concurrent use of anticonvulsants, antidepressants or antipsychotics Illicit drug use was not a criteria of exclusion
Interventions	1. 50 mg naltrexone (n = 28) 2. 5 to 15 mg aripiprazole (n = 29) **Psychosocial treatment:** no psychosocial treatment provided; patients were free to attend a supportive self-help group; **therapeutic aim:** abstinence; **dosing:** naltrexone started with a dose of 10 mg, aripiprazole with a dose of 5 mg; aripiprazole: flexible dosing
Outcomes	1. Time to first drink (survival curve) 2. return to any drinking 3. return to heavy drinking* 4. days abstinent 5. heavy drinking days 6. craving 7. gamma-glutamyltransferase (GGT) 8. aspartate aminotransferase (AST) 9. alanine aminotransferase (ALT) 10. side effects * heavy drinking: drinking ≥ 5 (4) SDU for men (women)
Financial support	Not supported by any pharmaceutical company
Data assessment methods	**Assessment of drinking:** participant's self-evaluation and a family member interview (week 2, 8, 16); **assessment of side-effects:** Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar; Sullivan 1989; week 2, 8, 16); **assessment of compliance:** not reported
Treatment adherence	**Drop-out rates**: naltrexone: 25% (n = 7); placebo: 24.1% (n = 7); **lost to follow-up rates**: not reported; **compliance rates**: not reported
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Random assignment was achieved with an interactive voice-response central randomisation service
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Unclear	**Persons blinded:** double-blind; no detailed information provided; **placebo appearance:** identical to active medication
Blinding? patient-reported outcomes	Yes	Blood alcohol concentration and collateral information were used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Unclear	**Principle of analysis:** ITT; **handling of missing data:** not explicitly reported; it was assumed for the meta-analysis that lost to follow-ups have been classified as relapsers
Incomplete outcome data addressed? Continuous outcomes	Unclear	**Principle of analysis:** ITT; **handling of missing data:** not reported
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Unclear	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: *not reported;* drinking history or treatment history: *not reported*
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** blood alcohol concentration, collateral information; **laboratory assessment of drop-outs:** not reported

Mason 1994

Methods	**Title: A double-blind, placebo-controlled pilot study to evaluate the efficacy and safety of oral nalmefene HCl for alcohol dependence** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks; **principle of analysis:** ITT / ITT modified; **setting:** outpatient; **study sites:** 1; **country:** United States
Participants	**Diagnosis:** alcohol dependence (DSM-III-R); **required abstinence:** not reported; **baseline characteristics:** 71.4% male; mean age: 42.0 (SD = 9.4) years; **pre-baseline drinking:** 47.1% drinking days; 8.8 (SD = 4.7) drinks per drinking day; 28.4 (SD = 8.4) years of alcohol dependence; **exclusionary psychiatric conditions:** 1. a concurrent drug abuse or dependence (other than alcohol); 2. a lifetime diagnosis of opioid dependence; 3. a concurrent major psychiatric disorder; 4. a concurrent use of psychotropic or anti seizure medications or disulfiram
Interventions	1. 10 mg nalmefene (n = 7) 2. 40 mg nalmefene (n = 7) 3. placebo (n = 7) **Psychosocial treatment:** no psychosocial treatment provided; patients were free to attend a supportive self-help group **Trial started with a 2-week run-on placebo phase, followed by a 1-week titration period**
Outcomes	1. Return to heavy drinking* 2. drinking days 3. drinks per drinking day 4. side effects heavy drinking: drinking ≥ 5 (4) STD for men (women)
Financial support	Baker Norton Pharmaceuticals, Miami, FL.
Data assessment methods	**Assessment of drinking:** computerized version of the TLFB interview (Sobell 1988; Sobell 1992); **assessment of side-effects:** documentation of treatment emergent signs and symptoms; **assessment of compliance:** pill count
Treatment adherence	**Drop-out rates**: naltrexone: 57.1% (n = 8); placebo: 71.4% (n = 5); **lost to follow up rates**: not reported; **compliance rates** (patients who took at least 75% of the prescribed medication): no group specific values provided
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Unclear	**Persons blinded:** double-blind; no detailed information provided; **placebo appearance:** identical to active medication
Blinding? patient-reported outcomes	Yes	Breathalyzer test (weekly) was used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
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	No	**Principle of analysis:** ITT modified version; patients who did not attend at least one week of treatment (n = 2) were excluded in the primary analysis; **handling of missing data:** for calculating *drinking days*, any alcohol use during a given study week resulted in that week being coded as a non-abstinent week; no further information provided
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported in the results section
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** breathalyzer test (weekly); **laboratory assessment of drop-outs:** not reported

Mason 1999

Methods	**Titel: A double-blind, placebo-controlled study of oral nalmefene for alcohol dependence** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks; **principle of analysis:** ITT; **setting:** outpatient; **study sites:** 1; **country:** USA
Participants	**Diagnosis:** alcohol dependence; **required abstinence:** not reported; **baseline characteristics:** 67% male; mean age: 41.8 (SD = 8.8) years; 37.5% married: 70% employed; **pre-baseline drinking:** 57% drinking days: 8.0 (SD = 4.4) drinks per drinking day; days abstinent prior to random assignment: nalmefene: 13.0 days (SD = 17.4); placebo: 16.0 days (SD = 19.7); **exclusionary psychiatric conditions:** 1. a concurrent drug abuse or dependence of illicit drugs; 2. a concurrent major psychiatric disorder including mood and anxiety disorders; 3. a concurrent use of naltrexone, disulfiram, narcotic-containing medication, or psychotropic medications
Interventions	1. 80 mg of nalmefene (n = 35) 2. 20 mg of nalmefene (n = 35) 3. placebo (n = 35) **Psychosocial treatment:** cognitive behavioral therapy (CBT); **applied manual:** Kadden 1992 as applied in Project Match (Project Match Research Group 1997); patients were free to attending self-help groups or to receive other forms of therapy outside the study **Dosing:** the dose was gradually increased during the first week
Outcomes	1. Time to first relapse (survival curve) 2. return to any drinking 3. return to heavy drinking 4. days abstinent 5. drinks per drinking day 6. gamma-glutamyltransferase (GGT) 7. side effects * relapse: drinking ≥ 6 (4) SDU per drinking for men (women) or having ≥ 5 drinking days per week
Financial support	National Institute on Alcohol Abuse and Alcoholism (NIAAA)
Data assessment methods	**Assessment of drinking:** TLFB interview (Sobell 1988; Sobell 1992); **assessment of side-effects:** not reported; **assessment of compliance:** medication management system (MMS); pill count
Treatment adherence	**Drop-out rates**: naltrexone: 35.7% (n = 25); placebo: 34.3% (n = 12); **lost to follow-up rates**: naltrexone: 0%; placebo: 0%; **compliance rates** (% of prescribed medication taken): 86.1%; no group specific values provided
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Yes	**Persons blinded:** double-blind; no detailed information provided; **placebo appearance:** identical to active medication; all patients received the same number of identical tablets The validity of the double-blind procedure was examined and confirmed at the end of treatment by estimations of group allocation from patients and staff members
Blinding? patient-reported outcomes	Yes	Knowledge of the allocated interventions was adequately prevented during the study (see "Blinding (all outcomes)") Breathalyzer test and collateral information were used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Yes	**Principle of analysis:** ITT; **handling of missing data:** none of the participants was lost to follow-up
Incomplete outcome data addressed? Continuous outcomes	Yes	**Principle of analysis:** ITT; **handling of missing data:** none of the participants was lost to follow-up
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** collateral information; breathalyzer test (weekly); **laboratory assessment of drop-outs:** not reported

Monterosso 2001

Methods	**Title: Predicting treatment response to naltrexone: the Influence of craving and family history** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks; **principle of analysis:** ITT; **setting:** outpatient; **study sites:** 1; **country:** USA
Participants	**Diagnosis:** alcohol dependence; **required abstinence:** 3 to 28 days; **baseline characteristics:** 72.8% male; mean age: 46.2 (SD = 11.5) years; **pre-baseline drinking:** 63.1% heavy drinking days. ASI score: 0.71 (SD = 0.16); **exclusionary psychiatric conditions:** 1. a concurrent drug abuse or dependence (other than alcohol, nicotine or cannabis); 2. a concurrent major psychiatric disorder such as psychosis or dementia ; 3. a concurrent use of disulfiram or opioid use in the past 30 days
Interventions	1. 100 mg naltrexone (n = 121) 2. placebo (n = 62) **Psychosocial treatment:** motivational enhancement (ME) + bio-psychosocial feedback; **applied manual:** BRENDA intervention (Volpicelli 2001) **Trial started with a placebo run-in week** **Dosing:** Patients reporting side-effects of naltrexone were instructed to temporarily reduce their medication to a single dose per day (50 mg)
Outcomes	1. Heavy drinking days 2. gamma-glutamyltransferase
Financial support	National Institute on Alcoholism and Alcohol Abuse (NIAAA)
Data assessment methods	**Assessment of drinking:** TLFB interview (Sobell 1988; Sobell 1992); **assessment of side-effects:** not reported; **assessment of compliance:** pill count
Treatment adherence	**Drop-out rates**: 17.9% (no group specific values provided); **lost to follow-up rates**: not reported; **compliance rates** (90% of prescribed medication taken): 78.3%; no group specific values provided
Notes	No binary data were available for "return to heavy drinking"; accordingly no outcomes from trial were included in the statistical analysis

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Unclear	**Persons blinded:** no detailed information provided; **placebo appearance:** identical to active medication
Blinding? patient-reported outcomes	Yes	Collateral information was used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Unclear	No binary outcomes considered in the study
Incomplete outcome data addressed? Continuous outcomes	Unclear	No continuous outcomes considered in the study
Free of selective reporting?	Yes	**Outcome reporting:** primary outcomes were stated in the methods section and adequately reported in the results section
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: *not reported*
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** collateral information; **laboratory assessment of drop-outs:** not reported

Monti 2001

Methods	**Title: Naltrexone and cue exposure with coping and communication skills training for alcoholics: treatment process and 1-year outcomes** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks (treatment); 12 months (post-treatment); **principle of analysis:** ITT / available case analysis; **setting:** outpatient; **study sites:** 1; **country:** USA
Participants	**Diagnosis:** alcohol dependence (DSM-IV); **required abstinence:** 7 to 27 days; **baseline characteristics:** 76% male; mean age: 39.2 (SD = 9.3) years; 46% married or cohabiting: 84% employed; **pre-baseline drinking:** 66.1% (SD = 28.3) drinking days; 12.0 (SD = 7.5) drinks per drinking day; 19.4 (SD = 8.5) years of drinking; ADS score: 17.1 (SD = 7.3); 50% of patients were committed to total abstinence; **exclusionary psychiatric conditions:** 1. a concurrent opiate abuse, opiate use (past 2 weeks), or urine screen positive for opiates; 2. a concurrent psychotic symptoms or currently suicidal, homicidal, or a symptomatic posttraumatic stress disorder; 3. a concurrent use of disulfiram
Interventions	1. 50 mg naltrexone (n = 64) 2. placebo (n = 64) **Psychosocial treatment:** cue exposure + coping and communication skills training (CET); **applied manual:** Monti 1989; **dosing:** The first two days, the dosing started with 25mg, than naltrexone was taken 25 mg twice a day
Outcomes	1. Return to heavy drinking* 2. heavy drinking days 3. drinks per drinking day 4. time to first drink 5. craving 6. gamma-glutamyltranspeptidase (GGT) 7. side effects * relapse / heavy drinking: drinking ≥6 (5) SDU for men (women)
Financial support	National Institute on Alcoholism and Alcohol Abuse (NIAAA)
Data assessment methods	**Assessment of drinking:** TLFB (week 1, 2, 3, 4, 6, 8, 10, 12); **assessment of side-effects:** open-ended assessment of side effect symptoms (week 1, 2, 3, 4, 6, 8, 10, 12); **assessment of compliance:** pill count, riboflavin detection
Treatment adherence	**Treatment phase / drop-out rates**: not reported; **lost to follow-up rates**: 9% (n = 12; no group specific values provided); **compliance rates** (number of days on medication): 61%; no group specific values provided **Follow-up phase / drop-out rates**: not reported; **lost to follow-up rates**: 13% (n=17; no group specific values provided)
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Stratified random assignment was used to balance treatment conditions for sex and socialization scale scores; no further details provided
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Yes	**Persons blinded:** double-blind, including patients and research assistants; **placebo appearance:** identical to active medication (each identical capsule contained 25 mg of either NTX or acetaminophen to provide a bitter taste)
Blinding? patient-reported outcomes	Yes	Knowledge of the allocated interventions was adequately prevented during the study (see "Blinding (all outcomes)") Breathalyzer tests and collateral information were used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Unclear	No binary outcomes considered in the study
Incomplete outcome data addressed? Continuous outcomes	Unclear	No continuous outcomes 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	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: *not reported*
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** collateral information, breathalyzer test; **laboratory assessment of drop-outs:** not reported

Morley 2006

Methods	**Title: Naltrexone versus acamprosate in the treatment of alcohol dependence** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks; **principle of analysis:** ITT; **setting:** outpatient; **study sites:** 3; **country:** Australia
Participants	**Diagnosis:** alcohol dependence (DSM-IV); **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: 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 (other than alcohol, nicotine or low-potency benzodiazepines); 2. a concurrent major psychiatric disorder; 3. a treatment with naltrexone or acamprosate (past 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 *heavy drinking: drinking ≥6 (4) for men (women)
Financial support	National Health and Medical Research Council of Australia, University of Sydney Sesqui Fund
Data assessment methods	**Assessment of drinking:** TLFB interview (week 1, 2, 6, 12); daily monitoring cards; **assessment of side-effects:** open-ended enquiry; **assessment of compliance:** pill count
Treatment adherence	**Drop-out rates**: naltrexone: 32.1% (n = 17); acamprosate: 25.5% (n = 14); placebo: 34.4% (n = 21); **lost to follow-up rates**: naltrexone: 3.8% (n = 2); acamprosate: 3.3% (n = 2); placebo: 1.6% (n = 1); **compliance rates** (patients who took at least 80% of the prescribed medication): 79.7% (of study completers); no group specific values provided
Notes	Information on the GGT values, "heavy drinking days" and the study design was subsequently provided by the investigator Subgroup analysis: Completer analyses available

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 and 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
Blinding? all outcomes	Yes	**Persons blinded:** double-blind, including patients, researchers and 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
Blinding? patient-reported outcomes	Yes	Knowledge of the allocated interventions was adequately prevented during the study (see "Blinding (all outcomes)") Urine alcohol concentration was used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Yes	**Principle of analysis:** ITT; **handling of missing 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 / available case analyses; **handling of missing data:** for the calculations of drinking days, individuals lost to follow-up were assumed to have relapsed from the last date of contact (drinking days); for the calculations of *drinks per drinking day*, individuals lost to follow-up (n = 4) were excluded
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**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 covariates in the statistical analyses
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** urine alcohol concentrations, randomly selected; **laboratory assessment of drop-outs:** not reported

Morris 2001

Methods	**Tilte: Naltrexone for alcohol dependence: a randomised controlled trial** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks; **principle of analysis**: ITT; **setting:** outpatient; **study sites:** 1; **country:** Australia
Participants	**Diagnosis:** alcohol dependence; **required abstinence:** 3 to 30 days; **baseline characteristics:** 100% male; mean age: 47.5 (SD=8.0) years; 48% married; **pre-baseline drinking:** 71% (SD = 29) drinking days: 11.7 (SD = 6.4) drinks per day; 30 (SD = 8) years of drinking; 8.5. (SD = 5.5) days abstinent; **exclusionary psychiatric conditions:** 1. a concurrent drug abuse or dependence (other than alcohol or nicotine); 2. an acute psychotic illness, dementia or suicidal behaviour (other psychiatric disorders were included); 3. a concurrent use of opioids (including opioid analgesics) or disulfiram Patients with current co-morbid psychiatric disorders (apart from acute psychotic illness, dementia or suicidal behaviour) were included in the study
Interventions	1. 50 mg naltrexone (n = 55) 2. placebo (n = 56) **Psychosocial treatment:** cognitive behavioral therapy (CBT); psycho-education and social support; **aim:** harm reduction (information provided by the investigator)
Outcomes	1. Time to first relapse* (survival curve) 2. time to first drink 3. drinking days 4. heavy drinking days 5. drinks per drinking day (completer sample) 6. gamma-glutamyltransferase (GGT) 7. side effects
Financial support	Department of Veterans' Affairs
Data assessment methods	**Assessment of drinking:** TLFB interview (Sobell 1988; Sobell 1992; weekly); **assessment of side-effects:** systematic enquiries about adverse experiences (weekly); **assesment of compliance:** pill count
Treatment adherence	**Drop-out rates**: naltrexone: 30.9% (n = 17); placebo: 41.1% (n = 23); **lost to follow-up rates**: 5.4% (n = 6); no group specific values provided; **compliance rates** (80% of prescribed medication taken): naltrexone: 69%; placebo: 59%.
Notes	Information on the GGT values, drinking days and drinks per drinking day were subsequently provided by the investigator

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Yes	**Persons blinded:** double-blind, including patients, clinicians and research staff; **placebo appearance:** identical to active medication
Blinding? patient-reported outcomes	Yes	Knowledge of the allocated interventions was adequately prevented during the study (see "Blinding (all outcomes)") Breathalyzer test (weekly) was used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Unclear	**Principle of analysis:** ITT; **handling of missing data:** not reported; it was supposed for the meta-analysis that lost to follow-ups have been categorized as relapsers
Incomplete outcome data addressed? Continuous outcomes	No	**Principle of analysis:** available case analysis; **handling of missing data:** data were censored for patients who dropped-out
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes
Susceptibility to bias reduced?	Unclear	**Validation of patient-reported outcomes:** breathalyzer test (weekly); **laboratory assessment of drop-outs:** not reported

O'Malley 1992

Methods	**Tilte: Naltrexone and coping skills therapy for alcohol dependence** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks (treatment); 6 months (post-treatment); **principle of analysis:** ITT modified (first week drop-outs excluded); **setting:** outpatient; **study sites:** 1; **country:** USA
Participants	**Diagnosis:** alcohol dependence; **required abstinence:** 7 to 30 days; **baseline characteristics:** 74% male; mean age: 40.5 (SD=9.7) years; 34% married: 73% employed full time; **pre-baseline drinking:** 60% drinking days: 11.2 (SD = 9.2) drinks per drinking occasion; 1.0 (SD = 1.6) previous alcohol treatments; ASI score: 7.3 (SD = 1.9); **exclusionary psychiatric conditions:** 1. a concurrent drug abuse or dependence (other than alcohol or nicotine); 2. a lifetime diagnosis of opioid dependence; 3. a history of psychosis; 4. a current suicidality, homocidality or psychiatric symptoms that required other psychotropic medication; 4. a concurrent use of disulfiram
Interventions	1. 50 mg of naltrexone + CBT (n = 24 + 3*) 2. 50 mg of naltrexone + MET (n = 22 + 1*) 3. 50 mg of placebo + CBT (n = 24 + 1*) 4. 50 mg of placebo + MET (n = 27) ***** subsequently added to available case sample **Psychosocial treatment:** a) group 1 and 3: cognitive behavioral therapy (CBT); **applied manual:** Marlatt 1985 with focus on coping skills to keep a slip-up from developing into relapse; **aim:** harm reduction; b) group 2 and 4: motivation enhancement (ME); **aim**: abstinence; patients were free to attend self-help groups
Outcomes	1. Time to first relapse (survival curve) 2. time to first drink (survival curve) 3. return to any drinking 4. return to heavy drinking 5. drinking days 6. drinks per drinking occasion 7. time to first drink 8. craving * relapse / heavy drinking: drinking ≥5 (4) STD for men (women)
Financial support	National Institute on Alcohol Abuse and Alcoholism NIAAA)
Data assessment methods	**Assessment of drinking:** TLFB interview (Sobell 1988; Sobell 1992; weekly); **assessment of side-effects:** side effects checklist; **assessment of compliance:** riboflavin detection
Treatment adherence	**Treatment phase / drop-out rates**: naltrexone: 28.8% (n = 15); placebo: 40.4% (n = 21); **lost to follow-up rates**: not reported; **compliance rates** (% of prescribed medication taken): naltrexone: 92%; placebo: 78% **Follow-up phase / lost to follow-up rates**: naltrexone: 13.0% (n = 6); placebo: 21.6% (n = 11)
Notes	Post-treatment results provided in O'Malley 1996

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Unclear	**Persons blinded:** double-blind, including patients and research staff; **placebo appearance:** not reported
Blinding? patient-reported outcomes	Yes	Collateral information was used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	No	**Principle of analysis:** ITT modified version; patients who not receive at least one week of study medication (naltrexone: n = 6; placebo: n = 1) were excluded from the primary analysis, but subsequently considered in the meta-analysis; **handling of missing data:** individuals lost to follow-up excluded from the analyses and subsequently included as relapsers in the meta-analysis
Incomplete outcome data addressed? Continuous outcomes	No	**Principle of analysis:** ITT modified version; patients who not receive at least one week of study medication (naltrexone: n = 6; placebo: n = 1) were excluded from the primary analysis; **handling of missing data:** not reported
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes (except age*); drinking frequency and intensity: yes; drinking history or treatment history: yes *naltrexone-treated patients were older (42.8 years) than placebo-treated patients (38.5 years), but no other group differences were shown
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** collateral information; **laboratory assessment of drop-outs:** not reported

O'Malley 2007

Methods	**Title: Naltrexone for the treatment of alcohol drinking and eating disorder in alcohol-dependent women** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks; **principle of analysis:** ITT (modified); **setting:** outpatient; **study sites:**1; **country:** USA
Participants	**Diagnosis:** alcohol dependence; **other psychiatric diagnosis:** comorbid eating disorder (28% of the sample); **required abstinence:** 3 to 5 days; **baseline characteristics:** 100% female; mean age: 40.34 (SD = 8.0) years; 52% married: 75% employed; **pre-baseline drinking:** 65.6 (SD = 25.3) drinking days; 7.1 (SD = 4.5) drinks per drinking episode; ADS score: 16.5 (SD = 8.0); **exclusionary psychiatric conditions:** 1. a concurrent drug abuse or dependence (other than alcohol or nicotine); 2. a concurrent psychosis or other severe psychiatric disability (e.g., suicidal, manic state); 3. a concurrent use of opioid analgesics or disulfiram.
Interventions	1. 50 mg naltrexone (n = 57) 2. Placebo (n = 50) **Psychosocial treatment:** cognitive behavioral therapy (CBT); **applied manual:** (Kadden 1992 as applied in Project MATCH (Project Match Research Group 1997) Dosing: 25 mg naltrexone daily for the first two treatment days
Outcomes	1. Time to first relapse* (survival curve) 2. time to first drink (survival curve) 3. drinks per drinking day 4. craving 5. gamma-glutamyltransferase (GGT) 6. time to the second day of drinking (non-abstinent participants) 7. side effects ** relapse / heavy drinking: drinking ≥ 4 SDU
Financial support	Grants RO1AA10225, U10AA11787, KO5-AA014715 (SSO), KO2DA017232 (RS), K24DK070052 (CMG), P50 DA09421, K05-DA00089 (BJR)
Data assessment methods	**Assessment of drinking:** TLFB interview (Sobell 1988; Sobell 1992); **assessment of side-effects:** not reported; **assessment of compliance:** Microelective events monitoring system (MEMS)
Treatment adherence	**Drop-out rates**: naltrexone: 40.4% (n = 23); placebo: 46.0% (n = 23); **lost to follow-up rates**: naltrexone: 22.8% (n = 13); placebo: 24% (n = 12); **compliance rates** (% of days on which study medication was taken): 65%; no group specific values provided
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomization was stratified by the presence or absence of eating disturbance and the use of antidepressant therapy was balanced across medication conditions; no further details provided
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Yes	**Persons blinded:** double-blind, including patients and research staff; **placebo appearance:** identical to active medication
Blinding? patient-reported outcomes	Yes	Knowledge of the allocated interventions was adequately prevented during the study (see "Blinding (all outcomes)") Breathalyzer test and collateral information were used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Unclear	**Principle of analysis:** ITT modified version; patients who did receive at least one dose of treatment (naltrexone: n = 4; placebo: n = 0) were excluded from the primary analysis; **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 modified version; patients who did receive at least one dose of treatment (naltrexone: n = 4; placebo: n = 0) were excluded from the primary analysis; **handling of missing data:** for the calculation of days abstinent, individuals lost to follow-up were assumed to have failed on the day following their last recorded data point
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported **Diversity of outcomes:** continuous abstinence: yes; drinking frequency: yes; drinking intensity (amount per drinking day/occasion): yes; laboratory indicators: yes
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: *not reported*
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** collateral information, breathalyzer test; **laboratory assessment of drop-outs:** not reported

O'Malley 2008

Methods	**Title: Naltrexone alone and with sertraline for the treatment of alcohol dependence in Alaska natives and non-natives residing in rural settings** **Allocation:** random; **blinding:** double-blind; **study duration:** 16 weeks (treatment); 68 weeks (post-treatment); **principle of analysis:** ITT; **setting:** outpatient; **study sites:** 5; **country:** USA
Participants	**Diagnosis:** alcohol dependence; **required abstinence:** 4 to 30 days; **baseline characteristics:** 66% male; mean age: 40.0 (SD = 9.8) years; 37% married: 59% employed. Native Alaskans (n = 68); non-native Alaskans (n = 33): **pre-baseline drinking:** 57.5% (SD = 25.7) drinking days: 17.9 (SD = 11.5) drinks per drinking day; ADS score: 19.5 (SD = 8.0); **exclusionary psychiatric conditions:** 1. a concurrent cocaine, opioid, or amphetamine drug abuse or dependence; 2. a concurrent major psychiatric condition that required use of psychotropic medications or could jeopardize safety (e.g. suicidality, psychosis); 3. a concurrent use of opioids or psychotropic medications
Interventions	1. 50 mg naltrexone (n = 34) 2. 50 mg naltrexone + 100 mg sertraline (n = 33) 3. placebo (n = 34) **Psychosocial treatment:** medial management (MM); **applied manual:** Pettinati 2004 as applied in Anton 2006; **aim:** flexible (with recommendation to abstinence) **Dosing:** 12.5 mg naltrexone for the fist treatment day, 25 mg naltrexone for the second and third treatment day
Outcomes	1. Time to first relapse* (survival curve) 2. time to first drink (survival curve) 3. return to any drinking 4. return to heavy drinking* 5. days abstinent 6. heavy drinking days 7. drinks per drinking day 8. craving 9. gamma-glutamyltransferase level (GGT) 10. carbohydrate-deficient transferrin (CDT) 11. side effects * heavy drinking: drinking ≥5 (4) STD for men (women)
Financial support	National Institute on Alcohol Abuse and Alcoholism (NIAAAA); National Center on Minority Health and Health Disparities
Data assessment methods	**Assessment of drinking:** TLFB interview (Sobell 1988; Sobell 1992; week 0, 8, 16); **assessment of side-effects:** not reported; **assessment of compliance:** Electronic Microchip System (EMS)
Treatment adherence	**Drop-out rates**: naltrexone: 23.5% (n = 8); naltrexone + sertraline: 36.4% (n = 12); placebo: 38.2% (n = 13); **lost to follow-up rates:** naltrexone: 9% (n = 3); naltrexone + sertraline: 12% (n = 4); placebo: 9% (n = 3); **compliance rate** (% of bottle openings): naltrexone: 66%; naltrexone + sertraline: 58%; placebo: 61%
Notes	The report focuses on the 16-week treatment period; post-treatment results presented

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Study participants were randomised to conditions in blocks of 12 within native and non-native groups and within study sites; no further information provided
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Yes	**Persons blinded:** double-blind, including patients and all study staff (besides pharmacists, who did not interact directly with participants); **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)
Blinding? patient-reported outcomes	Yes	Knowledge of the allocated interventions was adequately prevented during the study (see "Blinding (all outcomes)") GGT was used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Yes	**Principle of analysis:** ITT; **handling of missing data:** individuals lost to follow-up were assumed to have failed on the day following their last recorded data point in the primary analysis
Incomplete outcome data addressed? Continuous outcomes	Yes	**Principle of analysis:** ITT; **handling of missing data:** for the calculation of percent drinking days, individuals lost to follow-up were assumed to have failed on the day following their last recorded data point; for the calculation of further continuous outcomes(drinks per drinking day, GGT), handling of lost to follow-ups was not reported
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: *not reported*
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** GGT; **laboratory assessment of drop-outs:** not reported

Oslin 1997

Methods	**Title: Naltrexone as an adjunctive treatment for older patients with alcohol dependence** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks; **principle of analysis:** ITT; **setting:** outpatient; **study sites:** 1; **country:** USA
Participants	**Diagnosis:** alcohol dependence (veterans; > 50 years); **required abstinence:** ≥ 3 days; **baseline characteristics:** 100% male; mean age: 57.8 (SD = 6.8) years; 15.9% married; **pre-baseline drinking:** 10.7 (SD = 7.3) drinks per drinking occasion; ASI score (McLellan 1980): 0.48 (SD = 0.18); **exclusionary psychiatric conditions:** 1. drug abuse or dependence other than alcohol or nicotine (past 6 weeks); 2. a diagnosis of severe dementia, seizure disorder, mental retardation or psychosis; 3. a concurrent use of psychoactive substances
Interventions	1. 50 mg naltrexone (n = 21) 2. placebo (n=23) **Psychosocial treatment:** group therapy, case management, peer support, education; **aim:** abstinence
Outcomes	1. Time to first relapse* (survival curve) 2. return to any drinking 3. return to heavy drinking 4. days abstinent 5. craving 6. gamma-glutamyltransferase 7. side effects * relapse: drinking ≥ 5 (4) SDU per drinking for men (women) or having ≥ 5 drinking occasions per week or a blood alcohol concentration (BAC) > 100mg/dl
Financial support	Dupont Merck Pharmaceuticals
Data assessment methods	**Assessment of drinking:** not reported; **assessment of side-effects:** weekly checklist for selected adverse events; **assessment of compliance:** not reported
Treatment adherence	**Drop-out rates**: naltrexone: 14.3% (n = 3); placebo: 30.4% (n = 7); **lost to follow-up rates**: naltrexone: 14.3% (n = 3); placebo: 30.4% (n = 7); **compliance rate** (doses of medication taken): naltrexone: 26.8 (SD = 8.1); placebo: 25.6 (SD = 12.6)
Notes	Information on drop-out rates and the study design were provided by the investigator

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Unclear	**Persons blinded:** double-blind; no detailed information provided; **placebo appearance:** not reported
Blinding? patient-reported outcomes	Yes	Blood alcohol concentration was used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Unclear	**Principle of analysis:** ITT; **handling of missing data:** not explicitly reported; it was assumed for the meta-analysis that lost to follow-ups have been classified as relapsers
Incomplete outcome data addressed? Continuous outcomes	No	**Principle of analysis:** available case analysis; **handling of missing data:** considered as censored at the time of drop out (information provided by the investigator)
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** blood alcohol concentration; **laboratory assessment of drop-outs:** not reported

Oslin 2005

Methods	**Title: Treatment of late-life depression complicated by alcohol dependence** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks (treatment); **principle of analysis:** not reported; **setting:** outpatient; **study sites:** 1; **country:** USA
Participants	**Diagnosis:** alcohol dependence (DSM-IV); **concurrent psychiatric diagnosis:** major depression (100%); **required abstinence:** ≥ 3 days; **baseline characteristics:** 79.8% male; mean age: 63.4 (SD=6.3) years; 44.6% married; **pre-baseline drinking:** 79% drinking days; 67.5% heavy drinking days; 8.4 (SD = 5.5) drinks per drinking day; 17.3 (SD = 9.9) years of drinking-to-intoxication; 48.6% had received formal treatment of alcohol dependence before; ASI score: 0.7 (SD = 0.2); **exclusionary psychiatric conditions:** 1. a concurrent drug abuse or dependence (other than alcohol or nicotine); 2. an opioid use during the last 30 days
Interventions	1. 50 mg naltrexone + 100mg sertraline (n = 37) 2. placebo + 100mg sertraline (n = 37) **Psychosocial treatment:** motivational enhancement (ME)+ bio-psychosocial feedback; **applied manual**: BRENDA intervention (Volpicelli 2001); **aim:** flexible
Outcomes	1. Time to first relapse* 2. return to any drinking 3. return to heavy drinking* 4. side effects * heavy drinking: drinking ≥4 (3) SDU for men (women)
Financial support	National Institute of Mental Health; Department of Veterans Affairs
Data assessment methods	**Assessment of drinking:** TLFB interview (Sobell 1988; Sobell 1992); **assessment of side-effects:** SAFTEE (Levine 1986, Rabkin 1992); **assessment of compliance:** pill count
Treatment adherence	**Drop-out rates**: naltrexone: 18.9% (n = 7); placebo: 10.8% (n = 4); **lost to follow-up rates**: not reported; **compliance rates:** not reported
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	No detailed information provided.
Blinding? all outcomes	Unclear	**Persons blinded:** double-blind; no detailed information provided; **placebo appearance:** identical to active medication
Blinding? patient-reported outcomes	Unclear	No objective outcomes were used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Unclear	No objective outcomes reported in the trial publication
Incomplete outcome data addressed? Binary outcomes	Unclear	**Principle of analysis:** not reported; **handling of missing data:** not reported; it was supposed for the meta-analysis that lost to follow-ups have been categorized as relapsers
Incomplete outcome data addressed? Continuous outcomes	Unclear	**Principle of analysis:** not reported; **handling of missing data:** not reported
Free of selective reporting?	Yes	**Outcome reporting:** primary outcomes were stated in the methods section and adequately reported in the results section
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: no*; drinking history or treatment history: *not reported* * those randomized to naltrexone were significantly less depressed, had fewer drinks on a drinking day and had fewer heavy drinking before randomization than patients in the placebo group; these variables were considered as covariates in the statistical analyses and were shown not have a significant influence on the treatment effects
Susceptibility to bias reduced?	Unclear	**Validation of patient-reported outcomes:** not reported; **laboratory assessment of drop-outs:** not reported

Oslin 2008

Methods	**Tilte: A placebo-controlled randomized clinical trial of naltrexone in the context of different levels of psychosocial intervention** **Allocation:** random; **blinding:** double-blind; **study duration:** 24 weeks; **principle of analysis:** ITT modified (treatment received analysis); **setting:** outpatient; **study sites:** 1; **country:** USA
Participants	**Diagnosis:** alcohol dependence; **required abstinence**: ≥ 3 days; **baseline characteristics:** 72.9% male; mean age: 41.0 (SD = 9.4) years; 34.5% married: 85% employed; **pre-baseline drinking:** 71.6 (SD = 27.4) % drinking days; 8.7 (SD = 6.6) drinks per day; ASI score (McLellan 1980): 0.70 (SD = 0.18); **exclusionary psychiatric conditions:** 1. a concurrent psychoactive substance dependence (other than alcohol or nicotine); 2. opioid abuse in the past 30 days; 3. concurrent severe psychiatric symptoms; 4. a concurrent use of psychotropic medications
Interventions	1. 100 mg naltrexone + physician visit (n = 41 +1*) 2. placebo * physician visit (n = 40 +1*) 3. 100 mg naltrexone + BRENDA (n = 39 +3*) 4. placebo + BRENDA (n = 40 +1*) 5. 100 mg naltrexone + CBT (n = 40 + 2*) 6. placebo + CBT (n = 40) * patients excluded who did not receive at least one dose of study medication Psychosocial treatment: a) group 1 and 2: physician visit; no formal psychotherapy; b) group 3 and 4: motivational enhancement (ME) + bio-psychosocial feedback; **applied manual**: BRENDA (Volpicelli 2001); c) group 5 and 6: cognitive behavioral therapy (CBT); **applied manual:** Kadden 1992 as applied in Project Match (Project Match Research Group 1997) **Dosing:** flexible (in case of side-effects, patients were maintained on 50 mg)
Outcomes	1. Return to any drinking 2. return to heavy drinking 3. days abstinent 4. heavy drinking days 5. drinks per drinking day 6. side effects * relapse / heavy drinking: drinking ≥5 (4) SDU for men (women)
Financial support	National Institute on Alcoholism and Alcohol Abuse (NIAAA); National Institute on Mental Health; National Institute on Drug Abuse
Data assessment methods	**Assessment of drinking:** TLFB interview (Sobell 1988; Sobell 1992; week 4, 8, 12, 16, 20, 24); **assessment of side-effects:** research physician's probing for side effects commonly (weekly); **assessment of compliance:** pill count
Treatment adherence	**Drop-out rates**: naltrexone: 24.2% (n = 29); placebo: 19.2% (n = 23); **lost to follow-up rates**: 77% of the patients provided complete data on drinking during the 24-week trial; **compliance rates** (80% of days on which prescribed medication was taken over 24 weeks): naltrexone: 50%; placebo: 51%
Notes	Information on the study design were subsequently provided by the investigator

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Random numbers were generated in block sequences by a blinded statistician; no further information provided
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Yes	**Persons blinded:** double-blind, including patients and research staff (information provided by the investigator); **placebo appearance:** identical to active medication
Blinding? patient-reported outcomes	Yes	Knowledge of the allocated interventions was adequately prevented during the study (see "Blinding (all outcomes)")
Blinding? objective outcomes	Unclear	No objective outcomes reported in the trial publication
Incomplete outcome data addressed? Binary outcomes	Yes	Blinding? (objective outcomes)
Incomplete outcome data addressed? Continuous outcomes	Yes	**Principle of analysis:** ITT modified version; patients who did not receive one dose of the treatment were excluded from the primary analysis; **handling of missing data:** handling was conducted against non-adherence patterns; a GEE model with a pattern mixture strategy (Park 1999) Pwas used to assess the sensitivity of the results to the assumption that missing data were ignorable.
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: *not reported*
Susceptibility to bias reduced?	Unclear	**Validation of patient-reported outcomes:** not reported; **laboratory assessment of drop-outs:** not reported

Petrakis 2004

Methods	**Tile: Naltrexone augmentation of neuroleptic treatment in alcohol abusing patients with schizophrenia** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks; **principle of analysis:** ITT; **setting:** outpatient; **study sites:** 1; **country:** USA
Participants	**Diagnosis:** alcohol dependence (97%); alcohol abuse (3%); **concurrent psychiatric diagnosis**: schizophrenia (58%); schizoaffective disorder (42%); **required abstinence:** ≤ 29 days; **baseline characteristics:** 100% male; mean age: 46 (SD=5.7) years; 16% employed; **pre-baseline drinking:** 39% (SD = 27.7) drinking days; 30% (SD = 26.3) heavy drinking days; 4.26 (SD = 4.2) drinks per day; **exclusionary psychiatric conditions:** 1. a concurrent drug abuse or dependence (other than alcohol or nicotine); 2. serious psychiatric symptoms, such as suicidal or homicidal ideation or an unstable psychotic condition
Interventions	1. 50 mg naltrexone (n = 16) 2. placebo (n = 15) **Psychosocial treatment:** skills training for schizophrenia; **applied manual:** Roberts 1999
Outcomes	1. Drinking days 2. heavy drinking days* 3. drinks per day 4. craving 5. side effects * relapse / heavy drinking: drinking ≥ 5 (4) SDU for men (women)
Financial support	National Alliance for Research on Schizophrenia and Depression (NARSAD); Department of Veterans Affairs; VA-Yale Alcoholism Research Center; VISN I Mental Illness Research and Clinical Center; National Institute on Alcohol Abuse and Alcoholism (NIAAA).
Data assessment methods	**Assessment of drinking:** TLFB interview (Sobell 1988; Sobell 1992; weekly); **assessment of side-effects:** Hopkins symptom checklist (HSCL; Derogatis 1974); **assessment of compliance:** pill count
Treatment adherence	**Drop-out rates**: naltrexone: 25% (n = 4); placebo: 13.4% (n = 2); **lost to follow-up rates**: naltrexone: 12.5% (n = 2); placebo: 6.7% (n = 1); **compliance rate** (% of days taking medication): naltrexone: 68.4%; placebo: 77.5%
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Unclear	**Persons blinded:** double-blind; no detailed information provided; **placebo appearance:** identical to active medication
Blinding? patient-reported outcomes	Yes	Breathalyzer test (weekly) was used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Unclear	No binary outcomes considered in the study
Incomplete outcome data addressed? Continuous outcomes	Yes	**Principle of analysis:** ITT; **handling of missing data:** hierarchical linear modelling (HLM) analyses with group specific imputations have been used
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes*; psychiatric comorbidity: yes; drinking history or treatment history: *not reported* * baseline differences between groups (drinking days) were entered as a covariate in the random regression analysis
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** breathalyzer test (weekly); **laboratory assessment of drop-outs:** not reported

Petrakis 2005

Methods	**Title: Naltrexone and disulfiram in patients with alcohol dependence and comorbid psychiatric disorders** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks; **principle of analysis:** ITT; **setting:** outpatient; **study sites:** 3; **country:** USA
Participants	**Diagnosis:** alcohol dependence (DSM-IV); **other psychiatric diagnosis:** comorbid axis I disorders (major depression: 70.1%; posttraumatic stress disorder: 42.9%; schizophrenia or schizoaffective disorder: 7.4%; cocaine dependence 19.7%; **required abstinence**: 3 to 29 days; **baseline characteristics:** 97.2% male; mean age: 47.0 (SD=8.2) years; **pre-baseline drinking:** 52% (SD = 4) drinking days: 19.4 (SD = 12.5) drinks per drinking day; ADS score: 21.7 (SD = 8.9); **exclusionary psychiatric conditions:** 1. an unstable psychotic symptoms or serious current psychiatric symptoms, such as suicidal or homicidal ideation; 2. a psychiatric medications change (unstable regimen) for at least 2 weeks before randomisation
Interventions	1. 50 mg naltrexone (n = 59) 2. 50 mg naltrexone + 250 mg disulfiram (n = 65)* 3. 250 mg disulfiram (n = 66)* 4. placebo (n = 64) * study arms not included in the review (open-label) **Psychosocial treatment:** supportive therapy and compliance enhancement therapy; **applied manual:** Carroll 1998; **aim:** abstinence
Outcomes	1. Return to any drinking 2. days abstinent 3. heavy drinking days* 4. time to first drink 5. craving 6. gamma-glutamyltransferase (GGT) 7. carbohydrate-deficient (CDT) 8. glutamic-oxaloacetic transaminase 9. glutamic pyruvic transaminase 10. side effects * relapse / heavy drinking: drinking ≥ 5 (4) SDU for men (women)
Financial support	Department of Veterans Affairs; Veterans Affairs New England Mental Illness Research and Clinical Center (MIRECC)
Data assessment methods	**Assessment of drinking:** TLFB interview (Sobell 1988; Sobell 1992; weekly); **assessment of side-effects:** Hopkins symptom checklist (HSC; Derogatis 1974); **assessment of compliance:** Microelective Events Monitoring System (MEMS)
Treatment adherence	**Drop-out rates**: naltrexone: 22% (n = 13); placebo: 37.5% (n = 24); **lost to follow-up rates**: naltrexone: 5.1% (n = 3); placebo: 15.6% (n = 10); **compliance rates** (% number of days pills taken related to the number of potential medication days): naltrexone: 82%; placebo: 86%
Notes	Information on the study design was subsequently provided by the investigator Study arms with disulfiram did not meet the inclusion criteria of the review and were not included in the meta-analysis

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	Phamacist prepared medication (information provided by the investigator); no further information provided
Blinding? all outcomes	Yes	**Persons blinded:** double-blind, including patients, research staff (information provided by the investigator); **placebo appearance:** identical to active medication (information provided by the investigator)
Blinding? patient-reported outcomes	Yes	Knowledge of the allocated interventions was adequately prevented during the study (see "Blinding (all outcomes)")
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
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	Unclear	**Principle of analysis:** ITT; **handling of missing data:** not reported
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: *not reported*
Susceptibility to bias reduced?	Unclear	**Validation of patient-reported outcomes:** not reported; **laboratory assessment of drop-outs:** not reported

Pettinati 2008a

Methods	**Title: Gender differences with high-dose naltrexone in patients with co-occurring cocaine and alcohol dependence** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks; **principle of analysis:** ITT; **setting:** outpatient; **study sites:** 1; **country:** USA
Participants	**Diagnosis:** alcohol dependence (DSM-IV); **concurrent psychiatric diagnosis:** cocaine dependence; **required abstinence:** ≥ 3 days; **baseline characteristics:** 70.7% male; mean age: 39.1 (SD = 7.0) years; 47.8 % ever married: 70.9% employed; **pre-baseline drinking:** 57.1% (SD = 26.6) drinking days; 12.0 (SD = 7.2) drinks per drinking day; 2.0 (SD = 2.5) previous alcohol treatments; 19.7 (SD = 8.2) years of problematic drinking; ASI score (McLellan 1980): 0.61 (SD = 0.2); **pre-baseline cocaine use:** 71.1% crack cocaine preference; 1122 US Dollars (SD = 1138) spent on cocaine during the last 30 days; **exclusionary psychiatric conditions:** 1. a concurrent drug abuse or dependence (other than alcohol or cocaine); 2. opiate use (past 30 days); 3. psychosis, suicidal or homicidal ideation, or mania; 4. a concurrent treatment with psychiatric medications, including antipsychotic, antidepressant, and antianxiety medications
Interventions	1. 150 mg naltrexone + CBT(n = 44) 2. placebo + CBT (n = 37) 3. 150 mg naltrexone + BRENDA (n = 38) 4. placebo + BRENDA (n = 45) **Psychosocial treatment: a)** group 1 and 2: cognitive behavioral therapy (CBT); **applied manual:** Marlatt 1985, adapted by Carroll 1998 for the treatment of concurrent cocaine and alcohol dependence; b) group 3 and 4: motivational enhancement (ME) + bio-psychosocial feedback; **applied manual**: BRENDA (Volpicelli 2001) **Dosing:** ascending; starting with 50 mg naltrexone up to for the first two treatment days up to 150 mg/day of naltrexone, as tolerated
Outcomes	1. Drinking days 2. heavy drinking days* 3. drinks per drinking day 4. side effects * relapse / heavy drinking: drinking ≥5 (4) for men (women)
Financial support	National Institute on Drug Abuse; Mental Health Research Education and Clinical Center at the Philadelphia Veterans Affairs Medical Center
Data assessment methods	**Assessment of drinking:** TLFB interview (Sobell 1988; Sobell 1992; weekly; extended version for cocaine self-reports; weekly); **assessment of side-effects** (weekly): SAFTEE (Levine 1986, Rabkin 1992)
Treatment adherence	**Drop-out rates**: naltrexone: 39% (n=32); placebo: 32.9% (n=27); **lost to follow-up rates**: not reported; **compliance rates** (% of patients who took ≥ 80% of the medication): naltrexone: 49%; placebo: 42.7%
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Participants were stratified by gender and then randomly assigned to one of four treatment conditions; no further details provided
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Unclear	**Persons blinded:** no detailed information provided; **placebo appearance:** identical to active medication
Blinding? patient-reported outcomes	Unclear	No objective measures used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Unclear	No objective outcomes reported in the trial publication
Incomplete outcome data addressed? Binary outcomes	Yes	**Principle of analysis:** ITT; **handling of missing data:** generalized estimating equations (GEE) models with a pattern mixture strategy (Park 1999) was used to assess the sensitivity of the results to the assumption that missing data were ignorable
Incomplete outcome data addressed? Continuous outcomes	Yes	**Principle of analysis:** ITT; **handling of missing data:** generalized estimating equations (GEE) models with a pattern mixture strategy (Park 1999) was used to assess the sensitivity of the results to the assumption that missing data were ignorable
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes
Susceptibility to bias reduced?	Unclear	**Validation of patient-reported outcomes:** not reported; **laboratory assessment of drop-outs:** not reported

Pettinati 2008b

Methods	**Title: A double blind, placebo-controlled trial that combines disulfiram and naltrexone for treating co-occurring cocaine and alcohol dependence** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks; **principle of analysis:** ITT; **setting:** outpatient; **study sites:** 1; **country:** USA
Participants	**Diagnosis:** alcohol dependence; **other psychiatric diagnosis:** cocaine dependence (100%); **required abstinence:** ≥ 3 days; **baseline characteristics:** 40.1% male; mean age: 41.2 (SD=6.8) years; 31.5% days employed in past 30 days; **pre-baseline drinking:** 55.8% drinking days; 14.4 (SD = 12.0) drinks per drinking day; 3.6 (SD = 6.1) previous alcohol or drug treatments; **exclusionary psychiatric conditions:** 1. a concurrent drug abuse or dependence (other than cocaine, alcohol or nicotine); 2. a concurrent active psychosis, mania or dementia or the need for treatment with psychiatric medications.
Interventions	1. 100 mg of naltrexone (n = 52) 2. 100 mg of naltrexone and 250 mg disulfiram (n = 49) 3. 250 mg disulfiram (n = 53) 4. placebo (n = 54) **Psychosocial treatment:** cognitive behavioral therapy; **applied manual:** Kadden et al. (1994) as applied in Project Match (Project Match Research Group 1997) Dosing: ascending; starting with 25 mg naltrexone up to for the first two treatment days up to 100 mg/day of naltrexone in week 4
Outcomes	1. days abstinent 2. heavy drinking days (≥5 (4) STD for men (women)) 3. side effects * relapse / heavy drinking: drinking ≥ 5 (4) SDU for men (women)
Financial support	National Institute on Drug Abuse (NIDA)
Data assessment methods	**Assessment of drinking:** TLFB interview (Sobell 1988; Sobell 1992); **assessment of side-effects:** SAFTEE (Levine 1986, Rabkin 1992); **assessment of compliance:** pill count
Treatment adherence	**Drop-out rates**: naltrexone: 32.7% (n = 17); disulfiram: 22.6% (n = 12); disulfiram + naltrexone: 40.8%% (n = 20); placebo: 40.7% (n = 22); **lost to follow-up rates**: not reported; **compliance rates** (% patients who took ≥ 80% of the medication): naltrexone: 58.5%; disulfiram: 35.1%; placebo: not reported
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Unclear	**Persons blinded:** no detailed information provided; **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)
Blinding? patient-reported outcomes	Yes	Breathalyzer test was used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Unclear	No objective outcomes reported in the trial publication
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; sensitivity of the results to the handling of missing data was examined with pattern-mixture analyses
Incomplete outcome data addressed? Continuous outcomes	Yes	**Principle of analysis:** ITT; **handling of missing data:** any alcohol use during a given study week resulted in that week being coded as a non-abstinent week; sensitivity of the results to the handling of missing data was examined with pattern-mixture analyses
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes
Susceptibility to bias reduced?	Yes	**Validation of patient-reported outcomes:** breathalyzer test; **laboratory assessment of drop-outs:** not reported

Schmitz 2004

Methods	**Title: Treatment of cocaine-alcohol dependence with naltrexone and relapse prevention therapy** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks; **principle of analysis:** not reported; **setting:** outpatient; **study sites:** 1; **country:** USA
Participants	**Diagnosis:** alcohol dependence (DSM-IV); **concurrent psychiatric diagnosis:** cocaine dependence; **required abstinence:** abstinence from alcohol during the intake evaluation was encouraged, but not required; no further information required; **baseline characteristics:** 83.7% male; mean age: 35.9 (SD = 6.4) years; 41.3% employed; **pre-baseline drinking:** 59.7% drinking days; **pre-baseline cocaine use:** 48.7% day with cocaine use; **exclusionary psychiatric conditions:** 1. a concurrent drug dependence (other than alcohol, cocaine, cannabis or nicotine); 2. a concurrent axis I disorder.
Interventions	1. 50 mg naltrexone + CBT (n = 20) 2. placebo + CBT (n = 20) 3. 50 mg naltrexone + drug counselling (n = 20) 4. placebo + drug counselling (n = 20) Psychosocial treatment: a) group 1 and 2: cognitive behavioral therapy (CBT); **applied manual:** Marlatt 1985; b) group 3 and 4: drug counselling; **applied manual:** Woody 1983
Outcomes	1. Drinking days 2. drinks per drinking day 3. side effects
Financial support	National Institute on Drug Abuse (NIDA)
Data assessment methods	**Assessment of drinking:** TLFB interview (Sobell 1988; Sobell 1992); modified version (weekly); **asssessment of side-effects:** side-effects checklist; **assessment of compliance:** riboflavin detection
Treatment adherence	**Drop-out rates**: 67% (no group specific values provided); **lost to follow-up rates**: not reported; **compliance rates** (% of urine samples positive for riboflavin): naltrexone: 93%; placebo: 83%
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Unclear	**Persons blinded:** no detailed information provided; **placebo appearance:** identical to active medication
Blinding? patient-reported outcomes	Unclear	No objective outcomes were used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Unclear	No objective outcomes reported in the trial publication
Incomplete outcome data addressed? Binary outcomes	Unclear	No binary outcomes considered in the study
Incomplete outcome data addressed? Continuous outcomes	Unclear	**Principle of analysis:** not reported; **handling of missing data:** not reported
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: *not reported ;* **equivalence of treatment attendance:** drop-out: yes; reasons for drop-out: *not reported*; lost to follow-up: *not reported*; compliance: yes
Susceptibility to bias reduced?	Unclear	**Validation of patient-reported outcomes:** not reported; **laboratory assessment of drop-outs:** not reported

Schmitz 2009

Methods	**Title: High-dose naltrexone therapy for cocaine-alcohol dependence** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks; **principle of analysis:** ITT; **setting:** outpatient; **study sites:** 1; **country:** United States
Participants	**Diagnosis:** alcohol dependence (DSM-IV); **concurrent psychiatric diagnosis:** cocaine dependence; **required abstinence:** no prior detoxification required; **baseline characteristics:** 87.3% male; mean age: 34.4 (SD = 4.5) years; 36% employed; **pre-baseline drinking:** 70% drinking days; 47.1% previous alcohol treatment. detoxifications; 21.7 (SD = 8.0) years of drinking; **pre-baseline cocaine use:** 81.2% crack cocaine consumption; 55% days with cocaine use during the last 30 days; **exclusionary psychiatric conditions:** 1. a concurrent drug abuse or dependence (other than alcohol, cocaine, cannabis or nicotine); 2. a concurrent major psychiatric disorder
Interventions	1. 100 mg naltrexone + CBT (n = 20) 2. 100 mg naltrexone + CBT + CM (n = 25) 3. Placebo + CBT (n = 27) 4. Placebo + CBT + CM (n = 14) **Psychosocial treatment:** a) group 1 and 3: cognitive behavioral therapy (CBT); **applied manual:** Marlatt 1985; **aim:** abstinence; b) group 2 and 4: contingency management (CM); **aim:** abstinence
Outcomes	1. Return to any drinking 2. Return to heavy drinking* 3. side effects * relapse / heavy drinking: drinking ≥ 5 (4) SDU for men (women)
Financial support	National Institute on Drug Abuse
Data assessment methods	**Assessment of drinking:** TLFB interview (week 0, 12, 24, 48; Sobell 1988; Sobell 1992); **assessment of side-effects:** standardized reporting system; **assessment of compliance:** pill count
Treatment adherence	**Drop-out rates**: 76%; no group specific values provided; **lost to follow-up rates:** not reported; **compliance rates** (% of urine samples positive for riboflavin): 50% - 80%; no group specific values provided
Notes	Information on the study design was subsequently provided by the investigators The manuscript has been provided from the investigators before publication

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Urn randomisation (information provided by the investigator)
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Unclear	**Persons blinded:** double-blind; no detailed information provided; **placebo appearance:** no detailed information provided
Blinding? patient-reported outcomes	Unclear	No objective outcomes were used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Unclear	No objective outcomes were reported in the trial publication
Incomplete outcome data addressed? Binary outcomes	Unclear	**Principle of analysis:** ITT; **handling of missing data:** not reported; it was supposed for the meta-analysis that lost to follow-ups have been categorized as relapsers in the survival analyses
Incomplete outcome data addressed? Continuous outcomes	Unclear	No continuous outcomes 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	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes
Susceptibility to bias reduced?	Unclear	**Validation of patient-reported drinking outcomes:** not reported; **laboratory assessment of drop-outs:** not reported

Volpicelli 1992

Methods	**Title: Naltrexone in the treatment of alcohol dependence** **Allocation:** random; **blinding:** double-blind; **study duration:** 12 weeks; **principle of analysis:** ITT; **setting:** outpatient; **study sites:** 1; **country:** USA
Participants	**Diagnosis:** alcohol dependence (DSM-III-R); **required abstinence:** ≤ 21 days; **baseline characteristics:** 100% male; mean age: 43.4 (SD=9.2) years; 44.3% married: 41.6% employed; **pre-baseline drinking:** 19.9 (SD = 9.0) years of heavy drinking; **exclusionary psychiatric conditions:** 1. a concurrent drug abuse of opiates, amphetamines, cocaine or barbiturates; 2. the use of narcotics within the past 30 days; 3. a concurrent major psychiatric disorder associated with psychosis, dementia, suicidality or homocidality
Interventions	1. 50 mg naltrexone (n = 35) 2. placebo (n = 35) **Psychosocial treatment:** standard rehabilitation treatment (group therapy, individual counselling, education) **Trial started with a placebo run-in week**
Outcomes	1. Return to any drinking 2. Return to heavy drinking* 3. drinking days 4. drinks per drinking day 5. craving 6. gamma-glutamyltransferase (GGT) 7. aspartate-aminotransferase (AST) *relapse / heavy drinking: drinking ≥ 5 (4) SDU per drinking for men (women) or having ≥ 5 drinking occasions per week or a blood alcohol concentration (BAC) ≥ 100mg/dl
Financial support	National Institute on Drug Abuse Research; National Institute on Alcohol Abuse and Alcoholism (NIAAA); Penn Veterans Affairs Addiction Research Center
Data assessment methods	**Assessment of drinking:** alcohol use questionnaire (weekly); **assessment of side-effects:** not reported; **assessment of compliance:** not reported
Treatment adherence	**Drop-out rates**: naltrexone: 31% (n = 11); placebo: 40.0% (n = 14); **lost to follow-up rates**: naltrexone: 5.7% (n = 2); placebo: 8.6% (n = 3); **compliance rates:** not reported
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomized; no detailed information provided
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Unclear	**Persons blinded:** double-blind; no detailed information provided; **placebo appearance:** identical to active medication
Blinding? patient-reported outcomes	Unclear	No objective outcomes were used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Unclear	No objective outcomes were reported in the trial publication
Incomplete outcome data addressed? Binary outcomes	Unclear	**Principle of analysis:** ITT; **handling of missing data:** not reported; it was supposed for the meta-analysis that lost to follow-ups have been categorized as relapsers
Incomplete outcome data addressed? Continuous outcomes	Unclear	**Principle of analysis:** ITT; **handling of missing data:** not reported
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency and intensity: yes; drinking history or treatment history: yes
Susceptibility to bias reduced?	Unclear	**Validation of patient-reported outcomes:** not reported; **laboratory assessment of drop-outs:** not reported

Volpicelli 1997

Methods	**Title: Naltrexone and alcohol dependence** **Allocation**: random; **blinding:** double-blind; **study duration:** 12 weeks; **principle of analysis:** ITT / available case analysis; **setting:** outpatient; **study sites:** 1; **country:** USA
Participants	**Diagnosis:** alcohol dependence (DSM-III-R); **required abstinence:** ≤ 21 days; **baseline characteristics:** 77.8% male; mean age: 41.2 (SD = 9.0) years; 44.5% married: 67.7% employed; **pre-baseline drinking:** 70% (SD = 2.9) drinking days; 15.4 (SD = 9.2) years of regular drinking; **exclusionary psychiatric conditions:** 1. the use of narcotics (past 30 days); 2. a concurrent major psychiatric disorder associated with psychosis, dementia, suicidality or homocidality; 3. a concurrent treatment with disulfiram
Interventions	1. 50 mg naltrexone (n = 48) 2. placebo (n = 49) **Psychosocial treatment:** individual psychotherapy; **applied manual:** Gorski 1986 **Trial started with a placebo run-in week**
Outcomes	1. Return to any drinking 2. Return to heavy drinking* 3. drinking days 4. craving (10-point scale) 5. gamma-glutamyltransferase level (GGT) 6. side-effects *relapse / heavy drinking: drinking ≥ 5 (4) SDU per drinking for men (women) or having ≥ 5 drinking occasions per week or a blood alcohol concentration (BAC) ≥ 100mg/dl
Financial support	National Institute on Alcohlism and Alcohol Abuse (NIAAA), Pennsylvania Veterans Affairs Medical Center, National Institute on Drug Abuse Center
Data assessment methods	**Assessment of drinking:** alcohol use questionnaire (weekly); **assessment of side-effects:** side-effects checklist (week 4, 8, 12); **assessment of compliance:** pill count
Treatment adherence	**Drop-out rates**: naltrexone: 27.1% (n = 13); placebo: 26.5% (n = 13); **lost to follow-up rates**: naltrexone: 0%; placebo: 0%; **compliance rates** (% patients taking medication on 90% of the study days): naltrexone: 58,3%; placebo: 46.9%
Notes	Subgroup analysis: degree of compliance

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Randomized in computer-generated blocks
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Unclear	**Persons blinded:** double-blind; no detailed information provided; **placebo appearance:** identical to active medication
Blinding? patient-reported outcomes	Unclear	No objective outcomes were used for a validity check of patient-reported drinking outcomes
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Unclear	**Principle of analysis:** ITT; **handling of missing data:** not reported; it was supposed for the meta-analysis that lost to follow-ups have been categorized as relapsers
Incomplete outcome data addressed? Continuous outcomes	No	**Principle of analysis:** available case analysis; **handling of missing data:** if data were not obtained beyond the baseline period, the subject was dropped from the data analysis for that particular variable
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency: yes; drinking history or treatment history: yes
Susceptibility to bias reduced?	Unclear	**Validation of patient-reported outcomes:** not reported; **laboratory assessment of drop-outs:** not reported

Ziółkowski 2000

Methods	**Title: Naltrexone exerts a favourable effect on drinking in patients with alcohol dependence** **Allocation:** random; **blinding:** double-blind; **study duration:** 16 weeks (treatment); 8 months (post-treatment); **principle of analysis:** ITT; **setting:** inpatient (week 1-4); outpatient (week 5-16); **study sites:** 1; **country:** Poland
Participants	**Diagnosis:** alcohol dependence (ICD-10); **required abstinence:** not reported; **baseline characteristics:** 100% male; mean age: 39.0 (SD = 7) years; **pre-baseline drinking:** 52.3% (SD = 30.7) drinking days; 7.5 (SD = 6.9) drinks per day; 13 (SD = 6) years of alcohol dependence; MAST score: 42 (SD = 13); **exclusionary psychiatric conditions:** a concurrent treatment with psychoactive medication others than benzodiazepines
Interventions	1. 50 mg naltrexone (n = 40) 2. 600-800 mg carbamazepine (n = 40) 3. 500-1000 mg lithium carbonate (n = 39) 4. Placebo (n = 41) **Psychosocial treatment:** before randomisation, patients were treated with psychosocial therapy for four weeks
Outcomes	1. Return to any drinking 2. Return to heavy drinking* 3. total cholesterol 4. HDL cholesterol 5. LDL cholesterol 6. fasting triglyceride 7. gamma-glutamyltransferase (GGT) 8. aspartat-amino-transferase (AST) 9. alanine-amino-transferase (ALT) * relapse / heavy drinking: drinking ≥ 5 (4) SDU for men (women)
Financial support	Polish-American M. Curie-Sklodowska grant
Data assessment methods	**Assessment of drinking:** TLFB interview (week 2, 4, 6, 8, 10, 12, 14, 16, 24, 28, 42; Sobell 1988; Sobell 1992); **assessment of side-effects:** not reported; **assessment of compliance:** riboflavin detection
Treatment adherence	**Drop-out rates**: no information available; **lost to follow-up rates**: naltrexone: 0%; placebo: 0%; **compliance rates:** no information available
Notes	Rates of continuous abstinence and information on the study design was subsequently provided by the investigator Published in book format; language: Polish (partly translated by the investigators for the review) A publication of the trial (Budzynski 2000), which mainly concerns effects on laboratory values has additionally been used for data extraction

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Computer randomisation (information provided by the investigator)
Allocation concealment?	Unclear	No detailed information provided
Blinding? all outcomes	Yes	**Persons blinded:** double-blind, including patients, research stuff (information provided by the investigator); **placebo appearance:** identical to active medication
Blinding? patient-reported outcomes	Yes	Knowledge of the allocated interventions was adequately prevented during the study (see "Blinding (all outcomes)")
Blinding? objective outcomes	Yes	Objective outcomes are less susceptible to bias due to a lack of blindness
Incomplete outcome data addressed? Binary outcomes	Yes	**Principle of analysis:** ITT; **handling of missing data:** none of the patients were lost to follow up
Incomplete outcome data addressed? Continuous outcomes	Unclear	No continuous outcomes provided
Free of selective reporting?	Yes	**Outcome reporting:** all outcomes stated in the methods section are adequately reported in the results section
Free of other bias?	Yes	**Baseline equivalence:** socio-demographic variables: yes; drinking frequency: yes; drinking history or treatment history: *not reported*
Susceptibility to bias reduced?	Unclear	**Validation of patient-reported outcomes:** various laboratory indicators like Glutamat-Pyruvat-Transaminase (GPT) and aspartate aminotransferase (AspAT) were assessed; unclear if used to validate patient-reported outcomes; **laboratory assessment of drop-outs:** collateral reports

Footnotes

Characteristics of excluded studies

Buri 2007

Reason for exclusion	open trial; non-randomised

Caputo 2003

Reason for exclusion	open trial

Caputo 2007

Reason for exclusion	open trial

Carroll 1993

Reason for exclusion	open trial

Croop 1997

Reason for exclusion	open trial; non-randomised

Davidson 2004

Reason for exclusion	sample: hazardous drinkers

Davidson 2007a

Reason for exclusion	no active or placebo control group (naltrexone + broad-spectrum treatment versus naltrexone + MET)

Davidson 2007b

Reason for exclusion	multiphase study, starting with open-label naltrexone treatment in the intervention and control group

De Sousa 2004

Reason for exclusion	open trial

Deas 2005

Reason for exclusion	open trial

Drobes 2000

Reason for exclusion	treatment duration: 7 days (laboratory study)

Drobes 2004

Reason for exclusion	treatment duration: 7 days (laboratory study)

Dunbar 2006

Reason for exclusion	sample: healthy patients (pharmacokinetic study)

Farren 2009

Reason for exclusion	no active or placebo control for naltrexone (naltrexone + sertraline placebo versus naltrexone + sertraline)

Galloway 2005

Reason for exclusion	open trial

Hermos 2004

Reason for exclusion	open trial

Hernandez-Avila 2006

Reason for exclusion	sample: problem drinkers

Johnson 2003

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

Karhuvaara 2007

Reason for exclusion	sample: heavy drinkers

Knox 1999

Reason for exclusion	treatment duration: 21 days

Kranzler 1997

Reason for exclusion	sample: problem drinkers

Kranzler 2004a

Reason for exclusion	treatment duration: 7 days (laboratory study)

Kranzler 2004b

Reason for exclusion	sample: problem drinkers

Kranzler 2008

Reason for exclusion	open trial

Laaksonen 2008

Reason for exclusion	open trial

Landabaso 1999

Reason for exclusion	open trial

Martinotti 2007

Reason for exclusion	open trial

Mason 2002

Reason for exclusion	sample: healthy patients (pharmacokinetic study)

Modesto-Lowe 1997

Reason for exclusion	treatment duration: 7 days (laboratory study)

Myrick 2008

Reason for exclusion	treatment duration: 7 days (laboratory study)

Nava 2006

Reason for exclusion	open trial

O'Malley 2003

Reason for exclusion	multiphase study, starting with open-label naltrexone treatment in the intervention and control group

Ooteman 2007

Reason for exclusion	treatment duration: 21 days

Oslin 1999

Reason for exclusion	open trial

Palfai 1999

Reason for exclusion	sample: hazardous drinkers

Ponce 2005

Reason for exclusion	single-blinded

Ray 2007

Reason for exclusion	sample: heavy drinkers

Rubio 2001

Reason for exclusion	single-blind

Rubio 2002

Reason for exclusion	open trial

Rubio 2005

Reason for exclusion	single-blinded

Stella 2008

Reason for exclusion	open trial

Tidey 2008

Reason for exclusion	sample: heavy drinkers

Tucker 2004

Reason for exclusion	no active or placebo control group (naltrexone + group counselling program versus naltrexone + structured treatment program)

Turncliff 2005

Reason for exclusion	sample: hepatic impaired patients (pharmacokinetic study)

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

ALK21-010

Study name	Long-Term Safety Study of Naltrexone Long Acting Injection in Alcohol Dependent Adults
Methods	Randomized, double-blind, placebo-control, parallel assignment
Participants	Alcohol dependent patients
Interventions	Naltrexone (extended release) and Placebo
Outcomes	1. Long-term safety 2. Social functioning 3. Healthcare utilization 4. Drinking behaviour
Starting date	October 2003
Contact information	---
Principal investigator	---
Collaborators	---
Sponsor	Alkermes
Notes	Completion date: January 2007

Anton 2009

Study name	Effectiveness of Gabapentin When Used With Naltrexone to Treat Alcohol Dependence Compared to Placebo and Naltrexone Alone
Methods	Randomized, double-blind, placebo-control, factorial assignment
Participants	Alcohol dependent patients
Interventions	Naltrexone, gabapentin, placebo
Outcomes	1. Time to relapse to drinking 2. Percent days drinking 3. Drinks per drinking dayRetention in the protocol 4. Craving for alcohol 5. CDT and GGT 6. Psychological and general health functioning 7. Consequences of drinking 8. Urinary riboflavin 9. Liver function tests (ALT and AST)
Starting date	January 2003
Contact information	---
Principal investigator	Raymond F. Anton, MD, Medical University of South Carolina
Collaborators	---
Sponsor	National Institute on Alcohol Abuse and Alcoholism (NIAAA)
Notes	completion date: April 2009

Batki 2007

Study name	Naltrexone Treatment of Alcohol Abuse in Schizophrenia
Methods	Randomized, double-blind, placebo-control, single group assignment
Participants	Patients with alcohol abuse or alcohol dependence and with schizophrenia or schizoaffective disorder
Interventions	Naltrexone vs. placebo
Outcomes	1. Measures of Alcohol Use 2. Psychiatric Symptom Severity
Starting date	April 2003
Contact information	Steven L Batki, M.D. batkis@upstate.edu
Principal investigator	Steven L Batki, MD, State University of New York, Upstate Medical University
Collaborators	National Institute on Alcohol Abuse and Alcoholism (NIAAA)
Sponsor	State University of New York - Upstate Medical University
Notes	Related publication: PMID: 18701256; no NTX vs. PBO results provided: completion date: October 2007

Brown

Study name	Naltrexone for Bipolar Disorder and Alcohol Dependence
Methods	Randomized, double-blind, placebo-control, crossover assignment
Participants	Alcohol dependent patients with concurrent bipolar disorder (I or II)
Interventions	Naltrexone vs. placebo
Outcomes	---
Starting date	May 2005
Contact information	----
Principal investigator	Edson S Brown, MD, PhD, UT Southwestern Medical Center Dallas
Collaborators	---
Sponsor	University of Texas Southwestern Medical Center
Notes	In PubMed only a open label study from the author is published (PMID: 16841344); no completion date mentioned

Foa 2009

Study name	Treatment for Alcoholism and Post-Traumatic Stress Disorder (Naltrexone)
Methods	Randomized, double-blind, placebo-controlled, factorial assignment
Participants	Alcohol dependent patients with post-traumatic stress disorder
Interventions	Naltrexone vs. placebo
Outcomes	1. Drinking frequency and amount (TLFB) 2. PTSD Symptom Scale 3. Beck Depression Inventory 4. Penn Alcohol Cravings Scale 5. Sheehan Disability Scale
Starting date	December 2000
Contact information	Edna B. Foa, PhD foa@mail.med.upenn.edu
Principal investigator	Edna B. Foa, PhD University of Pennsylvania
Collaborators	---
Sponsor	National Institute on Alcohol Abuse and Alcoholism (NIAAA)
Notes	Conpletion date: January 2009

Garbutt 2009

Study name	Combination of Naltrexone and Baclofen for Alcohol Dependence: A Pilot Study
Methods	Randomized, double-blind, placebo-controlled, parallel assignment
Participants	Alcohol dependent patients
Interventions	Naltrexone, Baclofen, Placebo
Outcomes	1. Retention of study 2. Compliance
Starting date	July 2007
Contact information	Linda S Kalka-Juhl lkjuhl@med.unc.edu
Principal investigator	James C Garbutt, M.D., The University of North Carolina, Chapel Hill
Collaborators	---
Sponsor	University of North Carolina
Notes	Completion date: March 2009

Grabowski 2007

Study name	Naltrexone as Adjunct in Alcoholic Cocaine Dependent Patients
Methods	---
Participants	alcohol dependent patients with concurrent cocaine dependence
Interventions	Naltrexone, placebo
Outcomes	Verified abstinence from cocaine
Starting date	April 2003
Contact information	---
Principal investigator	John Grabowski, Ph.D. University of Texas
Collaborators	University of Texas
Sponsor	National Institute on Drug Abuse (NIDA)
Notes	Completion date: April 2007

Haber 2005

Study name	Trial for the Treatment of Alcohol Dependence
Methods	Randomized, double-blind, placebo-control, parallel assignment
Participants	Alcohol dependent patients
Interventions	Naltrexone, acamprosate
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. Secondary Outcome Measure 7. Craving 8. Depression 9. Anxiety 10. Stress 11. Global physical health 12. Global mental health
Starting date	March 2003
Contact information	---
Principal investigator	Paul Haber, MBBAMDFRACP, Conjoint Associate Professor
Collaborators	National Health and Medical Research Council, Australia Sydney South West Area Health Service South Eastern Area Health Service Wentworth Area Health Services
Sponsor	University of Sydney
Notes	Completion date: June 2005

Johnson

Study name	Combined Pharmacotherapies for Alcoholism (Naltrexone/Ondansetron)
Methods	Randomized, double-blind
Participants	Alcohol dependent patients
Interventions	Naltrexone, ondansetron
Outcomes	---
Starting date	September 2001
Contact information	---
Principal investigator	---
Collaborators	---
Sponsor	National Institute on Alcohol Abuse and Alcoholism (NIAAA)
Notes	Completion date: August 2004

Johnson 2009

Study name	Combining Medications for the Treatment of Alcohol Dependence: An Inpatient Preliminary Study
Methods	Randomized, double-blind, placebo-control, cross-over assignment
Participants	Alcohol dependent patients
Interventions	Naltrexone, Topiramate, Placebo
Outcomes	Safety and efficacy
Starting date	October 2008
Contact information	Mindy Borszich uvacare@virginia.edu
Principal investigator	Bankole Johnson, DSc,MD.PhD, University of Virginia
Collaborators	---
Sponsor	University of Virginia
Notes	Completion date: December 2009

Lundbeck 2010

Study name	Safety of Nalmefene in Patients With Alcohol Dependence (SENSE)
Methods	Randomized, double-blind, placebo-control, parallel assignment
Participants	Alcohol dependent patients
Interventions	Nalmefene, placebo
Outcomes	1. Adverse events 2. Clinical safety laboratory tests, 3. Vital signs, weight, 4. Body mass index, electrocardiograms, 5. Profile of moods states and physical examination
Starting date	December 2008
Contact information	H. Lundbeck A/S LundbeckClinicalTrials@lundbeck.com
Principal investigator	--
Collaborators	--
Sponsor	H. Lundbeck A/S
Notes	Completion date: November 2010

Lundbeck 2011

Study name	Efficacy of Nalmefene in Patients With Alcohol Dependence (ESENSE1/2)
Methods	Randomized, double-blind, placebo-control, parallel assignment
Participants	Alcohol dependent patients
Interventions	Nalmefene, placebo
Outcomes	1. Heavy drinking days 2. Total alcohol consumption
Starting date	December 2008
Contact information	H. Lundbeck A/S LundbeckClinicalTrials@lundbeck.com
Principal investigator	--
Collaborators	--
Sponsor	H. Lundbeck A/S
Notes	Completion date: February 2011

Mann 2008

Study name	Individually Adapted Therapy of Alcoholism
Methods	Randomized, double-blind, placebo-control, parallel assignment
Participants	Alcohol dependent patients
Interventions	Naltrexone, acamprosate, 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, J5, 68159 Mannheim, Germany Michael N. Smolka, MD, Central Institute of Mental Health, J5, 68159 Mannheim, Germany
Collaborators	BMBF Federal Ministry of Education and Research Merck Dupont Pharmaceuticals
Sponsor	Central Institute of Mental Health, Mannheim
Notes	

Mann 2010

Study name	Efficacy and Safety of Vivitrol® After Enforced Abstinence
Methods	Randomized, double-blind, placebo-control, parallel assignment
Participants	Alcohol dependent patients
Interventions	Naltrexone (extended-release) vs. placebo
Outcomes	1. Heavy drinking days 2. Percent heavy drinking days 3. Percent days abstinent 4. Days to first drinking day 5. Days to first heavy drinking 6. Obsessive-Compulsive Drinking Scale scores 7. Gamma glutamyl-transferase levels
Starting date	July 2007
Contact information	Petra Falkenstein falkenstein.petra@kendle.com
Principal investigator	Karl Mann, Prof, MD, University of Heidelberg (Study Chair)
Collaborators	Kendle International
Sponsor	Alkermes
Notes	Completion date: August 2010

Mason

Study name	Naltrexone Maintenance Treatment of Alcoholism
Methods	Randomized, double-blind
Participants	Alcohol dependent patients
Interventions	Naltrexone, Placebo
Outcomes	---
Starting date	---
Contact information	---
Principal investigator	---
Collaborators	---
Sponsor	National Institute on Alcohol Abuse and Alcoholism (NIAAA)
Notes	April 2002

O'Brien 2007

Study name	Naltrexone in Two Models of Psychosocial Treatments for Cocaine and Alcohol Dependence - 1
Methods	Randomized, double-blind, placebo-controlled
Participants	Alcohol dependent patients with concurrent cocaine dependence
Interventions	Naltrexone, Placebo
Outcomes	Alcohol and Cocaine use
Starting date	April 1998
Contact information	---
Principal investigator	Charles O'Brien, M.D., Ph.D. University of Pennsylvania
Collaborators	University of Pennsylvania
Sponsor	National Institute on Drug Abuse (NIDA)
Notes	Completion date: November 2007

Oslin 2008b

Study name	Managing Alcoholism in People Who Do Not Respond to Naltrexone (EXTEND)
Methods	Randomized, double-blind, placebo-control, parallel assignment
Participants	Alcohol dependent patients
Interventions	Naltrexone vs. placebo
Outcomes	Reduction in alcohol use
Starting date	September 2003
Contact information	----
Principal investigator	David W. Oslin, M.D. University of Pennsylvania
Collaborators	---
Sponsor	National Institute on Alcohol Abuse and Alcoholism (NIAAA)
Notes	Cpmpletion data: September 2008

Petrakis 2009

Study name	Naltrexone & SSRI in Alcoholics With Depression/PTSD
Methods	Randomized, double-blind, placebo-control, parallel assignment
Participants	Alcohol dependent patients
Interventions	Naltrexone, paroxetine, desipramine, placebo
Outcomes	1. Alcohol consumption 2. Craving 3. Psychiatric and emotional distress 4. Psychiatric symptoms of depression and PTSD 5. Side effects
Starting date	Randomized, double-blind, placebo-control
Contact information	Alcohol dependent patients with comorbid PTSD and depression
Principal investigator	Naltrexone, paroxetine, desipramine, placebo
Collaborators	---
Sponsor	Yale University
Notes	Completion date: August 2009

Pettinati 2009

Study name	Sertraline for Alcohol Dependence and Depression
Methods	Randomized, double-blind, placebo-control, factorial assignment
Participants	Alcohol dependent patients with concurrent cocaine dependence
Interventions	Naltrexone, sertraline, placebo
Outcomes	1. Alcohol use 2. Depressive symptoms
Starting date	January 2000
Contact information	---
Principal investigator	Helen Pettinati, PhD University of Pennsylvania
Collaborators	---
Sponsor	National Institute on Alcohol Abuse and Alcoholism (NIAAA)
Notes	Completion date: April 2009

Pettinati 2012

Study name	Extended-Release Injectable Naltrexone as a Treatment for Alcohol and Cocaine Dependence
Methods	Randomized, double-blind, placebo-control, single group assignment
Participants	Alcohol dependent patients with concurrent cocaine dependence
Interventions	Naltrexone extended-release vs. placebo
Outcomes	1. Days of abstinence from drinking (TLFB) 2. urine assay for benzoylecgonine (BE) 3. craving
Starting date	November 2008
Contact information	Donna Simpson
Principal investigator	Helen Pettinati, Ph.D., University of Pennsylvania
Collaborators	University of Pennsylvania Alkermes
Sponsor	National Institute on Drug Abuse (NIDA)
Notes	Completion date: November 2012

Salloum

Study name	Drug Treatment for Depressed Alcoholics (Naltrexone/Fluoxetine)
Methods	Randomized, double-blind, controlled, parallel assignment
Participants	Alcohol dependent patients with comorbid major depressive disorder
Interventions	Naltrexone + fluoxetine, fluoxetine alone
Outcomes	1. Alcohol us (TLFB) 2. Hamilton Rating Scale for Depression
Starting date	March 2000
Contact information	----
Principal investigator	Ihsan M. Salloum, MD Western Psychiatric Institute, Clinic of the University of Pittsburgh Medical Center, Pittsburgh, PA
Collaborators	---
Sponsor	National Institute on Alcohol Abuse and Alcoholism (NIAAA)
Notes	not identified in PubMed; Completion date: January 2006

Salloum 2007

Study name	Optimizing Pharmacotherapy for Bipolar Alcoholics
Methods	Randomized, double-blind, controlled, parallel assignment
Participants	Alcohol dependent patients with comorbid bipolar disorder
Interventions	Naltrexone + valproate, valproate
Outcomes	1. Quantity of alcohol consumption 2. Frequency of alcohol consumption
Starting date	May 2006
Contact information	---
Principal investigator	Ihsan M Salloum, MD, MPH UPMC and University of Pittsburgh
Collaborators	National Institute on Alcohol Abuse and Alcoholism (NIAAA)
Sponsor	University of Pittsburgh
Notes	Completion date: March 2007

Schmitz

Study name	Combined Treatment for Cocaine-Alcohol Dependence - 1
Methods	Randomized, double-blind, placebo-control, single group assignment
Participants	Alcohol dependent patients with concurrent cocaine dependence
Interventions	Naltrexone, placebo
Outcomes	Urine toxicology for cocaine
Starting date	April 2003
Contact information	----
Principal investigator	Joy Schmitz, Ph.D., The University of Texas Health Science Center, Houston
Collaborators	The University of Texas Health Science Center, Houston
Sponsor	National Institute on Drug Abuse (NIDA)
Notes	only a older study was identified in PubMed PMID: 15370932; completion date: December 2007

Toneatto

Study name	Naltrexone in the Treatment of Concurrent Alcohol Dependence and Pathological Gambling
Methods	Randomized, double-blind, placebo-controlled
Participants	Alcohol dependent patient with concurrent pathological gambling
Interventions	Naltrexone vs. placebo
Outcomes	1. Frequency of drinking/gambling 2. Amount of drinking/gambling 3. Gambling Urge Questionnaire 4. Obsessive Compulsive Drinking Scale 5. Readiness to Change Questionnaire 6. Money spent of gambling
Starting date	June 2001
Contact information	---
Principal investigator	Tony Toneatto, PhD, Centre for Addiction and Mental Health
Collaborators	
Sponsor	Centre for Addiction and Mental Health
Notes	Not identified with PubMed; completion date: June 2004

Footnotes

Summary of findings tables

Additional tables

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Batki 2007

[ClinicalTrials.gov: NCT00145847; Other: SUNY UMU IRB # 4800]

Brown

[ClinicalTrials.gov: NCT00223275 ; Other: PA-03-107]

Foa 2009

Unpublished data only [ClinicalTrials.gov: NCT00006489; Other: NIAAAFOA12428]

Garbutt 2009

[ClinicalTrials.gov: NCT00614328; Other: 05-2988 GCRC 2497]

Grabowski 2007

Unpublished data only [ClinicalTrials.gov: NCT00000307; Other: NIDA-09262-4]

Haber 2005

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

Johnson

Unpublished data only [ClinicalTrials.gov: NCT00027079; Other: NIAAAJOH12964]

Johnson 2009

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Lundbeck 2010

[ClinicalTrials.gov: NCT00811941; Other: 12013A]

Lundbeck 2011

[ClinicalTrials.gov: NCT00811720; Other: 12013A]

Mann 2008

Unpublished data only [ClinicalTrials.gov: NCT00317031; Other: PREDICT]

Mann 2010

Unpublished data only [ClinicalTrials.gov: NCT00501631 ; Other: ALK21-014]

Mason

Unpublished data only [ClinicalTrials.gov: NCT00000450; Other: NIAAAMAS10518]

O'Brien 2007

Unpublished data only [ClinicalTrials.gov: NCT00218660; Other: NIDA-5186-1]

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Petrakis 2009

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Pettinati 2012

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Salloum

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Other published versions of this review

Classification pending references

Data and analyses

1 NTX versus PBO

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Return to heavy drinking	28	4433	Risk Ratio (M-H , Random , 95% CI)	0.83 [0.76, 0.90]
1.2 Return to any drinking	27	4693	Risk Ratio (M-H , Random , 95% CI)	0.96 [0.92, 1.00]
1.3 Drinking days	26	3882	Mean Difference (IV , Random , 95% CI)	-3.89 [-5.75, -2.04]
1.4 Heavy drinking days	15	1715	Mean Difference (IV , Random , 95% CI)	-3.25 [-5.51, -0.99]
1.5 Consumed amount per drinking day	16	1838	Mean Difference (IV , Random , 95% CI)	-10.83 [-19.69, -1.97]
1.6 GGT	16	1645	Mean Difference (IV , Random , 95% CI)	-10.37 [-18.99, -1.75]
1.7 Side effect: Any	9	1021	Risk Difference (M-H , Random , 95% CI)	0.05 [0.01, 0.09]
1.8 Side effect: Abdominal pain	13	1756	Risk Difference (M-H , Random , 95% CI)	0.08 [0.04, 0.11]
1.9 Side effect: Agitation	2	217	Risk Difference (M-H , Random , 95% CI)	-0.00 [-0.05, 0.04]
1.10 Side effect: Anxiety	9	1118	Risk Difference (M-H , Random , 95% CI)	0.02 [-0.02, 0.06]
1.11 Side effect: Arthralgia	2	327	Risk Difference (M-H , Random , 95% CI)	0.01 [-0.12, 0.13]
1.12 Aide effect: Back pain	4	1287	Risk Difference (M-H , Random , 95% CI)	0.01 [-0.02, 0.04]
1.13 Side effect: Blurred vision	3	278	Risk Difference (M-H , Random , 95% CI)	0.13 [0.04, 0.21]
1.14 Side effect: Confusion	3	517	Risk Difference (M-H , Random , 95% CI)	0.13 [-0.04, 0.31]

1.15 Side effect: Constipation	5	545	Risk Difference (M-H , Random , 95% CI)	0.03 [-0.04, 0.10]
1.16 Side effect: Coughing	2	327	Risk Difference (M-H , Random , 95% CI)	0.02 [-0.08, 0.12]
1.17 Side effect: Daytime sleepiness	12	2802	Risk Difference (M-H , Random , 95% CI)	0.09 [0.05, 0.14]
1.18 Side-effect: Decreased appetite	12	2141	Risk Difference (M-H , Random , 95% CI)	0.07 [0.03, 0.11]
1.19 Side-effect: Decreased libido	3	388	Risk Difference (M-H , Random , 95% CI)	0.08 [0.01, 0.16]
1.20 Side-effect: Depression	4	467	Risk Difference (M-H , Random , 95% CI)	0.04 [0.00, 0.08]
1.21 Side effect: Diarrhea	12	2294	Risk Difference (M-H , Random , 95% CI)	-0.01 [-0.05, 0.03]
1.22 Side effect: Dizziness	16	2655	Risk Difference (M-H , Random , 95% CI)	0.06 [0.04, 0.08]
1.23 Side effect: Drowsiness	5	495	Risk Difference (M-H , Random , 95% CI)	0.10 [0.00, 0.19]
1.24 Side effect: Dyspepsia	2	327	Risk Difference (M-H , Random , 95% CI)	-0.06 [-0.11, NaN]
1.25 Side effect: Dry mouth	8	863	Risk Difference (M-H , Random , 95% CI)	0.03 [-0.03, 0.08]
1.26 Side effect: Fatigue	7	882	Risk Difference (M-H , Random , 95% CI)	0.05 [0.01, 0.09]
1.27 Side effect: Fever	2	287	Risk Difference (M-H , Random , 95% CI)	-0.06 [-0.16, 0.05]
1.28 Side effect: Flue-like symptoms	3	902	Risk Difference (M-H , Random , 95% CI)	-0.01 [-0.06, 0.03]
1.29 Side effect: Headache	22	3633	Risk Difference (M-H , Random , 95% CI)	0.01 [-0.02, 0.04]
1.30 Side effect: Increased libido	3	367	Risk Difference (M-H , Random , 95% CI)	0.03 [-0.11, 0.16]
1.31 Side effect: Insomnia	14	2080	Risk Difference (M-H , Random , 95% CI)	0.03 [0.00, 0.06]
1.32 Side effect: Injection pain	4	1007	Risk Difference (M-H , Random , 95% CI)	0.06 [-0.03, 0.14]
1.33 Side effect: Irregular heartbeat	2	154	Risk Difference (M-H , Random , 95% CI)	0.01 [-0.15, 0.16]
1.34 Side effect: Irritability	4	594	Risk Difference (M-H , Random , 95% CI)	0.02 [-0.05, 0.08]
1.35 Side effect: Lethargy	2	227	Risk Difference (M-H , Random , 95% CI)	0.13 [0.04, 0.23]
1.36 Side effect: Lightheadedness	3	219	Risk Difference (M-H , Random , 95% CI)	0.15 [-0.08, 0.37]
1.37 Side effect: Muscle stiffness	2	195	Risk Difference (M-H , Random , 95% CI)	-0.05 [-0.46, 0.35]
1.38 Side effect: Nasal problems	3	1088	Risk Difference (M-H , Random , 95% CI)	0.03 [-0.07, 0.13]
1.39 Side effect: Nausea	25	4334	Risk Difference (M-H , Random , 95% CI)	0.10 [0.07, 0.13]
1.40 Side effect: Nervousness	2	210	Risk Difference (M-H , Random , 95% CI)	0.00 [-0.03, 0.03]
1.41 Side-effect Nightmares	3	258	Risk Difference (M-H , Random , 95% CI)	0.10 [0.04, 0.16]
1.42 Side effect: Pain	6	1154	Risk Difference (M-H , Random , 95% CI)	0.02 [-0.04, 0.07]

1.43 Side effect: Palpitation	2	73	Risk Difference (M-H , Random , 95% CI)	0.03 [-0.06, 0.12]
1.44 Side-effect Pruritus	3	320	Risk Difference (M-H , Random , 95% CI)	-0.00 [-0.07, 0.07]
1.45 Side effect: Restlessness	2	154	Risk Difference (M-H , Random , 95% CI)	0.02 [-0.32, 0.36]
1.46 Side effect: Serious adverse events	9	1526	Risk Difference (M-H , Random , 95% CI)	-0.02 [-0.05, NaN]
1.47 Side effect: Sexual dysfunction	3	348	Risk Difference (M-H , Random , 95% CI)	-0.03 [-0.06, 0.00]
1.48 Side effect: Skin rash	5	313	Risk Difference (M-H , Random , 95% CI)	0.01 [-0.04, 0.05]
1.49 Side effect: Somnolence	5	974	Risk Difference (M-H , Random , 95% CI)	0.10 [0.05, 0.14]
1.50 Side effect: Tremor	3	207	Risk Difference (M-H , Random , 95% CI)	0.09 [-0.01, 0.20]
1.51 Side effect: Upper respiratory problems	5	1221	Risk Difference (M-H , Random , 95% CI)	-0.02 [-0.08, 0.05]
1.52 Side effect: Vomiting	14	2746	Risk Difference (M-H , Random , 95% CI)	0.07 [0.04, 0.09]
1.53 Side effect: Weakness	2	188	Risk Difference (M-H , Random , 95% CI)	0.17 [0.05, 0.29]
1.54 Drop-outs due to adverse events	22	3393	Risk Ratio (M-H , Random , 95% CI)	1.60 [1.15, 2.23]
1.55 Drop-outs	37	5572	Risk Ratio (M-H , Random , 95% CI)	0.92 [0.83, 1.01]
1.56 Post-treatment: Return to heavy drinking	5	1061	Risk Ratio (M-H , Random , 95% CI)	0.86 [0.75, 0.99]
1.57 Post-treatment: Return to any drinking	2	185	Risk Ratio (M-H , Fixed , 95% CI)	0.94 [0.79, 1.11]
1.58 Sensitivity analysis: Statistical model	27	4693	Risk Ratio (M-H , Fixed , 95% CI)	0.95 [0.92, 0.98]
1.59 Sensitivity analysis: Funding source	26	4246	Risk Ratio (M-H , Random , 95% CI)	0.86 [0.79, 0.92]
1.59.1 Industry sponsored	7	1121	Risk Ratio (M-H , Random , 95% CI)	0.90 [0.78, 1.05]
1.59.2 Non-profit sponsored	19	3125	Risk Ratio (M-H , Random , 95% CI)	0.84 [0.77, 0.91]
1.60 Outcome selection bias	27	4693	Risk Ratio (M-H , Random , 95% CI)	0.96 [0.92, 1.00]
1.60.1 Reported results	20	2917	Risk Ratio (M-H , Random , 95% CI)	0.94 [0.90, 1.00]
1.60.2 Subsequently provided results	7	1776	Risk Ratio (M-H , Random , 95% CI)	0.98 [0.92, 1.04]

2 Subgroup analysis: NTX injectable

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Return to any drinking	2	486	Risk Ratio (M-H , Random , 95% CI)	0.92 [0.84, 1.00]
2.2 Drinking days	2	335	Mean Difference (IV , Fixed , 95% CI)	-8.54 [-15.77, -1.31]
2.3 Heavy drinking days	3	357	Mean Difference (IV , Random , 95% CI)	-3.05 [-8.46, 2.35]
2.4 Side effect: Abdominal pain	3	487	Risk Difference (M-H , Random , 95% CI)	0.12 [-0.01, 0.26]
2.5 Side effect: Daytime sleepiness	2	50	Risk Difference (M-H , Random , 95% CI)	0.22 [0.02, 0.42]

2.6 Side effect: Decreased appetite	2	654	Risk Difference (M-H , Random , 95% CI)	0.08 [0.04, 0.11]
2.7 Side effect: Dizziness	2	654	Risk Difference (M-H , Random , 95% CI)	0.08 [0.04, 0.12]
2.8 Side effect: Fatigue	2	957	Risk Difference (M-H , Random , 95% CI)	0.06 [0.01, 0.10]
2.9 Side effect: Headache	4	1007	Risk Difference (M-H , Random , 95% CI)	0.03 [-0.02, 0.08]
2.10 Side effect: Insomnia	2	644	Risk Difference (M-H , Random , 95% CI)	0.02 [-0.04, 0.07]
2.11 Side effect: Injection pain	4	1007	Risk Difference (M-H , Random , 95% CI)	0.06 [-0.03, 0.14]
2.12 Side effect: Nasopharyngitis	2	957	Risk Difference (M-H , Random , 95% CI)	-0.01 [-0.08, 0.05]
2.13 Side effect: Nausea	4	1007	Risk Difference (M-H , Random , 95% CI)	0.10 [-0.01, 0.22]
2.14 Side effect: Serious adverse events	3	977	Risk Difference (M-H , Random , 95% CI)	-0.02 [-0.05, NaN]
2.15 Side effect: Vomiting	2	654	Risk Difference (M-H , Random , 95% CI)	0.06 [0.02, 0.11]
2.16 Drop-outs due to adverse events	3	969	Risk Ratio (M-H , Random , 95% CI)	1.57 [0.92, 2.69]
2.17 Drop-out	3	979	Risk Ratio (M-H , Random , 95% CI)	0.98 [0.68, 1.40]

3 NTX versus ACAM

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
3.1 Return to heavy drinking	3	800	Risk Ratio (M-H , Random , 95% CI)	0.96 [0.87, 1.06]
3.2 Return to any drinking	3	800	Risk Ratio (M-H , Random , 95% CI)	0.97 [0.91, 1.04]
3.3 Drinking days	2	720	Mean Difference (IV , Random , 95% CI)	2.98 [-7.45, 13.42]
3.4 Side-effect: Diarrhea	2	720	Risk Difference (M-H , Random , 95% CI)	-0.27 [-0.34, -0.20]
3.5 Side-effect: Nausea	3	800	Risk Difference (M-H , Random , 95% CI)	0.08 [0.03, 0.13]
3.6 Side-effect: Somnolence	2	720	Risk Difference (M-H , Random , 95% CI)	0.07 [0.01, 0.13]
3.7 Drop-out due to adverse events	3	800	Risk Ratio (M-H , Random , 95% CI)	1.31 [0.63, 2.73]
3.8 Drop-out	3	800	Risk Ratio (M-H , Random , 95% CI)	0.92 [0.77, 1.10]

4 NTX + ACAM versus PBO

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
4.1 Return to heavy drinking	2	694	Risk Ratio (M-H , Random , 95% CI)	0.71 [0.38, 1.35]
4.2 Return to any drinking	2	694	Risk Ratio (M-H , Random , 95% CI)	0.70 [0.35, 1.39]
4.3 Side effects: Diarrhea	2	694	Risk Difference (M-H , Random , 95% CI)	0.20 [0.13, 0.27]
4.4 Side effects: Nausea	2	694	Risk Difference (M-H , Random , 95% CI)	0.20 [0.14, 0.26]
4.5 Drop-out due to adverse events	2	694	Risk Ratio (M-H , Random , 95% CI)	3.75 [1.33, 10.55]

4.6 Drop-out	2	694	Risk Ratio (M-H , Random , 95% CI)	0.83 [0.28, 2.49]

5 NTX + ACAM versus NTX

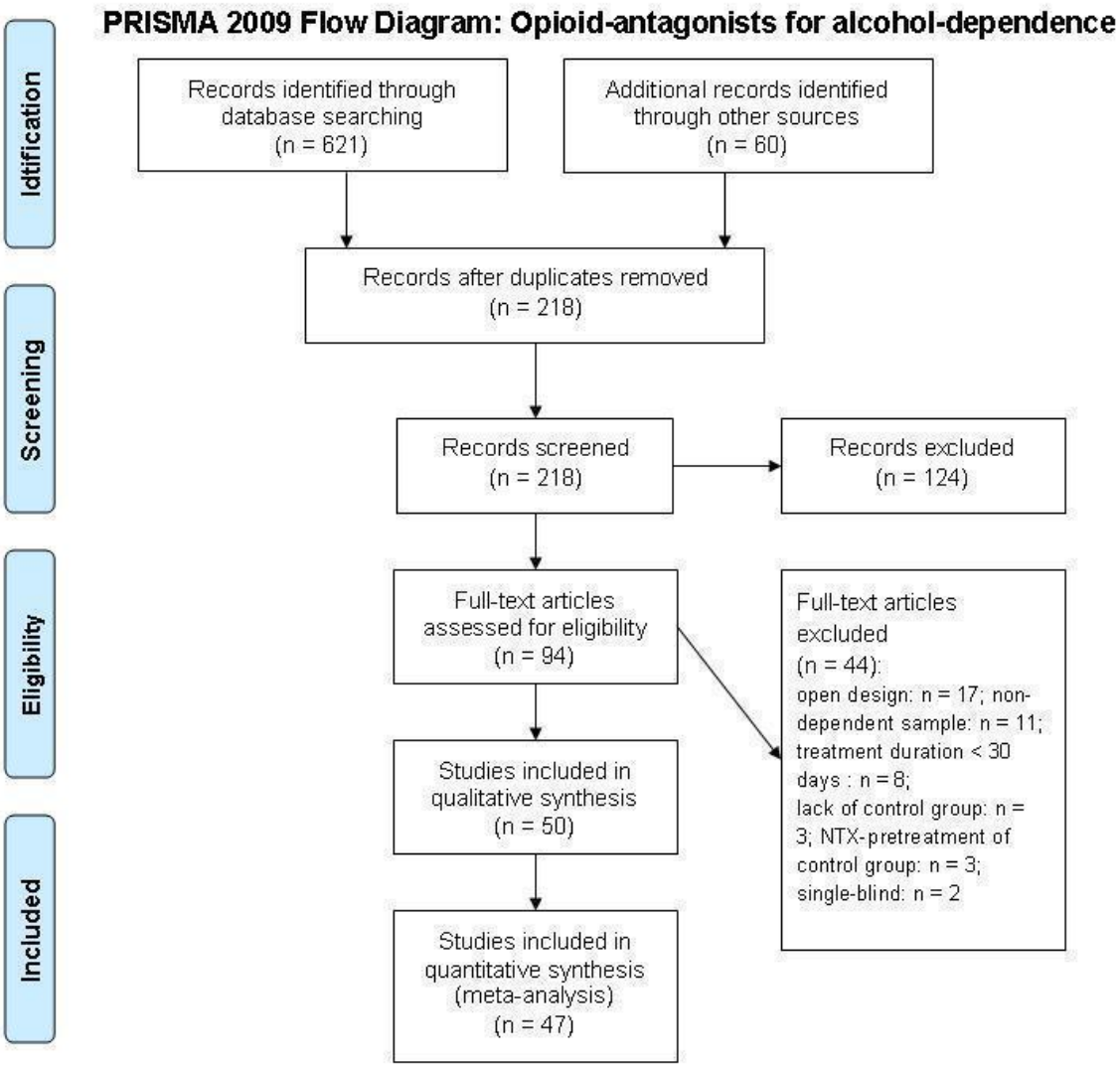
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
5.1 Return to heavy drinking	2	694	Risk Ratio (M-H , Random , 95% CI)	0.97 [0.75, 1.26]
5.2 Return to any drinking	2	694	Risk Ratio (M-H , Random , 95% CI)	0.88 [0.61, 1.28]
5.3 Side effects: Diarrhea	2	694	Risk Difference (M-H , Random , 95% CI)	0.37 [0.10, 0.65]
5.4 Side effects: Nausea	2	694	Risk Difference (M-H , Random , 95% CI)	0.09 [0.02, 0.16]
5.5 Drop-out due to adverse events	2	694	Risk Ratio (M-H , Random , 95% CI)	1.07 [0.55, 2.08]
5.6 Drop-out	2	694	Risk Ratio (M-H , Random , 95% CI)	1.03 [0.72, 1.48]

6 NMF versus PBO

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
6.1 Return to heavy drinking	3	396	Risk Ratio (M-H , Random , 95% CI)	0.85 [0.67, 1.08]
6.2 Consumed amount per drinking day	2	126	Mean Difference (IV , Random , 95% CI)	-4.16 [-32.69, 24.37]
6.3 Side effect: Insomnia	2	375	Risk Difference (M-H , Random , 95% CI)	0.12 [0.05, 0.19]
6.4 Side effect: Nausea	2	694	Risk Difference (M-H , Random , 95% CI)	0.20 [0.14, 0.26]
6.5 Drop-out	3	396	Risk Ratio (M-H , Random , 95% CI)	0.92 [0.68, 1.25]
6.6 Drop-out due to adverse events	3	396	Risk Ratio (M-H , Random , 95% CI)	1.43 [0.22, 9.24]

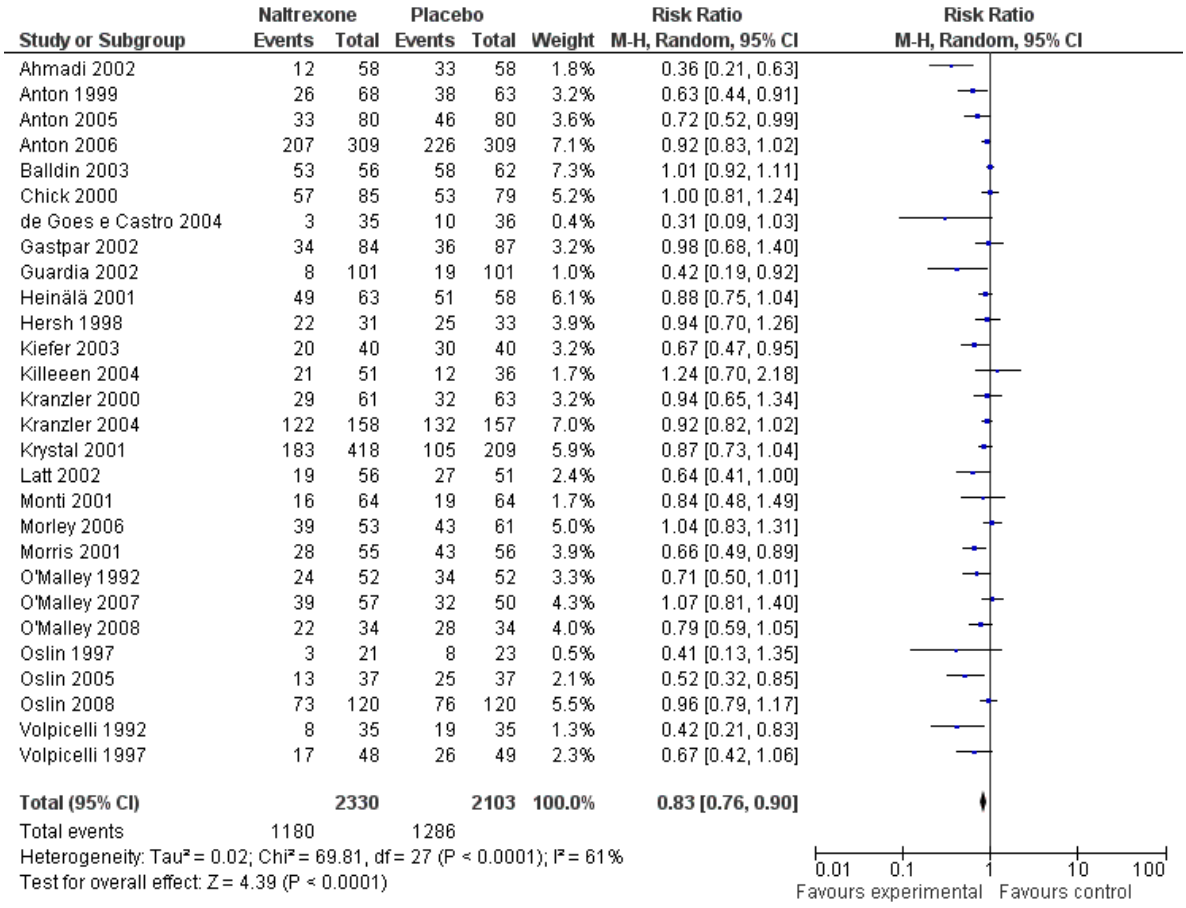
Figures

Figure 1



Caption

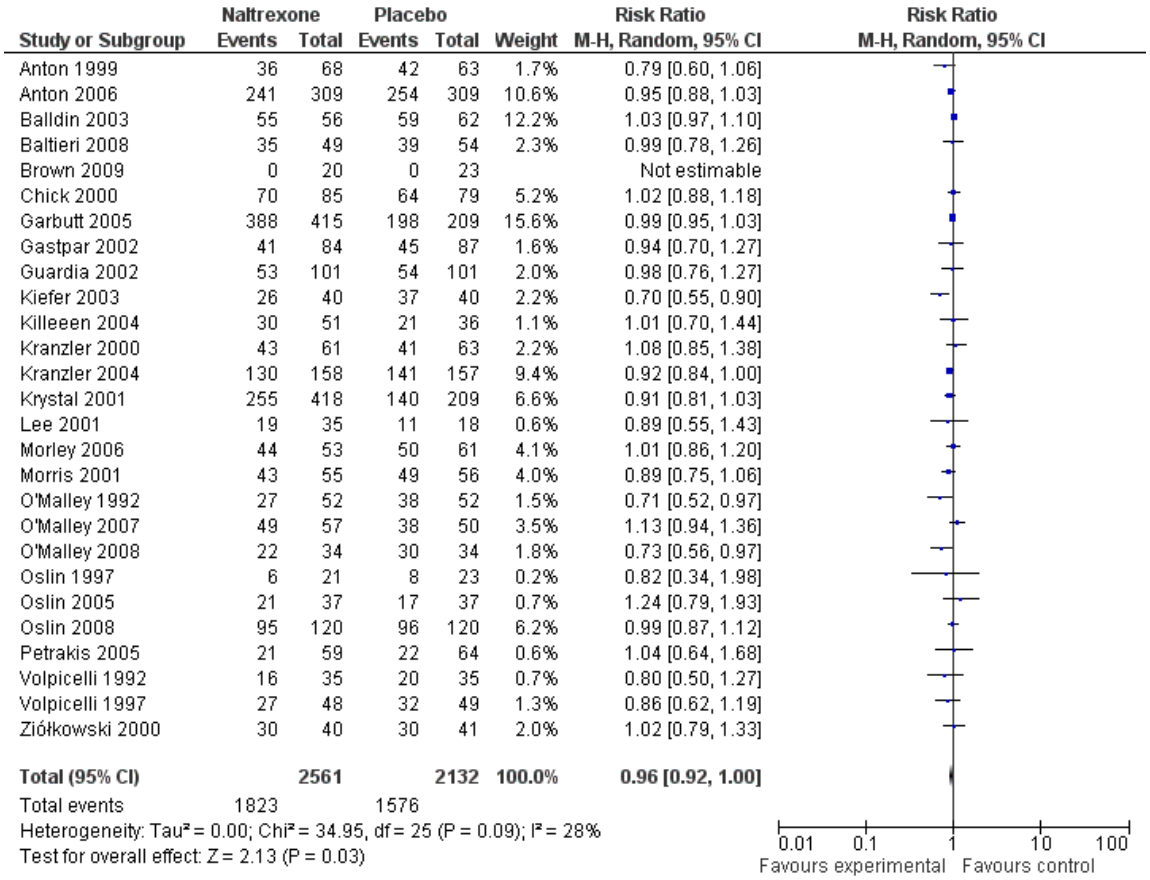
Figure 2 (Analysis 1.1)



Caption

Forest plot of comparison: 1 NTX versus PBO, outcome: 1.1 Return to heavy drinking.

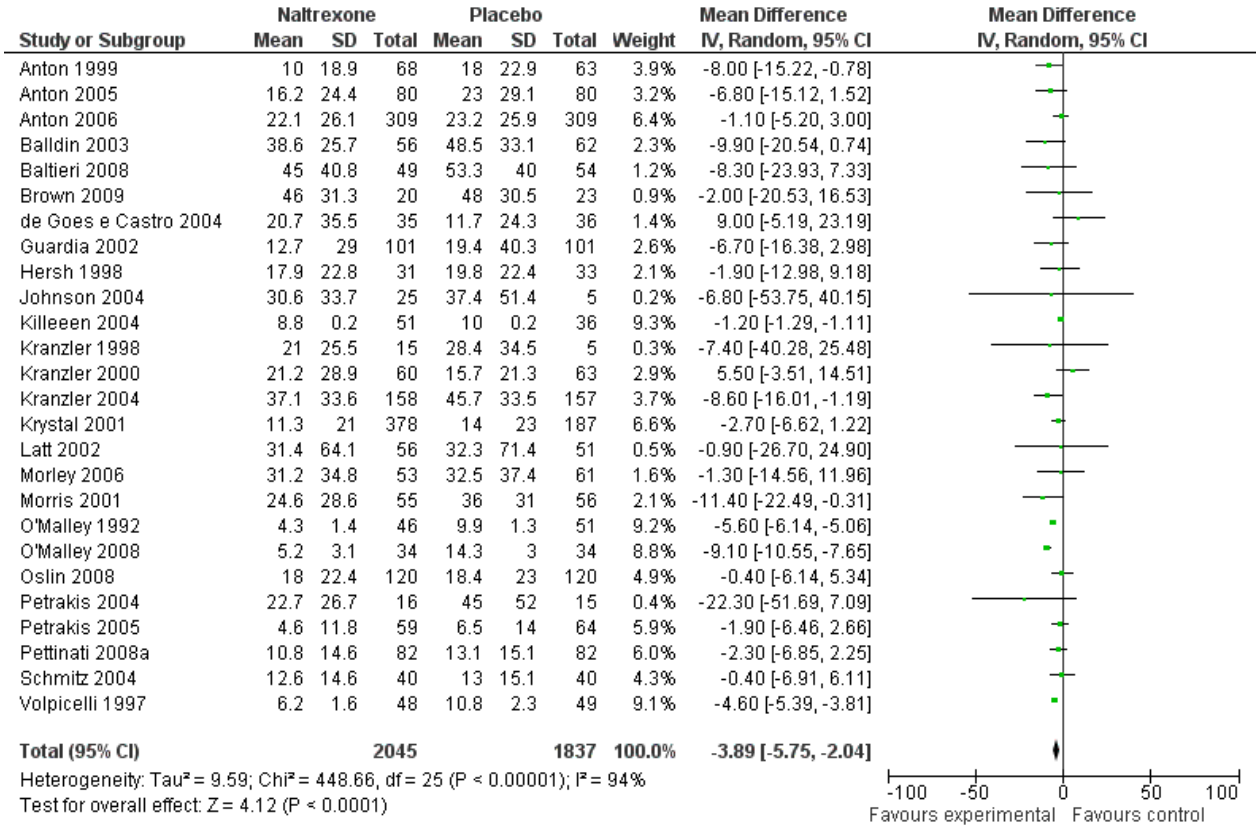
Figure 3 (Analysis 1.2)



Caption

Forest plot of comparison: 1 NTX versus PBO, outcome: 1.2 Return to any drinking.

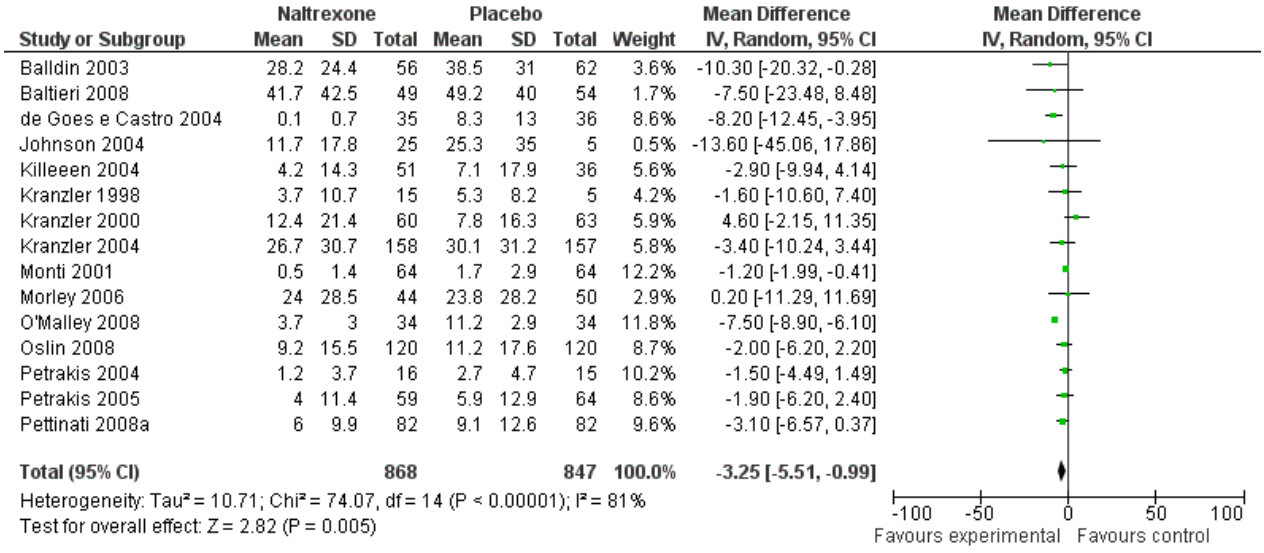
Figure 4 (Analysis 1.3)



Caption

Forest plot of comparison: 1 NTX versus PBO, outcome: 1.3 Drinking days.

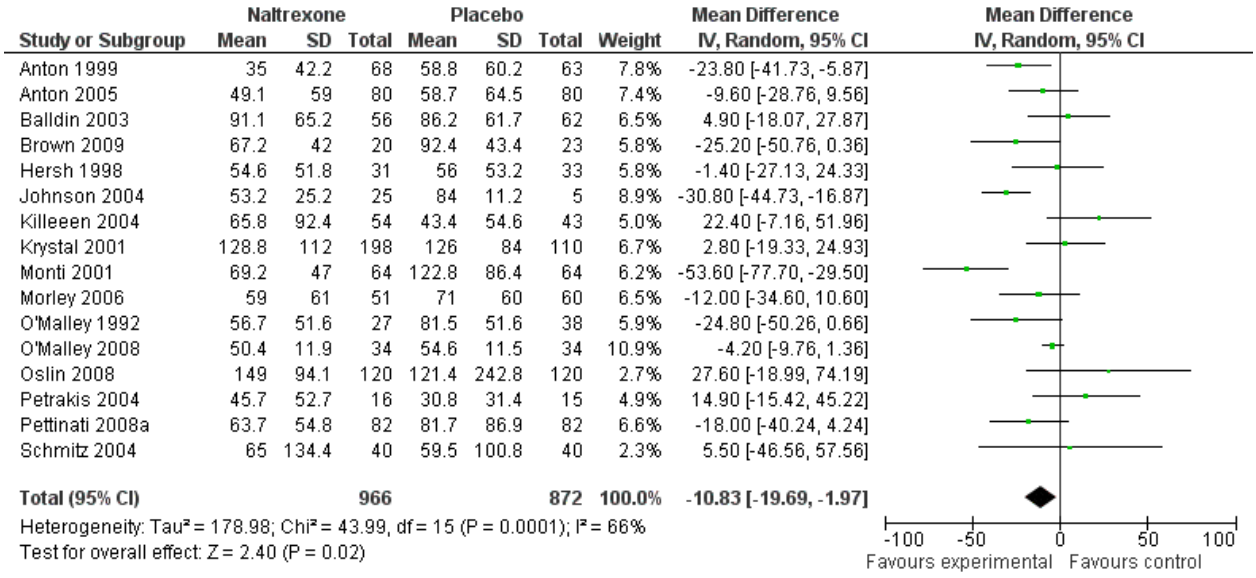
Figure 5 (Analysis 1.4)



Caption

Forest plot of comparison: 1 NTX versus PBO, outcome: 1.4 Heavy drinking days.

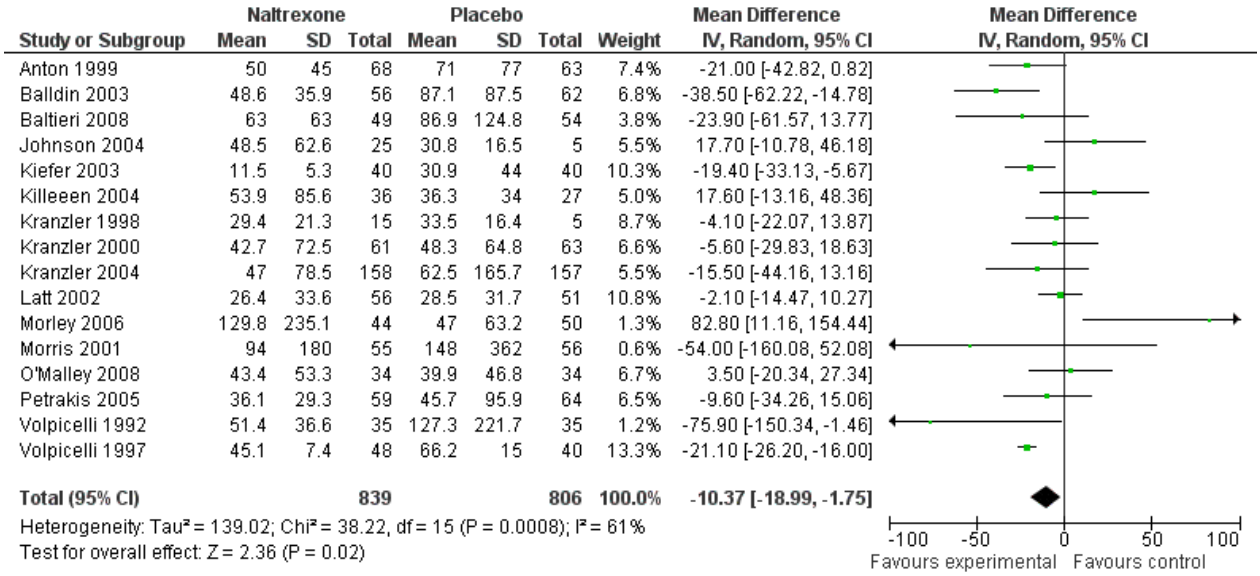
Figure 6 (Analysis 1.5)



Caption

Forest plot of comparison: 1 NTX versus PBO, outcome: 1.5 Consumed amount per drinking day.

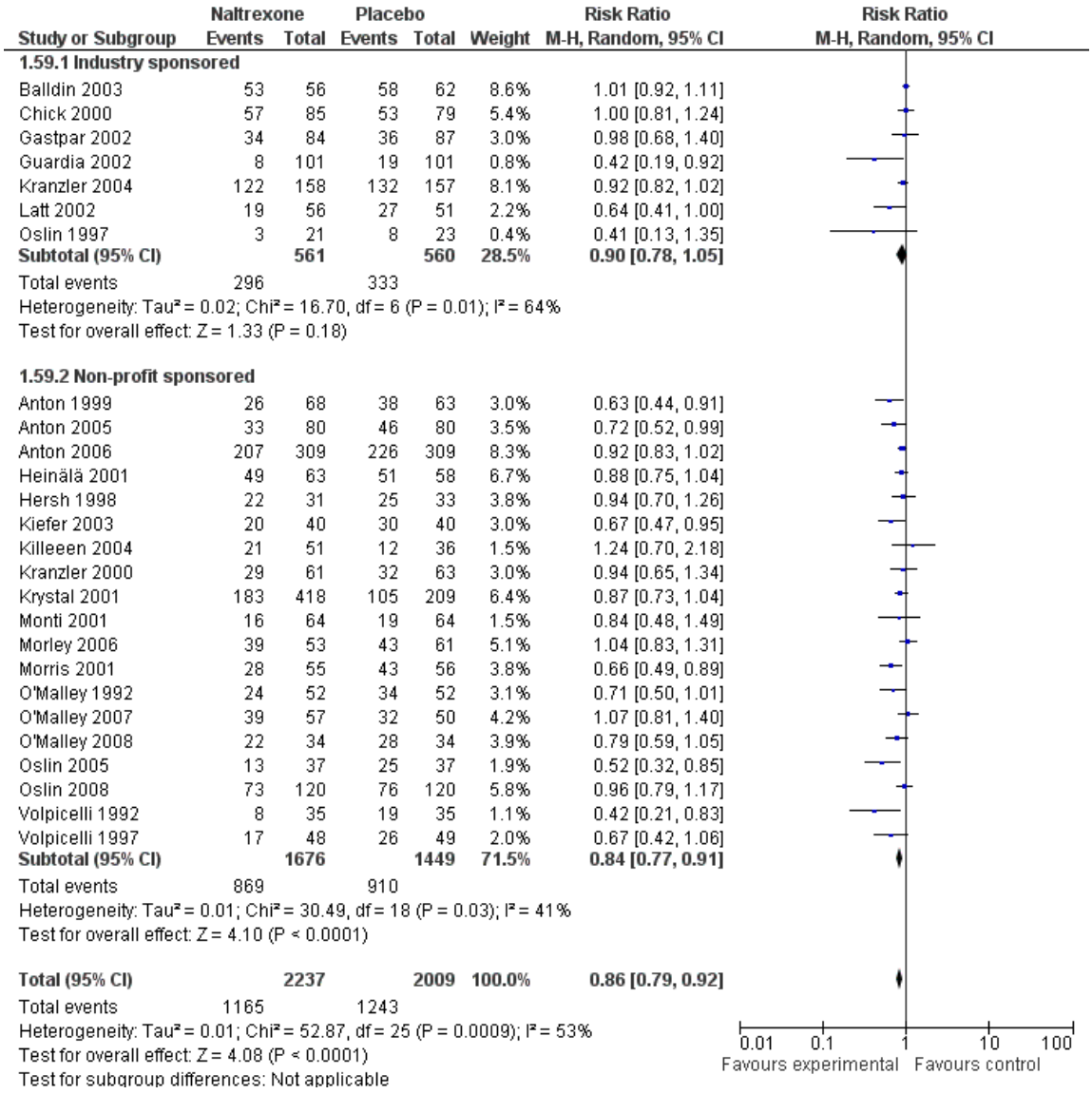
Figure 7 (Analysis 1.6)



Caption

Forest plot of comparison: 1 NTX versus PBO, outcome: 1.6 GGT.

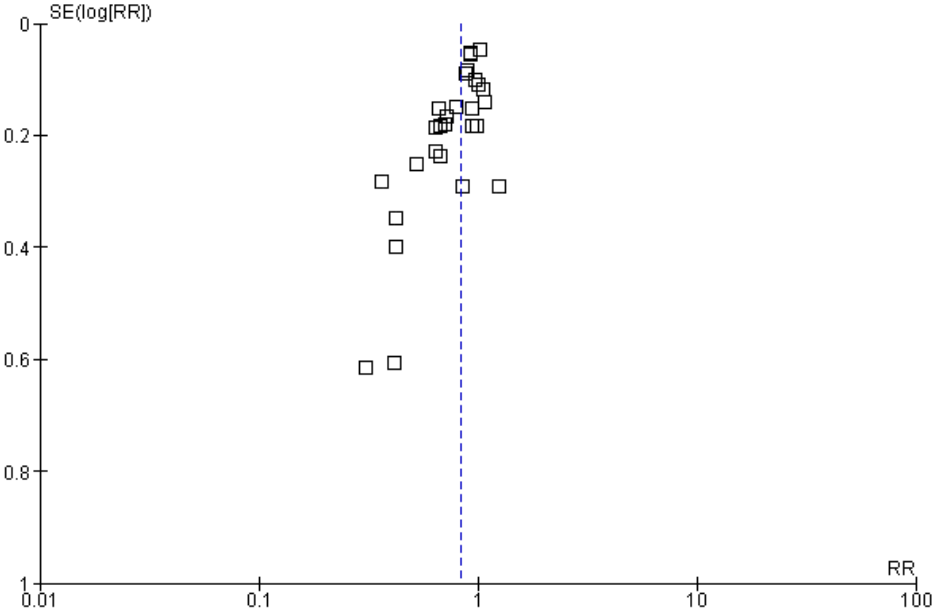
Figure 8 (Analysis 1.59)



Caption

Forest plot of comparison: 1 NTX versus PBO, outcome: 1.93 Sensitivity analysis: Funding source.

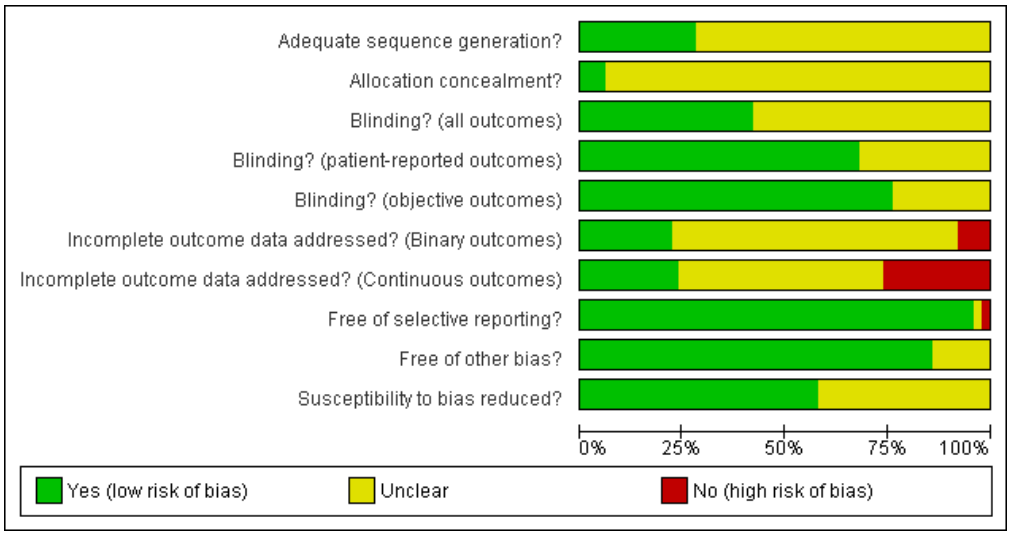
Figure 9 (Analysis 1.1)



Caption

Funnel plot of comparison: 1 NTX versus PBO, outcome: 1.1 Return to heavy drinking.

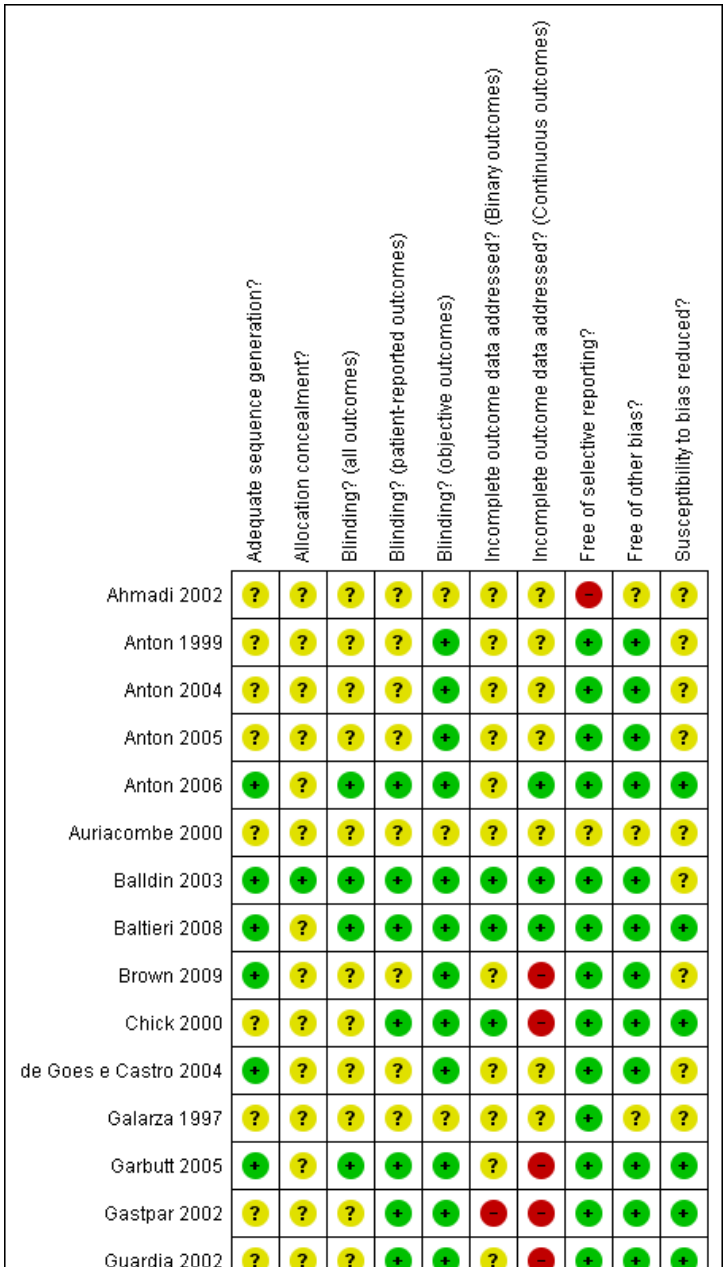
Figure 10

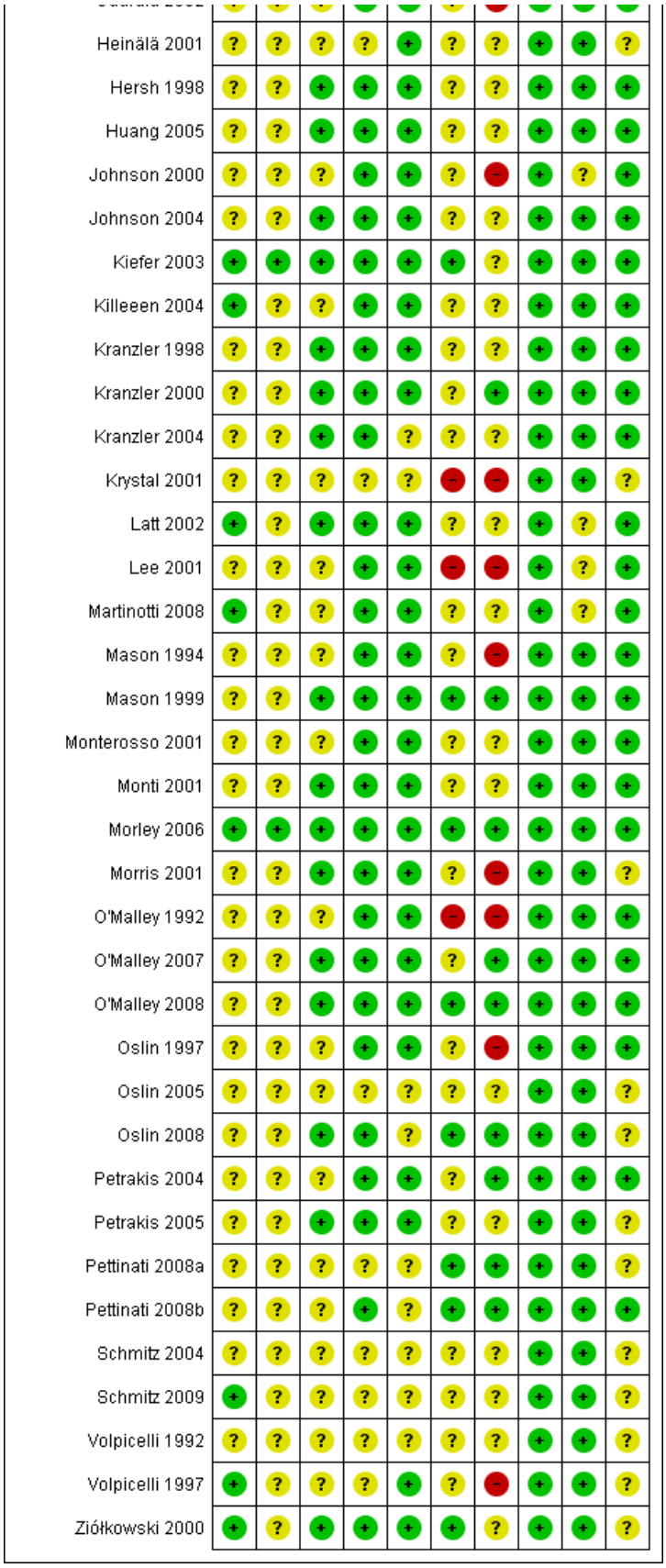


Caption

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

Figure 11





Caption

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

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

- Chiang Mai University, Thailand
  provision of infrastructure and related services

External sources

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

Feedback

Appendices

1 Search strategy

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. naltrexone [mesh]
8. naltrexone or nalmefene or vivitrol or revia
9. opioid near/2 antagonist
0. #7 or #8 or #9
1. #6 AND #10

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
6. #1 OR #2 OR #3 OR #4 OR #5
7. naltrexone [mesh]
8. Narcotic Antagonists [mesh]
9. naltrexone [tiab]
0. ReVia [tiab]
1. Vivitrol [tiab]
2. Nalmefene [substance name]
3. nalmefene [tiab]
4. (opioid AND antagonist) [tiab]
5. #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR OR 14
6. randomized controlled trial[pt]
7. controlled clinical trial[pt]
8. random*[tiab]
9. placebo[tiab]
0. drug therapy[mesh]
1. trial[tiab]
2. groups[tiab]
3. #16 OR #17 OR #18 OR #9 OR #20 OR #21 OR #22
4. animals [mesh]
5. humans [mesh]
6. animals NOT (24 and 25)
7. 23 NOT 26
8. 6 AND 15 AND 27

Search strategy for EMBASE (Host: OVID)

1. exp alcoholism
2. exp drinking behaviour
3. ((alcohol) AND (abuse* OR dependen* OR disorder*or drink*o disorder* or consumption))
4. alcohol*
5. 1 or 2 or 3 or 4
6. exp naltrexone
7. exp Narcotic Antagonists

8. (ReVia or Vivitrol or naltrexone or nalmefene).ti,ab
9. (opioid ADJ2 antagonist).ti,ab
0. 6 OR 7 OR 8 OR 9
1. random*.ti,ab
2. placebo. ti,ab
3. (control* or prospective* or volunteer*).ti,ab
4. (singl* or doubl* or trebl* or tripl*) ADJ2 (blind* or mask*)).ti,ab
5. crossover*.ti,ab
6. exp randomized controlled trial/
7. clinical-trial/
8. exp double blind procedure/
9. exp single blind procedure/
0. exp crossover procedure/
1. exp Latin square design/
2. exp placebos/
3. exp multicenter study/
4. 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23
5. 5 AND 10 AND 24
6. limit 25 to human

Search strategy for CINAHL (Host: EBSCO)

1. MH alcohol-related disorders
2. TX (((alcohol) and (abuse* OR dependen* OR disorder*or drink* or consumption or intoxication))
3. alcohol*
4. 1 OR 2 OR 3
5. MH naltrexone
6. TW naltrexone OR ReVia OR Vivitrol OR nalmefene
7. TW (opioid AND antagonist)
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 (singl* or doubl* or tripl* or trebl*) and (mask* or blind*)
5. MH crossover design
6. TW (crossover* or allocate* or assign*)
7. 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16
8. 4 AND 8 AND 17

2 Abbreviations

Term (abbreviation)

Acamprosate (ACAM)

Acceptable Quality Level (AQL)

Alcohol Dependence Scale (ADS)

Alcoholics Anonymous (AA)

Addiction Severity Index (ASI)

Aspartate aminotransferase (AspAT)

Blood alcohol concentration (BAC)

Carbohydrate-deficient transferrin (CDT)

Cognitive behavioural therapy (CBT)

Case report form (CRF)

Cognitive Behavioral Intervention (CBI)

Combined behavioral intervention (CBI)

Clinical Trials Registry Platform Search Portal (ClinicalTrials.gov)

Cochrane Drugs and Alcohol Group (CDAG)

Confidence interval (CI)

Contingency management (CM)

Cumulative abstinence duration (CAD)

Diagnostic and Statistical Manual of Mental Disorders (DSM)

Electronic microchip system (EMS)

Food and Drug Administration (FDA)

Gamma-glutamyltransferase (GGT)

Glutamat-Pyruvat-Transaminase (GPT)

Good Clinical Practice (GCP)

Hopkins symptom checklist (HSCL)

Individual patient database (IPD)

Intention-to-treat (ITT)

International Statistical Classification of Diseases (ICD)

International Unit (IU)

Mean corpuscular volume (MCV)

Mean difference (MD)

Medial management (MM)

Meta-analysis based on literature (MAL)

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

Microelective events monitoring system (MEMS)

Motivational Enhancement (ME)

Naltrexone (NTX)

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

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

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

Ondansetrone (ONDAN)

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)

Weighted mean difference (WMD)

3 Criteria for risk of bias

	Item	Judgment	Description
Sequence generation	Was the method of randomization adequate?	Yes	Methods used for sequence generation are based on a random process, in which every study participant has an equal chance to be assigned to each of the treatment conditions (e.g. random number table, computer random number generator, coin tossing, shuffling cards or envelopes, throwing dice)
		No	Methods used for sequence generation permit any prediction of assignment in advance (e.g. date of birth, date of admission, hospital or clinic record number)
		Unclear	Insufficient information about the sequence generation process to permit judgement of 'Yes' or 'No'

Allocation concealment	Was the treatment allocation concealed?	Yes	Randomization and drug preparation were a) undertaken centralized and remote from the patient recruitment centre(s) AND allocation codes were protected against identification by the use of sealed randomization envelopes
		No	Methods for allocation were used that allow unconcealment such as an open random allocation schedule, assignment envelopes without appropriate safeguards, alternation or rotation
		Unclear	Insufficient information to permit judgement of 'Yes' or 'No'
Blinding (all outcomes)	Was knowledge of the allocated interventions adequately prevented during the study?	Yes	Patients and research staff were included in the blinding procedures; AND active medication and placebo were of identical appearance The integrity of blinding was checked and confirmed at the end of the treatment
		No	Participants, providers and outcome assessor were not blinded or incompletely blinding OR placebo with a different appearance to the active medication was used
		Unclear	Insufficient information to permit judgement of 'Yes' or 'No'
Blinding (subjective outcomes)		Yes	Knowledge of the allocated interventions was adequately prevented during the study (see criteria "Blinding (all outcomes)") Objective measures were used for a validity check of patient-reported drinking outcomes
		No	Participants, providers and outcome assessor were not blinded or incompletely blinding OR placebo with a different appearance to the active medication was used No objective measures were used for a validity check of patient-reported drinking outcomes
		Unclear	Insufficient information to permit judgement of 'Yes' or 'No'
Handling of incomplete outcome data	Were incomplete outcome data adequately addressed? For all outcomes except retention in treatment or drop out	Yes	All randomized patients (intention-to-treat analysis) or at least those who have received at least one dose of treatment (treatment received analysis) were analyzed in the group they were allocated to by randomization AND drop-outs or lost to follow-ups were adequately handled, considering the potential association between absence from a study visit and a patient's drinking status, either by generally assigning missing participants to the relapse category (substitution by "worst case") or by analyzing the pattern of missingness (e.g. pattern-mixture analyses)
		No	Patients who have received treatment were excluded from the analysis OR drop-outs or lost to follow-ups were handled in a way which does not consider the potential association between absence from a study visit and a patient's drinking status
		Unclear	Insufficient reporting of attrition/exclusions to permit judgement of 'Yes' or 'No'
Selective reporting	Are reports of the study free of suggestion or selective outcome reporting?	Yes	All outcomes listed in the protocol or the methods section of the publication were adequately reported in the results section
		No	One or more outcomes listed in the study protocol or the methods section of the publication were not adequately reported in the results section
		Unclear	Outcomes are not explicitly stated in the study protocol or the methods section of the trial publication

Other bias: Equivalence of baseline characteristics	Equivalence between groups at baseline?	Yes	Baseline equivalence in potentially effect-determining baseline characteristics (age AND gender AND (baseline drinking OR treatment / drinking history)) If differences between groups at baseline became evident, these were controlled in the statistical analyses
		No	Differences between groups in one or more of the potentially effect-determining baseline characteristics became evident and were not controlled in the statistical analyses
		Unclear	Insufficient reporting of baseline equivalence to permit judgement of 'Yes' or 'No'
Susceptability to bias effects	Was the susceptibility to bias reduced by objective measures?	Yes	Objective outcomes including either laboratory indicators or collateral reports were used as a validity check for patient-reported drinking data
		No	The validity of patient-reported drinking data was not checked by either laboratory indicators or by collateral reports
		Unclear	It is unclear whether objective outcomes were used as a validity check