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Disulfiram for the treatment of cocaine dependence

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Abstract

Background

Cocaine dependence is a mental disorder with no pharmacological treatment of proven efficacy. This is an update of a Cochrane Systematic Review first published in 2010.

Objectives

To evaluate the efficacy and safety of disulfiram for the treatment of cocaine dependence.

Search methods

We updated our searches of the following databases to August 2022: the Cochrane Drugs and Alcohol Group Specialised Register, CENTRAL, MEDLINE, Embase, CINAHL, and PsycINFO. We also searched for ongoing and unpublished studies via two trials registries. We handsearched the references of topic-related systematic reviews and included studies. The searches had no language restrictions.

Selection criteria

We included randomised controlled trials that evaluated disulfiram alone or associated with psychosocial interventions versus placebo, no intervention, other pharmacological interventions, or any psychosocial intervention for the treatment of cocaine dependence.

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

Main results

Thirteen studies (1191 participants) met our inclusion criteria.

Disulfiram versus placebo or no treatment

Disulfiram compared to placebo may increase the number of people who are abstinent at the end of treatment (point abstinence; risk ratio (RR) 1.58, 95% confidence interval (CI) 1.05 to 2.36; 3 datasets, 142 participants; low-certainty evidence). However, compared to placebo or no pharmacological treatment, disulfiram may have little or no effect on frequency of cocaine use (standardised mean difference (SMD) –0.11 standard deviations (SDs), 95% CI –0.39 to 0.17; 13 datasets, 818 participants), amount of cocaine use (SMD –0.00 SDs, 95% CI –0.30 to 0.30; 7 datasets, 376 participants), continuous abstinence (RR 1.23, 95% CI 0.80 to 1.91; 6 datasets, 386 participants), and dropout for any reason (RR 1.20, 95% CI 0.92 to 1.55; 14 datasets, 841 participants). The certainty of the evidence was low for all these outcomes. We are unsure about the effects of disulfiram versus placebo on dropout due to adverse events (RR 12.97, 95% CI 0.77 to 218.37; 1 study, 67 participants) and on the occurrence of adverse events (RR 3.00, 95% CI 0.35 to 25.98), because the certainty of the evidence was very low for these outcomes.

Disulfiram versus naltrexone

Disulfiram compared with naltrexone may reduce the frequency of cocaine use (mean difference (MD) –1.90 days, 95% CI –3.37 to –0.43; 2 datasets, 123 participants; low-certainty evidence) and may have little or no effect on amount of cocaine use (SMD 0.12 SDs, 95% CI –0.27 to 0.51, 2 datasets, 123 participants; low-certainty evidence). We are unsure about the effect of disulfiram versus naltrexone on dropout for any reason (RR 0.86, 95% CI 0.56 to 1.32, 3 datasets, 131 participants) and dropout due to adverse events (RR 0.50, 95% CI 0.07 to 3.55; 1 dataset, 8 participants), because the certainty of the evidence was very low for these outcomes.

Authors' conclusions

Our results show that disulfiram compared to placebo may increase point abstinence. However, disulfiram compared to placebo or no pharmacological treatment may have little or no effect on frequency of cocaine use, amount of cocaine use, continued abstinence, and dropout for any reason. We are unsure if disulfiram has any adverse effects in this population. Caution is required when transferring our results to clinical practice.

Plain language summary

Disulfiram as a medication for the treatment of cocaine dependence

Key messages

• In people who are addicted to cocaine, disulfiram compared to placebo may increase the number of people who are abstinent at the end of treatment, but may have little or no effect on the frequency and amount of cocaine use and on the number of people who have achieved and maintained abstinence for at least three weeks at the end of treatment. We are unsure if disulfiram has any unwanted effects in people who are addicted to cocaine..

• In people who are addicted to cocaine, disulfiram compared to naltrexone may may reduce the frequency of cocaine use but may have little or no effect on the amount of cocaine use.

• Of the 13 studies included in our review, 11 took place in the USA. Furthermore, most people included in the studies were men. Our results may not be applicable in other contexts because the effects of treatment could be strongly influenced by social environment, ethnicity, and sex.

What is cocaine dependence?

Cocaine is one of the most commonly used psychostimulants worldwide. Psychostimulants are medicines or illegal drugs that stimulate the nervous system and have mood-enhancing properties.. The latest estimates indicate that more than 0.4% of adults have used cocaine at least once in the past year.

Cocaine use is associated with medical, psychological, and social problems, including the spread of infectious diseases (e.g. AIDS, hepatitis, tuberculosis), crime, violence, and drug exposure during pregnancy. Cocaine use can increase the risk of HIV infection through high-risk injecting and sexual behaviours. Cocaine addiction is the most severe mental disorder due to the illegal use of cocaine.

How is cocaine dependence treated?

Cocaine addiction is usually treated with psychosocial treatments. No effective pharmacological treatments are available. Studies have evaluated whether a medicine called disulfiram could help people with cocaine addiction. Disulfiram is currently used to treat people with alcohol addiction. It works by causing unpleasant physical reactions if the person drinks alcohol.

What did we want to find out?

We wanted to find out whether disulfiram can help people with cocaine addiction reduce their cocaine use or stop using cocaine altogether. We also wanted to know whether treatment with disulfiram was acceptable and safe for people with cocaine addiction.

What did we do?

We searched thoroughly for randomised studies (where people were allocated at random to one of two or more treatment groups) comparing disulfiram with no medicines, placebo (dummy treatment), or other medicines.

We compared and summarised the results and rated our confidence in the evidence, based on factors such as methods and precision of the results of each study.

What did we find?

We found 13 studies, which enroled 1191 people with cocaine dependence. The average duration of treatment was about three months. Twelve studies compared disulfiram with placebo or no pharmacological treatment, and three studies compared disulfiram with naltrexone (a medicine used to treat people with alcohol dependence or opioid dependence).

Main results

Disulfiram compared with placebo may increase the number of people who are not using cocaine at the end of treatment, but may have little or no effect on the frequency of cocaine use (number of days or weeks of cocaine use at the end of treatment), the amount of cocaine use (weight of cocaine used or money spent on cocaine at the end of treatment), the number of people who achieve and maintain abstinence for at least three weeks, and the number of people who prematurely interrupt the treatment. We are unsure if disulfiram has any unwanted effects in people with cocaine addiction.

Disulfiram compared with naltrexone may decrease the frequency of cocaine use but may have little or no effect on the amount of cocaine use or on the number of people who prematurely interrupt treatment.

What are the limitations of the evidence?

We cannot be sure that the studies allocated people to groups in an appropriate way, as most studies did not describe this process in detail.

There were important variations in the characteristics of the people included in the studies: some had other additional substance use disorders, some were using other medicines, and some were receiving other psychosocial treatments.

In addition, most people included in the studies were men, and 11 of the 13 studies took place in the USA. Therefore, our results may not apply to women or people living in other countries.

How up to date is this evidence?

This review updates our previous review. The evidence is up to date to August 2022.

Summary of findings

Summary of findings 1

Summary of findings table – disulfiram compared to placebo or no pharmacological treatment for people with cocaine dependence

Disulfiram compared to placebo or no pharmacological treatment for people with cocaine dependence					
Patient or population: people with cocaine dependence **Setting:** outpatient **Intervention:** disulfiram **Comparison:** placebo or no treatment					
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**
	Risk with placebo or no treatment	**Risk with disulfiram**			
Frequency of cocaine use (mean number of days or weeks of cocaine use at the end of the treatment)	—	**SMD 0.11 SDs lower** (0.39 lower to 0.17 higher)	—	818 (13 RCTs)	⊕⊕⊖⊖ **Low**[a]
Amount of cocaine use (mean weight of cocaine used or money spent on cocaine at the end of treatment)	—	**SMD 0 SDs** (0.3 lower to 0.3 higher)	—	376 (7 RCTs)	⊕⊕⊖⊖ **Low**[b]
Continuous abstinence from cocaine (number of participants who had achieved and maintained abstinence for at least three weeks at the end of treatment)	245 per 1000	**301 per 1000** (196 to 467)	**RR 1.23** (0.80 to 1.91)	386 (6 RCTs)	⊕⊕⊖⊖ **Low**[c]
Point abstinence (number of participants who were abstinent at the end of the treatment)	309 per 1000	**488 per 1000** (324 to 729)	**RR 1.58** (1.05 to	142 (3 RCTs)	

			2.36)		⊕⊕⊖⊖ **Low**[c]
Dropout for any reason (number of participants who did not complete treatment)	273 per 1000	**328 per 1000** (251 to 423)	**RR 1.20** (0.92 to 1.55)	841 (14 RCTs)	⊕⊕⊖⊖ **Low**[c]
Dropout due to adverse events (number of participants who did not complete treatment due to adverse events)	0 per 1000	**0 per 1000** (0 to 0)	**RR 12.97** (0.77 to 218.37)	67 (1 RCT)	⊕⊖⊖⊖ **Very low**[d]
Any adverse events (number of participants who experienced at least one adverse event)	67 per 1000	**200 per 1000** (23 to 1000)	**RR 3.00** (0.35 to 25.68)	30 (1 RCT)	⊕⊖⊖⊖ **Very low**[e]

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio; **SD:** standard deviation; **SMD:** standardised mean difference.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded one level for risk of bias (all or most studies at unclear risk of bias for allocation concealment) and one level for inconsistency (I^2 = 72%; Chi^2 = 89.2%, P = 0.002).

[b] Downgraded one level for risk of bias (all or most studies at unclear risk of bias for allocation concealment) and one level for imprecision (fewer than 400 participants).

[c] Downgraded one level for risk of bias (all or most studies at unclear risk of bias for allocation concealment) and one level for imprecision (optimal information size not met).

[d] Downgraded one level for risk of bias (unclear risk of selection bias) and two levels for imprecision (single study with 67 participants).

[e] Downgraded one level for risk of bias (unclear risk of selection bias) and two levels for imprecision (single study with 30 participants).

Summary of findings 2

Summary of findings table – disulfiram compared to naltrexone for people with cocaine dependence

Disulfiram compared to naltrexone for people with cocaine dependence

Patient or population: people with cocaine dependence
Setting: outpatient
Intervention: disulfiram
Comparison: naltrexone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with Naltrexone	Risk with Disulfiram			
Frequency of cocaine use (mean number of days or weeks of cocaine use at the end of the treatment)	The mean frequency of cocaine use was **0 days**	**MD 1.9 days fewer** (3.37 fewer to 0.43 fewer)	—	123 (2 RCTs)	⊕⊕⊖⊖ **Low**[a]
Amount of cocaine use (mean weight of cocaine used or money spent on cocaine at the end of treatment)	—	**SMD 0.12 SDs higher** (0.27 lower to 0.51 higher)	—	123 (2 RCTs)	⊕⊕⊖⊖ **Low**[a]
Continuous abstinence from cocaine (number of participants who had achieved and maintained abstinence for at least three weeks at the end of treatment)	No studies reported this outcome.				
Point abstinence (number of participants who were abstinent at the end of the treatment)	No studies reported this outcome.				
Dropout for any reason (number of participants who did not complete treatment)	415 per 1000	**357 per 1000** (233 to 548)	**RR 0.86** (0.56 to 1.32)	131 (3 RCTs)	⊕⊖⊖⊖ **Very low**[b]
Dropout due to adverse events (number of participants who did not complete treatment due to adverse events)	500 per 1000	**250 per 1000** (35 to 1000)	**RR 0.50** (0.07 to 3.55)	8 (1 RCT)	⊕⊖⊖⊖ **Very low**[c]
Any adverse events (number of participants who experienced at least one adverse event)	No studies reported this outcome.				

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RCT:** randomised controlled trial; **RR:** risk ratio; **SD:** standard deviation; **SMD:** standardised mean difference.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect,

but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded one level for risk of bias (both studies at unclear of selection bias) and one level for imprecision (fewer than 400 participants).
[b] Downgraded one level for risk of bias (two studies at high risk of performance and detection bias; all three studies at unclear risk of selection bias) and two levels for imprecision (fewer than 100 events).
[c] Downgraded one level for risk of bias (unclear risk of selection bias) and two levels for imprecision (fewer than 100 events).

Background

Description of the condition

Cocaine is an alkaloid derived from the leaf of erythroxylon coca. Cocaine is commonly snorted or injected as powder or smoked as crack, a freebase form. Cocaine dependence is a major public health problem, characterised by recidivism and a host of medical and psychosocial complications (EMCDDA 2022). Another name for cocaine dependence is cocaine use disorder (DSM-5).

Acute and chronic use of cocaine is associated with a wide and well-documented range of medical, psychological, and social problems, including the spread of infectious diseases (e.g. AIDS, hepatitis, tuberculosis), crime, violence, and neonatal drug exposure (Farrell 2019). Cocaine use can increase the risk of HIV infection through high risk injecting and sexual behaviours (Farrell 2019).

The illicit use of cocaine has become a persistent health problem worldwide. According to the United Nations Office on Drugs and Crime, 21.5 million people (or 0.4% of the global population aged 15 to 64 years) used cocaine at least once in 2020 (UNOCD 2022); the highest prevalence levels were found in Oceania (2.7%), North America (2.0%), Western and Central Europe (1.4%), and South America (1.6%). The prevalence of use among young adults (aged 18 to 25 years) may be higher than the population average (Ryan 2019). For example, 6.2% of young adults in the USA reported past-year use of cocaine or crack cocaine in 2017 (SAMHSA 2018).

In 2016, the global age-standardised prevalence of cocaine use disorder was estimated at 77.6 (range 70.7 to 85.9) per 100,000 population, with higher values in men (105.5 per 100,000; range 96.3 to 116.3) than in women (49.4 per 100,000; range 44.7 to 54.9; GBD 2018). As women account for approximately one in three people with cocaine use disorder, treatment services should consider their specific needs (Motyka 2022). However, most people with cocaine use disorder have little contact with treatment services (Farrell 2019). One study estimated that from 2015 to 2018, only 10.6% of adults with substance use disorder (SUD) in the USA received treatment, and this proportion was similar in men and women (Martin 2022). Among people who expressed a need for SUD treatment, only one-fifth received it (20.1%, 95% CI 16.7% to 23.4%; Martin 2022).

Description of the intervention

There is currently no pharmacological treatment of proved efficacy for cocaine dependence, although considerable advances in the neurobiology of this mental disorder could guide future medication development (Farrell 2019). Several Cochrane Reviews have evaluated the efficacy of different drugs on cocaine dependence: antidepressants (Lima 2003; Pani 2011), antipsychotics (Amato 2007; Indave 2016), anticonvulsants (Minozzi 2008; Minozzi 2015a), dopamine agonists (Amato 2011; Minozzi 2015b; Soares 2003), and psychostimulant drugs (Castells 2016). However, no reviews have confirmed the efficacy of these treatments. Regarding psychosocial interventions, a systematic review published in 2021 found that only contingency management programmes significantly reduced cocaine use among adults (Bentzley 2021). Some experts have proposed that deep brain stimulation (DBS) may be useful in the treatment of cocaine dependence (Eskandari 2022). However, clinical experience is still scarce.

Published evidence suggests that the effect of cocaine relates to its capacity to increase the availability of monoamines (dopamine, serotonin, and noradrenaline) in the brain. The dopamine increase in specific areas of the meso-limbic system – which also occurs with drugs like heroin, alcohol, cannabis, and nicotine – mediates the rewarding effect of drugs and self-administration behaviour in animals and humans (Di Chiara 1988; Drevets 1999; Drevets 2001; Volkow 2003).

Some compounds approved for the treatment of other pathologies may also prove useful for treating cocaine dependence (Preti 2007; Sofuoglu 2006; Vocci 2005). In particular, preclinical and clinical observations support the use of disulfiram, a medication marketed for the treatment of alcohol use disorder (Buchholz 2019; Kleczkowska 2021).

How the intervention might work

In people with alcohol use disorder, disulfiram works by inhibiting aldehyde dehydrogenase, an enzyme involved in the metabolism of alcohol. Early studies suggested that an observed reduction in cocaine use in people treated with disulfiram for their alcohol use disorder was caused by the interruption of alcohol-related disinhibition and impaired judgement (Carroll 1993). However, more recent studies have indicated that disulfiram has a specific

mechanism of action for treating cocaine dependence: because disulfiram is a generalised enzyme inhibitor, its effect on cocaine addiction could be ascribed to its ability to interfere with enzymes involved in the metabolism of cerebral monoamines. In particular, researchers have proposed that by inhibiting dopamine-beta-hydroxylase and thus producing an excess of dopamine and decreased synthesis of norepinephrine, disulfiram could improve the functioning of the meso-limbic circuits disrupted by cocaine addiction (Buchholz 2019; Kleczkowska 2021).

Why it is important to do this review

Despite decades of clinical trials evaluating the effects of antidepressants, anticonvulsants, psychostimulants, and dopaminergic medications on cocaine dependence, there are still no approved pharmacological treatments for this mental disorder. Several preclinical and clinical studies have investigated the potential efficacy of disulfiram for cocaine dependence, the neurobiological basis for its effect, and related safety issues. Considering adverse effects of disulfiram-cocaine interactions is particularly important because several safety issues have been associated with disulfiram and disulfiram-alcohol interactions (e.g. hepatic, psychiatric, and cardiovascular effects; Malcolm 2008).

This is an update of a previous Cochrane Review, which found low-certainty evidence to support the clinical use of disulfiram for the treatment of cocaine dependence (Pani 2010).

Objectives

To evaluate the efficacy and safety of disulfiram for the treatment of cocaine dependence.

Methods

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) focused on the use of disulfiram for cocaine dependence.

Types of participants

We included trials in people with a diagnosis of cocaine dependence or cocaine use disorder, according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III-R, DSM-IV, or DSM-5). Trials that enroled people with additional diagnoses of substance dependence or with comorbid mental health conditions were also eligible. We excluded people aged under 18 years and pregnant women, as the clinical management of these populations is substantially different from that of the general adult population.

Types of interventions

The experimental intervention was disulfiram alone or in combination with any psychosocial intervention. Eligible control interventions were placebo, no intervention, other pharmacological interventions, or any psychosocial intervention.

Types of outcome measures

Primary outcomes

- Efficacy
    - Frequency of cocaine use (mean number of days or weeks of cocaine use at the end of treatment)
    - Amount of cocaine use (mean weight of cocaine used or money spent on cocaine at the end of treatment)
    - Continuous abstinence from cocaine (number of participants who had achieved and maintained abstinence for at least three weeks at the end of treatment)
    - Point abstinence from cocaine (number of participants who were abstinent at the end of treatment)
- Acceptability
    - Dropout for any reason (number of participants who did not complete treatment)
    - Dropout due to adverse events (number of participants who did not complete treatment due to adverse events)
- Safety
    - Any adverse events (number of participants who experienced at least one adverse event)
    - Serious adverse events (number of participants who experienced at least one serious adverse event)

Secondary outcomes

- Individual adverse events, measured subjectively or objectively (number of participants who experienced a specific adverse effect)
- Craving, as measured by validated scales such as the Brief Substance Craving Scale (BSCS) or a visual analogue scale (VAS)
- Severity of dependence, as measured by validated scales such as the Addiction Severity Index (ASI), the Clinical Global Impression (CGI) scale (self-report and observer versions), or the Severity of Dependence Scale (SDS)
- Psychiatric symptoms/psychological distress, diagnosed using standard instruments such as the Diagnostic and Statistical Manual of Mental Disorders (DSM), or measured by validated scales such as the Hamilton Depression Rating Scale (HDRS), the Profile of Mood States Scale (POMSS), or the Positive and Negative Syndrome Scale (PANSS)

Search methods for identification of studies

Electronic searches

For this update, we revised all our search strategies in line with current Cochrane Drugs and Alcohol Group practices. We searched the following databases up to 25 August 2022.

- Cochrane Drugs and Alcohol Group (CDAG) Specialised Register (searched 25 August 2022; Appendix 1)
- Cochrane Central Register of Controlled Trials (CENTRAL; 2022, issue 8) via onlinelibrary.wiley.com (Appendix 2)
- MEDLINE via Ovid (January 2009 to 25 August 2022; Appendix 3)
- Embase via Ovid (January 2009 to 25 August 2022; Appendix 4)
- PsycINFO via Ovid (January 2009 to 25 August 2022; Appendix 5)
- CINAHL (EBSCOhost; January 2009 to 25 August 2022; Appendix 6)

We also searched the following trials registries.

- U.S. National Institutes of Health Ongoing Trials Registry ClinicalTrials.gov (www.clinicaltrials.gov; searched 25 August 2022)
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch/; searched 25 August 2022)

Searching other resources

We also searched the reference lists of all relevant papers and conference proceedings likely to contain trials relevant to the review. We contacted investigators to ask about unpublished or incomplete trials.

All searches included non-English language literature and studies with English abstracts were assessed for inclusion. When considered likely to meet inclusion criteria, studies were translated.

Data collection and analysis

Selection of studies

Two review authors (FT, RA) screened the titles and abstracts of the records retrieved by the search and eliminated those that they considered were clearly ineligible. We obtained the full-text articles of all potentially eligible records, and the same two review authors independently assessed each article against our inclusion criteria. We resolved any disagreements by discussion among all review authors.

Data extraction and management

Three review authors (FT, RA, PP) independently extracted the following data from the included studies.

- Number and characteristics of participants
- Setting and country of the study
- Details of experimental and control interventions (e.g. dose, duration)
- Length of follow-up
- Types of outcomes
- Funding and conflicts of interest

We extracted relevant data reported in graphs using WebPlotDigitizer software (Rohatgi 2022). We resolved any disagreements by discussion.

Assessment of risk of bias in included studies

Two review authors (SM, FT) independently assessed the risk of bias of the included studies using the original Cochrane risk of bias tool (RoB 1), which covers the following domains (Higgins 2011).

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective outcome reporting (reporting bias)
- Other sources of bias (other bias)

See Appendix 7 for a detailed description of the criteria for assessing risk of bias.

We assessed performance bias and detection bias separately for objective outcomes (e.g. point abstinence) and subjective outcomes (e.g. craving).

Measures of treatment effect

For dichotomous outcomes, we calculated risk ratios (RRs) with 95% confidence intervals (CIs). For continuous outcomes, we calculated the mean difference (MD) with 95% CI when the studies used the same instrument for assessing the outcome, or the standardised mean difference (SMD) when the studies used different instruments.

We decided not to use data presented as number of positive urine tests over the total number of tests in the experimental and control group as a measure of substance use, because using tests instead of participants as the unit of analysis violates the hypothesis of independence among observations. When studies reported number of missing urine stated that they were considered as positive, we included them in the analysis.

Unit of analysis issues

If two or more comparisons in multiarm trial were eligible for inclusion in the same meta-analysis, and these comparisons had one or more arms in common (e.g. dose A versus placebo and dose B versus placebo) , we split the events and participants of the shared arm between the comparisons. This method avoids the multiple use of participants in the pooled estimate of treatment effect while retaining information from each arm of the trial, though it compromises the precision of the pooled estimate.

Dealing with missing data

If studies did not report the standard deviation (SD), we used the mean of the available SDs from the other included studies.

Assessment of heterogeneity

We analysed statistical heterogeneity using the I^2 statistic and the Chi^2 test (Higgins 2003). We regarded heterogeneity as substantial if the I^2 statistic was greater than 50% or if the P value of the Chi^2 test was below 0.10 (Deeks 2017). Following guidance in the *Cochrane Handbook for Systematic Reviews of Interventions*, we used the following rough guide to interpret the I^2 values (Deeks 2017).

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity

Assessment of reporting biases

If we included at least 10 datasets in a meta-analysis, we created a funnel plot (plot of the effect estimate from each study against the sample size or effect standard error) to assess publication bias.

Data synthesis

We combined the outcomes of the individual trials through meta-analysis where possible (when the interventions and outcomes of the different trials were comparable) using a random effects model, because we expected a certain degree of heterogeneity between trials. If we identified considerable statistical heterogeneity (i.e. I^2 value of 75% or greater) or clinical heterogeneity, we considered not pooling the data.

Subgroup analysis and investigation of heterogeneity

Where a meta-analysis of a primary outcome included 10 or more datasets, we performed a subgroup analysis to investigate sources of heterogeneity and assess differences in treatment efficacy and safety according to the presence of comorbid mental disorders (all participants versus some participants versus no participants). Based

on the evidence from the trials, we decided to perform subgroup analysis according to the presence of comorbid alcohol dependence and comorbid opioid dependence.

Sensitivity analysis

To incorporate our assessment of risk of bias in the review process, we first plotted the intervention effect estimates stratified by risk of bias for allocation concealment (selection bias). If studies with different risk of selection bias showed different effect estimates, we planned to perform sensitivity analysis by excluding studies at high risk of selection bias from the analysis.

Summary of findings and assessment of the certainty of the evidence

We created a summary of findings table for each comparison using GRADEpro software to present the findings for our primary outcomes (GRADEpro 2015). Two review authors (SM and SV) assessed the certainty of evidence using the GRADE approach. With GRADE, evidence from RCTs starts at high certainty but can be downgraded for limitations related to risk of bias, consistency of effect, imprecision, indirectness, and publication bias (Atkins 2004). We used the methods and recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022). We justified all decisions to downgrade or upgrade the certainty of evidence using footnotes. The final GRADE rating falls into one of the following four categories.

- High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Results

Description of studies

For a detailed descriptions of all studies, see the Characteristics of included studies, Characteristics of excluded studies, and Characteristics of ongoing studies tables.

Results of the search

Figure 1 shows the study selection process in a PRISMA flow diagram.

For this update, we identified 288 records through database searching. After removing duplicates, we were left with 166 unique references. We excluded 130 references on the basis of their title and abstract and retrieved the full-text articles of the remaining 36 references for more detailed evaluation. Thirteen articles were ineligible (see Characteristics of excluded studies table), three articles were from ongoing studies (see Characteristics of ongoing studies table), seven articles were already included in the previous version of the review, and 13 articles were from six new eligible RCTs (see Characteristics of included studies table).

In this update, we included 13 RCTs involving a total of 1191 participants, compared to seven RCTs with 492 participants in the previous version (Pani 2010). The secondary references of new included studies include four articles previously listed as ongoing studies (NCT00149630; NCT00218608; NCT00350649; NCT00395850) and one study previously listed as awaiting classification (Schottenfeld 2004).

Included studies

We extracted a single data set from six RCTs (Baldacara 2013; Carroll 1993; George 2000; Kosten 2013; Petrakis 2000; Schottenfeld 2013), two datasets from each of five RCTs (Carroll 1998 comparison a; Carroll 1998 comparison b; Carroll 2004 comparison a; Carroll 2004 comparison b; Carroll 2012 comparison a; Carroll 2012 comparison b; Carroll 2016 comparison a; Carroll 2016 comparison b; Grassi 2007 comparison a; Grassi 2007 comparison b; Pettinati 2008 comparison a; Pettinati 2008 comparison b), and three datasets each from two RCTs (Oliveto 2011 comparison a; Oliveto 2011 comparison b; Oliveto 2011 comparison c; Pettinati 2008 comparison a; Pettinati 2008 comparison b; Pettinati 2008 comparison c), for a total of 22 datasets. We created a study ID for each dataset, though this is not standard Cochrane practice.

Participants

The 13 RCTs included a total of 1191 participants with cocaine dependence or cocaine use disorder according to DSM criteria (DSM-III-R; DSM-IV). The proportion of male participants ranged from 48% to 100%; the mean age ranged from 28.6 years to 41.6 years.

Five RCTs enroled people with comorbid alcohol abuse or dependence (Carroll 1993; Carroll 1998 comparison a; Carroll 1998 comparison b; Carroll 2004 comparison a; Carroll 2004 comparison b; Grassi 2007; Pettinati 2008

comparison a; Pettinati 2008 comparison b); six RCTs recruited people with comorbid opioid dependence or opioid use disorder in treatment with methadone (Carroll 2012 comparison a; Carroll 2012 comparison b; Kosten 2013; Oliveto 2011 comparison a; Oliveto 2011 comparison b; Oliveto 2011 comparison c; Petrakis 2000) or buprenorphine (George 2000; Schottenfeld 2013).

Treatment regimens and setting

The disulfiram dose ranged from 62.5 mg/day (Oliveto 2011 comparison a) to 400 mg/day (Grassi 2007 comparison a; Grassi 2007 comparison b). Most studies used 250 mg/day, and the median dose was 250.5 mg/day.

In all RCTs, participants received psychosocial treatments in addition to disulfiram, though two multiarm studies included experimental and control arms with no psychosocial treatment (Carroll 2012 comparison b; Carroll 2016 comparison b). All RCTs except Carroll 1993 clearly defined the psychosocial treatment concomitantly given with disulfiram, as follows.

- Cognitive behavioural psychotherapy (Carroll 1998 comparison a; Carroll 2004 comparison a; Grassi 2007 comparison a; Grassi 2007 comparison b; Kosten 2013; Oliveto 2011 comparison a; Oliveto 2011 comparison b; Oliveto 2011 comparison c; Pettinati 2008 comparison a; Pettinati 2008 comparison b)
- Contingency management (Carroll 2016 comparison a)
- Motivational intervention (Baldacara 2013)
- 12-step facilitation (Carroll 1998 comparison b; Carroll 2012 comparison a)
- Interpersonal psychotherapy (Carroll 2004 comparison b)
- Counselling (George 2000; Petrakis 2000; Schottenfeld 2013)

Duration of trials

The mean duration of the trials was 11.7 weeks (range 8 weeks to 12 weeks).

Country

Eleven RCTs were conducted in the USA. One RCT was from XXX (Baldacara 2013), and one was from XXX (Grassi 2007 comparison a; Grassi 2007 comparison b). All the RCTs were conducted in outpatient setting.

Rating instruments

- Hamilton Anxiety Rating Scale (Hamilton 1959; score ranging from 0 to 56, with higher scores indicating higher levels of anxiety): one RCT (Pettinati 2008 comparison a; Pettinati 2008 comparison b; Pettinati 2008 comparison c)
- Hamilton Depression Rating Scale (Hamilton 1960; score ranging from 0 to 52, with higher scores indicating higher levels of depression): one RCT (Pettinati 2008 comparison a; Pettinati 2008 comparison b; Pettinati 2008 comparison c)
- Structured Clinical Interview for DSM-III-R (Spitzer 1990; Spitzer 1992): two RCTs (Carroll 1998 comparison a; Carroll 1998 comparison b; Petrakis 2000)
- Structured Clinical Interview for DSM-IV (First 1995): six RCTs (Carroll 2004 comparison a; Carroll 2004 comparison b; Carroll 2012 comparison a; Carroll 2012 comparison b; Carroll 2016 comparison a; Carroll 2016 comparison b; Oliveto 2011 comparison a; Oliveto 2011 comparison b; Oliveto 2011 comparison c; Pettinati 2008 comparison a; Pettinati 2008 comparison b; Pettinati 2008 comparison c; Schottenfeld 2013)
- Substance Abuse Calendar (similar to the Timeline Followback method; Robinson 2012): two RCTs (Carroll 2004 comparison a; Carroll 2004 comparison b; Carroll 2016 comparison a; Carroll 2016 comparison b)
- Systematic Assessment for Treatment Emergent Effect (Rabkin 1992): one RCT (Pettinati 2008 comparison a; Pettinati 2008 comparison b; Pettinati 2008 comparison c)
- Timeline Followback method (TLFB; Sobell 1992): two RCTs (Pettinati 2008 comparison a; Pettinati 2008 comparison b; Pettinati 2008 comparison c; Schottenfeld 2013)
- Visual Analogue Scale (VAS; Nicholson 1978; score ranging from 0 to 100, with higher scores indicating higher levels of craving): one RCT (Grassi 2007 comparison a; Grassi 2007 comparison b)

Comparisons

- Disulfiram versus placebo or no pharmacological treatment: 12 RCTs, 18 datasets, 1060 participants (Baldacara 2013; Carroll 1998 comparison a; Carroll 1998 comparison b; Carroll 2004 comparison a; Carroll 2004 comparison b; Carroll 2012 comparison a; Carroll 2012 comparison b; Carroll 2016 comparison a; Carroll 2016 comparison b; George 2000; Grassi 2007 comparison a; Kosten 2013; Oliveto 2011 comparison a; Oliveto 2011 comparison b; Oliveto 2011 comparison c; Petrakis 2000; Pettinati 2008 comparison a; Schottenfeld 2013)
- Disulfiram versus naltrexone: three RCTs, 131 participants (Carroll 1993; Grassi 2007 comparison b; Pettinati 2008 comparison b)

Subgroup analyses

We performed the following subgroup analyses

- Comorbid alcohol dependence
- Comorbid opioid dependence

Excluded studies

We excluded 13 studies (see Characteristics of excluded studies).

Risk of bias in included studies

See Figure 2 and Figure 3 for a summary of these results.

Allocation

Random sequence generation

We judged six RCTs at low risk of selection bias for random sequence generation and the remaining RCTs at unclear risk (the publications provided no information on method of sequence generation).

Allocation concealment

We considered 11 RCTs at unclear risk for allocation concealment, as they provided no information. The other two RCTs were at low risk of bias in this domain.

Blinding

Blinding of participants and personnel (performance bias)

Our risk of bias judgements were identical for selective and objective outcomes. We judged three RCTs at high risk of performance bias because they had an open-label design. Two RCTs were described as double-blind trials but provided no further details (unclear risk of bias). We considered the remaining RCTs at low risk of performance bias.

Blinding of outcome assessor (detection bias)

For subjective outcomes, we judged three RCTs at high risk of detection bias, two at unclear risk, and six at low risk.

For objective outcomes, we considered all RCTs at low risk of detection bias as the outcomes were unlikely to be influenced by lack of blinding.

Incomplete outcome data

All the RCTs were at low risk of attrition bias because they analysed all randomised participants in the arm to which they were randomised (intention-to-treat approach).

Selective reporting

The protocol was available for four RCTs; however, two of these protocols did not clearly describe the outcomes. Therefore, we judged only two RCTs at low risk for selective reporting because all the outcomes listed in the protocols were assessed and reported in the final publications. We considered one RCT at high risk and eight RCTs at unclear risk.

Other potential sources of bias

We did not assess other potential threats to validity.

Effects of interventions

Comparison 1. Disulfiram versus placebo or no pharmacological treatment

Primary outcomes

See Summary of findings table 1.

Frequency of cocaine use

We included 13 datasets (818 participants) in this meta-analysis (Baldacara 2013; Carroll 2004 comparison a; Carroll 2004 comparison b; Carroll 2012 comparison a; Carroll 2012 comparison b; Carroll 2016 comparison a; Carroll 2016 comparison b; George 2000; Petrakis 2000; Pettinati 2008 comparison a; Schottenfeld 2013). Disulfiram compared with placebo or no pharmacological treatment may have little or no effect on frequency of cocaine use (SMD −0.11 SDs, 95% CI −0.39 to 0.17; low-certainty evidence). The meta-analysis showed

substantial heterogeneity (Tau^2 = 0.18; Chi^2 = 43.39, degrees of freedom (df) = 12 (P < 0.001); I^2 = 72%). See Analysis 1.1 and Figure 4. Visual inspection of the funnel plot did not suggest publication bias (Figure 5).

Subgroup analysis: comparator

The test for subgroup difference suggested a significant difference in the effect according to the type of comparator (P = 0.002). The subgroup analysis suggested that disulfiram increased the frequency of cocaine use compared to no pharmacological treatment (SMD 0.57 SDs, 95% CI 0.14 to 0.99; 2 datasets, 90 participants) but had little or no effect compared to placebo (Analysis 1.1).

Subgroup analysis: comorbid alcohol dependence

The test for subgroup difference suggested a significant difference in the effect according to the presence of alcohol dependence (Chi^2 = 12.09, df = 2 (P = 0.002), I^2 = 83.5%). The subgroup analysis suggested that disulfiram reduced the frequency of cocaine use among participants without alcohol dependence (SMD −1.60 SDs, 95% CI −2.56 to −0.64; 2 studies, 50 participants), but not among participants with comorbid alcohol dependence, or in datasets that included people with and without alcohol dependence (Analysis 3.1).

Subgroup analysis: comorbid opioid dependence

All participants with comorbid opioid dependence received treatment with opioid agonists (methadone or buprenorphine). We found no differences between subgroups according to the presence of comorbid opioid dependence in opioid agonist treatment (Chi^2 = 1.08, df = 1 (P = 0.30), I^2 = 7.3%; Analysis 3.2)

Amount of cocaine use

We included seven datasets (376 participants) in this meta-analysis (Baldacara 2013; George 2000; Oliveto 2011 comparison a; Oliveto 2011 comparison b; Oliveto 2011 comparison c; Petrakis 2000; Pettinati 2008 comparison a). Disulfiram compared to placebo may have little or no effect on amount of cocaine use (SMD −0.00 SDs, 95% CI −0.30 to 0.30; low-certainty evidence). There was moderate heterogeneity between the datasets (Tau^2 = 0.07; Chi^2 = 10.62, df = 6 (P = 0.10); I^2 = 44%). See Analysis 1.2 and Figure 6.

Continuous abstinence from cocaine

We included six datasets (386 participants) in this meta-analysis (Carroll 1998 comparison a; Carroll 1998 comparison b; Carroll 2016 comparison a; Carroll 2016 comparison b; George 2000; Schottenfeld 2013). Disulfiram compared to placebo or no pharmacological treatment may have little or no effect on continuous abstinence from cocaine (RR 1.23, 95% CI 0.80 to 1.91; low-certainty evidence) The results of statistical tests suggested low or moderate heterogeneity between the datasets (Tau^2 = 0.11; Chi^2 = 8.02, df = 5 (P = 0.16); I^2 = 38%). See Analysis 1.3 and Figure 7.

Subgroup analysis: comparator

The subgroup analysis did not show a difference in the intervention effect on continuous abstinence from cocaine according to the type of comparator (Chi^2 = 3.50, df = 1 (P = 0.06); I^2 = 71.4%).

Point abstinence from cocaine

We included three datasets (142 participants) in this meta-analysis (Baldacara 2013; Carroll 2012 comparison a; Carroll 2012 comparison b). Disulfiram compared to placebo may increase point abstinence (RR 1.58, 95% CI 1.05 to 2.36; low-certainty evidence). There was no evidence of heterogeneity between the datasets (Tau^2 = 0.00; Chi^2 = 0.79, df = 2 (P = 0.67); I^2 = 0%). See Analysis 1.4 and Figure 8.

Dropout for any reason

We included 14 datasets (841 participants) in this meta-analysis (Baldacara 2013; Carroll 2012 comparison a; Carroll 2012 comparison b; Carroll 2016 comparison a; Carroll 2016 comparison b; George 2000; Grassi 2007 comparison b; Kosten 2013; Oliveto 2011 comparison a; Oliveto 2011 comparison b; Oliveto 2011 comparison c; Petrakis 2000; Pettinati 2008 comparison a; Schottenfeld 2013). Disulfiram compared with placebo or no pharmacological treatment may have little or no effect on dropout for any reason (RR 1.20, 95% CI 0.92 to 1.55; low-certainty evidence). The results of statistical tests suggested low heterogeneity (Tau^2 = 0.03; Chi^2 = 14.96, df = 13 (P = 0.31); I^2 = 13%). See Analysis 1.5. Visual inspection of the funnel plot did not suggest publication bias (Figure 9).

Subgroup analysis: comparator

The subgroup analysis showed no difference in the intervention effect on dropout according to the type of comparator.

Subgroup analyses: comorbid alcohol dependence and comorbid opioid dependence

We found no differences in the intervention effect according to the presence of comorbid alcohol dependence (Chi^2 = 0.39, df = 2 (P = 0.82), I^2 = 0%; Analysis 3.3) or opioid dependence (Chi^2 = 0.69, df = 1 (P = 0.41), I^2 = 0%; Analysis 3.4). All participants with comorbid opioid dependence received treatment with opioid agonists (methadone or buprenorphine).

Dropout due to adverse events

One RCT (67 participants) reported the number of participants who did not complete the treatment due to adverse events (Petrakis 2000). Disulfiram compared to placebo may have little or no effect on dropout due to adverse events, but the evidence is very uncertain (RR 12.97, 95% CI 0.77 to 218.37; very low-certainty evidence; Analysis 1.6).

Any adverse events

One RCT (30 participants) reported the number of participants who experienced at least one adverse event (Baldacara 2013). Disulfiram compared to placebo may have little or no effect on the occurrence of adverse events, but the evidence is very uncertain (RR 3.0, 95% CI 0.35 to 25.98), very low-certainty evidence; Analysis 1.7).

Serious adverse events

No RCTs reported the number of participants who experienced at least one serious adverse event.

Secondary outcomes

Individual adverse events

We included one, two, or three datasets in the analysis of individual adverse events (Baldacara 2013; Carroll 1998 comparison a; Pettinati 2008 comparison a). Evidence from Pettinati 2008 comparison a (109 participants) suggested that disulfiram compared to placebo may lower increased sexual desire (RR 0.41, 95% CI 0.17 to 0.97; Analysis 1.8). We found no difference between the effect of disulfiram and placebo on any of the other adverse events evaluated (headache, drowsiness/fatigue, anxiety/irritability, nausea, upper respiratory tract infections, decreased sexual desire, vomiting, skin rush, difficulty in achieving orgasm, toothache, diarrhoea, and slurred speech).

Craving

Evidence from Grassi 2007 comparison a (8 participants) suggested that disulfiram compared to no pharmacological treatment decreased craving measured on a VAS of 0 to 100 points (MD –25.00 points, 95% CI –44.52 to –5.48; Analysis 1.9).

Severity of dependence

No RCTs reported severity of dependence.

Psychiatric symptoms/psychological distress: depression

Evidence from Pettinati 2008 comparison a (107 participants) suggested no difference between the effect of disulfiram and placebo on depression measured by the Hamilton Depression Rating Scale, which ranges from 0 to 52 points(MD –1.00 points, 95% CI –4.13 to 2.13; Analysis 1.10).

Psychiatric symptoms/psychological distress: anxiety

Evidence from Pettinati 2008 comparison a (107 participants) suggested no difference between the effect of disulfiram and placebo on anxiety measured by the Hamilton Anxiety Rating Scale, which ranges from 0 to 56 points (MD –1.50 points, 95% CI –4.78 to 1.78; Analysis 1.11).

Comparison 2. Disulfiram versus naltrexone

Primary outcomes

See Summary of findings table 2.

Frequency of cocaine use

We included two datasets (123 participants) in this meta-analysis (Carroll 1993; Pettinati 2008 comparison b). Disulfiram compared to naltrexone may reduce the frequency of cocaine use (MD –1.90 days, 95% CI –3.37 to –0.43; low-certainty evidence). The results of statistical tests suggested low or moderate heterogeneity between the datasets ($Tau^2 = 0.57$; $Chi^2 = 1.48$, df = 1 (P = 0.22); $I^2 = 32\%$). See Analysis 2.1

Amount of cocaine use

We included two datasets (123 participants) in this meta-analysis (Carroll 1993; Pettinati 2008 comparison b). Disulfiram compared to naltrexone may have little or no effect on amount of cocaine use (SMD 0.12 SDs, 95% CI –0.27 to 0.51; low-certainty evidence). The results of statistical tests suggested low heterogeneity between the datasets ($Tau^2 = 0.01$; $Chi^2 = 1.07$, df = 1 (P = 0.30); $I^2 = 7\%$). See Analysis 2.2.

Continuous abstinence from cocaine

No RCTs reported continuous abstinence from cocaine.

Point abstinence from cocaine

No RCTs reported continuous abstinence from cocaine.

Dropout for any reason

We included three datasets (131 participants) in this meta-analysis (Carroll 1993; Pettinati 2008 comparison b; Grassi 2007 comparison b). Disulfiram compared to naltrexone may have little or no effect on the number of people who do not complete treatment (RR 0.86, 95% CI 0.56 to 1.32; very low-certainty evidence). The results of statistical tests suggested low heterogeneity between the datasets ($Tau^2 = 0.03$; $Chi^2 = 2.57$, df = 2 (P = 0.28); $I^2 = 22\%$). See Analysis 2.3.

Dropout due to adverse events

Evidence from Grassi 2007 comparison b (8 participants) suggested that disulfiram compared to naltrexone has no effect on the number of people who do not complete treatment due to adverse events, but the evidence is very uncertain (RR 0.50, 95% CI 0.07 to 3.55; very low-certainty evidence; Analysis 2.4).

Any adverse events

No RCTs reported the number of participants who experienced at least one adverse event.

Serious adverse events

No RCTs reported the number of participants who experienced at least one serious adverse event.

Secondary outcomes

Individual adverse events

We only included data from Pettinati 2008 comparison b in the analyses of individual adverse events, finding no difference between the effect of disulfiram and naltrexone on the occurrence of headache, drowsiness/fatigue, anxiety, nausea, upper respiratory tract infection, decreased sexual desire, increased sexual desire, vomiting, skin rush, difficulty in achieving orgasm, toothache, or diarrhoea (Analysis 2.5).

Craving

Evidence from Grassi 2007 comparison b (8 participants) suggested there was no difference between the effect of disulfiram and naltrexone on craving measured on a VAS of 0 to 100 points (MD –1.02 points, 95% CI –16.73 to 14.69; Analysis 2.6).

Severity of dependence

No RCTs reported severity of dependence.

Psychiatric symptoms/psychological distress: depression

Evidence from Pettinati 2008 comparison b (105 participants) suggested no difference between the effect of disulfiram and placebo on depression measured by the Hamilton Depression Rating Scale, which ranges from 0 to 52 points (MD –2.00 points, 95% CI –4.76 to 0.76; Analysis 2.7).

Psychiatric symptoms/psychological distress: anxiety

Evidence from Pettinati 2008 comparison b (105 participants) suggested no difference between the effect of disulfiram and placebo on anxiety measured by the Hamilton Anxiety Rating Scale, which ranges from 0 to 56 points (MD –1.00 points, 95% CI –4.27 to 2.27; Analysis 2.8).

Sensitivity analysis

We rated no RCTs at high risk of selection bias, so we were unable to perform our prespecified sensitivity analysis.

Discussion

Summary of main results

This review update included 13 RCTs with 1191 participants (71.2% males) compared to seven RCTs with 492 participants in the previous version (Pani 2010). We extracted a single data set from six RCTs, two datasets from each of five RCTs, and three datasets each from two RCTs, for a total of 22 datasets. Twelve RCTs (18 datasets) with 1060 participants evaluated disulfiram versus placebo or no pharmacological treatment, and three RCTs (3 datasets) with 131 participants evaluated disulfiram versus naltrexone.

Disulfiram versus placebo or no pharmacological treatment

Compared to placebo, disulfiram may increase point abstinence from cocaine (the number of people who are abstinent at the end of treatment). However, disulfiram compared to placebo or no pharmacological treatment may have little or no effect on frequency of cocaine use, amount of cocaine use, continuous abstinence, or dropout for any reason. Subgroup analyses suggested that disulfiram reduces the frequency of cocaine use when compared to no pharmacological treatment but not when compared to placebo, and among people without alcohol dependence but not among people with alcohol dependence. However, these subgroup results included only two datasets each and limited numbers of participants (90 in comparator subgroup analysis, 50 in alcohol

dependence subgroup analysis). We are uncertain about the effects of disulfiram compared to placebo on the number of people who drop out of treatment due to adverse events and on the number of people who experience at least one adverse event, as the evidence is of very low certainty.

Studies have shown that by inhibiting the primary pathways for cocaine metabolism, disulfiram increases plasma cocaine concentration significantly more than placebo, and, depending on the dosage of the two compounds and the method of cocaine administration, may also increase heart rate and systolic and diastolic blood pressure (McCance 1998a; McCance 1998b; Baker 2007). The inclusion criteria of the included RCTs took into account the risk of disulfiram and cocaine interactions. Some studies that specifically investigated these potential interactions reported that disulfiram-cocaine interactions may not constitute a major problem (Malcolm 2008; Roache 2011). However, given the inconclusive evidence in clinical practice, the possibility of adding further risks should be considered (Kleczkowska 2021). These potential interactions together with other adverse effects (i.e. hepatotoxicity, cardiovascular, and psychiatric complications) could worsen the safety profile of disulfiram in the treatment of cocaine dependence.

Disulfiram versus naltrexone

Disulfiram compared to naltrexone may reduce the frequency of cocaine use, but may have little or no effect on amount of cocaine use. We are uncertain about the effects of disulfiram compared to naltrexone on dropout for any reason and on dropout due to adverse events because the evidence is of very low certainty.

Overall completeness and applicability of evidence

Overall, the 13 RCTs included in this update provide limited evidence on the efficacy of disulfiram compared with placebo, no pharmacological treatment, or naltrexone in terms of efficacy, acceptability, and safety. Owing to lack of data, we were able to perform subgroup analyses for only three outcomes. Most participants were males (72.1%). Eleven RCTs were conducted in the USA, most at Yale University. This limits the generalisability of the results, because gender, sex, and social context influence the severity of dependence, the availability to enter an experimental design, and the response to treatment; and because different clinical contexts can influence differently the selection of participants and the results of the treatment. Furthermore, the selected RCTs differed in terms of design, quality, characteristics of participants, services, and treatments delivered: four were open-label studies; three compared disulfiram to naltrexone; four involved participants with comorbid alcohol dependence; six involved participants with comorbid opioid dependence co-treated with methadone or buprenorphine; three offered drug counselling as an ancillary intervention, six offered cognitive behavioural therapy, two offered twelve-step facilitation, one offered interpersonal psychotherapy, and one offered no specified individual psychotherapy. The trials also differed in their definitions of outcome variables, so we were not always able to pool data and carry out meta-analyses and subgroup analyses.

Quality of the evidence

Applying the criteria recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), we judged that 75% of the RCTs had unclear risk of selection bias and about 25% had high risk of performance bias. Finally, 25% of the RCTs were at high risk of detection bias (subjective outcomes).

Overall, comparing disulfiram to placebo or no pharmacological treatment, we rated the certainty of evidence as low or very low for all the primary outcomes considered. Reasons for downgrading were risk of bias, inconsistency, and imprecision of the overall estimates. Similarly, comparing disulfiram to naltrexone, we rated the evidence as low or very low for all the primary outcomes considered. Reasons for downgrading were risk of bias and imprecision of the overall estimates.

Potential biases in the review process

Visual inspection of funnel plots did not suggest the presence of publication bias (Figure 5; Figure 9).

Agreements and disagreements with other studies or reviews

One systematic review published in 2019 showed a worse retention rate of participants treated with disulfiram than those treated with placebo (RR 0.90, 95% CI 0.83 to 0.99; 7 RCTs) and no differences between disulfiram and placebo in the number of participants with three or more consecutive weeks of negative urinalyses (RR 0.96, 95% CI 0.63 to 1.45; 3 RCTs, 296 participants) in line with our finding for continuous abstinence (Chan 2019). The numbers of trials and participants in the analyses of Chan 2019 were lower than those included in our systematic review, and there was considerable heterogeneity in the rate of negative urinalyses (I^2 = 97%).

Authors' conclusions

Implications for practice

Our results show that disulfiram compared to placebo may increase point abstinence (the proportion of people who are abstinent at the end of treatment). However, disulfiram compared to placebo or no pharmacological treatment may have little or no effect on frequency of cocaine use, amount of cocaine use, continued abstinence, and dropout for any reason. We are unsure if disulfiram has any adverse effects in people with cocaine dependence. Caution is required when transferring our results to clinical practice.

Implications for research

Larger studies are needed to confirm our results. Future studies should investigate the efficacy and safety profile of disulfiram in specific categories of people with cocaine dependence, such as women, people with other substance use disorders, people co-treated with other medications (methadone, buprenorphine), and people receiving specific psychosocial interventions. Conducting future studies in countries other than the USA would increase the generalisability of the evidence.

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Editorial and peer-reviewer contributions

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The following people conducted the editorial process for this article.

- Sign-off Editor (provided editorial guidance to authors, final editorial decision): Prof Michael Farrell, MB, BCh, BAO, MRCP, MRCPsych, Director Professor of Addiction Psychiatry National Drug and Alcohol Research Centre, University of New South Wales, Sydney, Australia
- Managing Editor (selected peer reviewers, collated peer-reviewer comments): Zuzana Mitrova, Cochrane Drugs and Alcohol
- Copy Editor (copy editing and production): Julia Turner, Cochrane Central Production Service
- Peer-reviewers (provided comments and recommended an editorial decision): Peter Blanken, Parnassia Addiction Research Centre (PARC), Brijder Addiction Treatment, Parnassia Group (clinical/content review), Blanca Iciar Indave, MD, MPH, PhD Scientific agent Support to practice sector Public health unit European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (clinical/content review)

Data and analyses

Comparison 1

Disulfiram versus placebo or no pharmacological treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Frequency of cocaine use	13	818	Std. Mean Difference (IV, Random, 95% CI)	-0.11 [-0.39, 0.17]
1.1.1 Versus placebo	11	728	Std. Mean Difference (IV, Random, 95% CI)	-0.22 [-0.50, 0.06]
1.1.2 Versus no pharmacological treatment	2	90	Std. Mean Difference (IV, Random, 95% CI)	0.57 [0.14, 0.99]
1.2 Amount of cocaine use	7		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.2.1 Versus placebo	7	376	Std. Mean Difference (IV, Random, 95% CI)	-0.00 [-0.30, 0.30]
1.3 Continuous abstinence	6	386	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.80, 1.91]
1.3.1 Versus placebo	4	296	Risk Ratio (M-H,	0.93 [0.57, 1.52]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
			Random, 95% CI)	
1.3.2 Versus no pharmacological treatment	2	90	Risk Ratio (M-H, Random, 95% CI)	1.87 [1.09, 3.22]
1.4 Point abstinence	3	142	Risk Ratio (M-H, Random, 95% CI)	1.58 [1.05, 2.36]
1.4.1 Versus placebo	3	142	Risk Ratio (M-H, Random, 95% CI)	1.58 [1.05, 2.36]
1.5 Dropout for any reason	14	841	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.92, 1.55]
1.5.1 Versus placebo	13	833	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.90, 1.48]
1.5.2 Versus no pharmacological treatment	1	8	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.76, 11.81]
1.6 Dropout due to adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.6.1 Versus placebo	1	67	Risk Ratio (M-H, Fixed, 95% CI)	12.97 [0.77, 218.37]
1.7 Any adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.7.1 Versus placebo	1	30	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.35, 25.68]
1.8 Individual adverse events	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.8.1 Headache	3	258	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.92, 1.55]
1.8.2 Drowsiness	3	258	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.93, 1.97]
1.8.3 Anxiety	2	228	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.83, 2.02]
1.8.4 Nausea	1	107	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.61, 1.35]
1.8.5 Decreased sexual desire	1	107	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.65, 2.07]
1.8.6 Increased sexual desire	1	107	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.17, 0.97]
1.8.7 Vomiting	1	107	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.41, 2.08]
1.8.8 Skin rush	1	107	Risk Ratio (M-H, Random, 95% CI)	1.63 [0.57, 4.66]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.8.9 Difficulty achieving orgasm	1	107	Risk Ratio (M-H, Random, 95% CI)	1.83 [0.66, 5.11]
1.8.10 Toothache	1	107	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.51, 3.65]
1.8.11 Diarrhoea	2	228	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.61, 1.88]
1.8.12 Slurred Speech	1	30	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 68.26]
1.9 Craving (measured on a visual analogue scale of 0−100 points)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.9.1 Versus no pharmacological treatment	1	8	Mean Difference (IV, Fixed, 95% CI)	-25.00 [-44.52, -5.48]
1.10 Depression (measured on a scale of 0−52 points)	1	107	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-4.13, 2.13]
1.10.1 Versus placebo	1	107	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-4.13, 2.13]
1.11 Anxiety (measured on a scale of 0−56 points)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.11.1 Versus placebo	1	107	Mean Difference (IV, Fixed, 95% CI)	-1.50 [-4.78, 1.78]

Comparison 2

Disulfiram versus naltrexone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Frequency of cocaine use	2	123	Mean Difference (IV, Random, 95% CI)	-1.90 [-3.37, -0.43]
2.2 Amount of cocaine use	2	123	Std. Mean Difference (IV, Random, 95% CI)	0.12 [-0.27, 0.51]
2.3 Dropout for any reason	3	131	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.56, 1.32]
2.4 Dropout due to adverse events	1	8	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.07, 3.55]
2.5 Individual adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.5.1 Headache	1	105	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.81, 1.41]
2.5.2 Drowsiness/fatigue	1	105	Risk Ratio (M-H,	1.08 [0.67, 1.73]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
			Random, 95% CI)	
2.5.3 Anxiety/irritability	1	105	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.81, 1.74]
2.5.4 Nausea	1	105	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.67, 1.73]
2.5.5 Upper respiratory tract infection	1	105	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.75, 1.85]
2.5.6 Decreased sexual desire	1	105	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.62, 1.98]
2.5.7 Increased sexual desire	1	105	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.23, 1.50]
2.5.8 Vomiting	1	105	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.34, 1.60]
2.5.9 Skin rush	1	105	Risk Ratio (M-H, Random, 95% CI)	1.96 [0.63, 6.12]
2.5.10 Difficulty achieving orgasm	1	105	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.51, 3.14]
2.5.11 Toothache	1	105	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.31, 1.63]
2.5.12 Diarrhoea	1	105	Risk Ratio (M-H, Random, 95% CI)	1.72 [0.53, 5.52]
2.6 Craving (measured on a visual analogue scale of 0–100 points)	1	8	Mean Difference (IV, Fixed, 95% CI)	-1.02 [-16.73, 14.69]
2.7 Depression (measured on a scale of 0–52 points)	1	105	Mean Difference (IV, Fixed, 95% CI)	-2.00 [-4.76, 0.76]
2.8 Anxiety (measured on a scale of 0–56 points)	1	105	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-4.27, 2.27]

Comparison 3

Disulfiram versus placebo or no pharmacological treatment (subgroup analyses)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Frequency of cocaine use (according to the presence of alcohol dependence)	12	641	Std. Mean Difference (IV, Random, 95% CI)	-0.10 [-0.42, 0.22]
3.1.1 With comorbid alcohol dependence	3	197	Std. Mean Difference (IV, Random, 95% CI)	0.31 [-0.18, 0.80]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size	
3.1.2 Without comorbid alcohol dependence	2	50	Std. Mean Difference (IV, Random, 95% CI)	-1.60 [-2.56, -0.64]	
3.1.3 Mix of participants with and without alcohol dependence	7	394	Std. Mean Difference (IV, Random, 95% CI)	-0.02 [-0.30, 0.26]	
3.2 Frequency of cocaine use (according to the presence of opioid dependence in opioid agonist treatment)	11	719	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.46, 0.11]	
3.2.1 With comorbid opioid dependence	5	371	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-0.78, 0.08]	
3.2.2 Without comorbid opioid dependence	6	348	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.44, 0.37]	
3.3 Dropout for any reason (according to the presence of comorbid alcohol dependence)	13	664	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.87, 1.69]	
3.3.1 With comorbid alcohol dependence	2	115	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.22, 5.90]	
3.3.2 Without comorbid alcohol dependence	3	124	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.30, 3.23]	
3.3.3 With intermediate comorbid alcohol dependence	8	425	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.97, 2.10]	
3.4 Dropout for any reason (according to the presence of opioid dependence in opioid agonist treatment)	12	742	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.90, 1.63]	
3.4.1 With comorbid opioid dependence	9	597	Risk Ratio (M-H, Random, 95% CI)	1.33 [1.05, 1.69]	
3.4.2 Without comorbid opioid dependence	3	145	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.21, 2.79]	

What's new

Date	Event	Description
29 May 2023	New citation required but conclusions have not changed	New authors and new studies
31 January 2022	New search has been performed	Research 2022 Update

History

Protocol first published: Issue 2, 2008
Review first published: Issue 1, 2010

Date	Event	Description
14 May 2009	New search has been performed	Final draft of the review
21 April 2008	Amended	Converted to new review format
19 December 2007	New citation required and major changes	Substantive amendment

Contributions of authors

RA and PP wrote the background section.
SM and RA wrote the methods section.
FT, PP, and RA conducted the screening.
FT, RA, and PP extracted data.
SM and FT assessed the risk of bias.
SM and SV assessed the certainty of evidence using the GRADE system.
FT, SM, and RA undertook data analysis.
SM and RA wrote the results section.
PP and RA wrote the discussion.
SM and RA wrote the conclusion sections.
All review authors revised and approved the final report.

Declarations of interest

FT: none known
SM is the Joint Co-ordinating Editor of Cochrane Drugs and Alcohol Group. She was not involved in the editorial process of the current protocol.
ET: none known
RV: none known
SV: none known
PP: none known
RA: is an Editor of Cochrane Drugs and Alcohol Group. She was not involved in the editorial process of the current protocol.

Sources of support

Internal sources

- Department of Epidemiology Lazio Region, Italy
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- Department of Biomedical Sciences, Section of Neurosciences and Clinical Pharmacology, University of Cagliari, Italy
  Sources of support

External sources

- New Source of support, Other
  No external sources

Differences between protocol and review

See Pani 2008 (protocol).

In the 2010 version of this review (Pani 2010), we changed the criteria to assess methodological quality of included studies to conform to the recommended methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.1 (Higgins 2008).

We made the following changes in the 2023 update.

- We incorporated an additional bibliometric database (PsycINFO) to achieve a broader literature coverage.
- We included only randomised controlled trials.
- We did not use data presented as number of positive urine tests over total number of tests in the experimental and control group as a measure of substance use: using tests instead of participants as the unit of analysis violates the hypothesis of independence among observations. When studies reported number of missing urine stated that they were considered as positive, we included them in the analysis.
- Regarding the participants using cocaine at follow-up, we decided to focus the update on the results at the end of treatment because studies included in the previous version did not provide follow-up data.
- We modified the definitions of the outcomes (see Types of outcome measures).
    - We changed "Dropouts from the treatment as number of participants who did not complete the treatment" to "Acceptability: Dropout for any reason (number of participants who did not complete treatment); Dropout due to adverse events (number of participants who did not complete treatment due to adverse events)"
    - We changed "Acceptability of the treatment as number and type of side effects experienced during the treatment" to "Safety: Any adverse events (number of participants who experienced at least one adverse event); Serious adverse events (number of participants who experienced at least one serious adverse event)"
    - We changed "The number of participants who developed single adverse events, both subjectively and objectively assessed" to "Individual adverse events, measured subjectively or objectively (number of participants who experienced a specific adverse event", and moved the outcome to Secondary outcomes.
    - We changed "Use of primary substance of abuse as number of participants that reported the use of cocaine during the treatment, and/or number of participants with urine samples positive for cocaine" to "Efficacy: Frequency of cocaine use (mean number of days or weeks of cocaine use at the end of treatment); Amount of cocaine use (mean weight of cocaine used or money spent on cocaine at the end of treatment); Continuous abstinence from cocaine (number of participants who had achieved and maintained abstinence for at least three weeks at the end of treatment); Point abstinence from cocaine (number of participants who were abstinent at the end of treatment)
    - We considered "Compliance" was part of the primary outcome of "Acceptability".
    - "Amount of cocaine use (as measured by grams used or money spent)" was included in the primary outcome of "Efficacy" in the 2023 update.
- We included in the same comparison studies comparing disulfiram with placebo and studies comparing disulfiram with no pharmacological treatment.
- We performed the subgroup analyses for the primary outcomes that involved at least 10 datasets.

Characteristics of studies

Characteristics of included studies [ordered by study ID]

Baldacara 2013

Study characteristics	
Methods	**Design:** double-blind, randomised, placebo-controlled study **Study dates:**
Participants	**Number randomised:** 30 **Sex (% male):** 100% **Age:** mean age of participants not reported **Ethic background:** not reported **Setting/country:** **Civil status:** not reported **Employment status:** not reported **Baseline cocaine use:** not reported **Method of cocaine use:** not reported **Baseline alcohol use:** not reported **Inclusion criteria** • Male • Diagnosis of crack cocaine dependence according to ICD-10 • Age 18–40 years

	Exclusion criteria • Negative history of crack cocaine dependence • Physical illness or another psychiatric disorder • Use of another drug • Inability or unwillingness to provide consent
Interventions	**EG:** disulfiram (250 mg/day) plus motivational interviewing and group therapy (n =15) **CG:** placebo for 60 days plus motivational interviewing and group therapy, 15 participants **Duration of intervention:** 60 days
Outcomes	• Treatment adherence (number of participants who received treatment for the full 60 days) • Frequency of drug use (mean of number of days per week that crack cocaine was used) • Drug dose (daily mean dose of crack cocaine used in grams) • Drug-free rate (number of participants who stopped crack cocaine use after 60 days, confirmed by urinalysis) • Side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Quote: "The subjects were randomly divided by permuted blocks into two groups."
Allocation concealment?	Unclear risk	No information provided.
Blinding? Objective outcomes	Unclear risk	The study reports that the design was double-blind; no further details provided.
Blinding? Subjective outcomes	Unclear risk	The study reports that the design was double-blind; no further details provided.
Blinding of outcome assessor Subjective outcomes	Unclear risk	The study reports that the design was double-blind; no further details provided.
Blinding of outcome assessor Objective outcomes	Low risk	Study described as double-blind and the objective outcome measured are unlikely to be influenced by (lack of) blinding.
Incomplete outcome data addressed?	Low risk	All randomised participants included in the analysis.
Free of selective reporting?	Unclear risk	Study protocol not available.

Carroll 1993

Study characteristics

Methods	Randomised controlled study
Participants	18 subjects; mean age 32 years; male 72.2%; white 61.1%; average baseline alcohol 5.3 standard drinks/day; average baseline cocaine 3.7 g/week. Inclusion criteria: fulfilling DSM-III-R criteria for cocaine dependence and alcohol dependence or abuse. Exclusion criteria: subjects with other substance dependence, psychotic, or bipolar disorder as assessed by the Structured Clinical Inteview for DSM-III-R.
Interventions	(1) Disulfiram plus individual psychotherapy, 9 participants; (2) naltrexone plus individual psychotherapy, 9 participants. Disulfiram dose: 250 mg/day; naltrexone 50 mg/day. Outpatient. Duration 12 weeks. Country of origin: USA.
Outcomes	Primary outcomes: frequency and intensity of alcohol and cocaine use measured as self-reports and toxicological screens. Secondary outcomes: retention in treatment.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	No information provided.
Allocation concealment?	Unclear risk	The method of concealment is not described.
Blinding? Objective outcomes	High risk	Open-label. Does not report any procedure to prevent investigators and participants from knowing the allocated intervention.
Blinding? Subjective outcomes	High risk	Open-label. Does not report any procedure to prevent investigators and participants from knowing the allocated intervention.
Blinding of outcome assessor Subjective outcomes	High risk	Even though self-reports of substance use were collected by a blind evaluator, participants were nor blinded from the allocated intervention.
Blinding of outcome assessor Objective outcomes	Low risk	Outcomes unlikely to be influenced by lack of blinding.

Incomplete outcome data addressed?	Low risk	Outcomes assessed from all randomised participants.
Free of selective reporting?	Unclear risk	Study protocol not available.

Carroll 1998 comparison a

Study characteristics	
Methods	**Design:** RCT **Study dates:**
Participants	**Number randomised:** 122 **Sex (% male):** 73% **Age:** mean 30.8 years **Setting/country:** outpatient clinic, USA **Ethic background:** 39% white **Civil status:** 59% single or divorced **Employment status:** 43% in work **Baseline cocaine use:** 14.1 days in the past 30 days **Method of cocaine use:** 20% intranasal; 3% IV **Baseline alcohol use:** 17.2 days in the past 30 days **Inclusion criteria** • Fulfilling DSM-III-R criteria for current cocaine dependence and alcohol dependence or abuse **Exclusion criteria** • Physical dependence on opiates or barbiturates, or principal drug of dependence other than cocaine • Meeting lifetime DSM-III-R criteria for a psychotic or bipolar disorder, or expressing significant suicidal or homicidal ideation • Current medical condition contraindicating use of disulfiram • Treatment for substance use during the previous 2 months or current psychotherapy or pharmacotherapy for any other psychiatric disorder • Condition of probation or parole requiring reports of drug use to officers of the court
Interventions	**EG1:** disulfiram 250–500 mg/day (mode 261.5 mg/day) + CBT (n = 26) **EG2:** disulfiram 250–500 mg/day (mode 261.5 mg/day) + TSF (n = 25) **EG3:** disulfiram + contingency management (n = 27) **CG1:** CBT + no medication (n = 19) **CG2:** TSF + no medication (n = 25) In our review, we compared EG1 with CG1 (Carroll 1998 comparison a) and EG2 with CG2 (Carroll 1998 comparison b).
Outcomes	• Duration of periods of abstinence from cocaine, alcohol, and both substances simultaneously • Frequency of cocaine use (number of days per week the participants reported cocaine use) • Quantity of cocaine use (grams per week) • Frequency of alcohol use (number of days per week the participants reported at least 1 standard drink per week) • Quantity of alcohol use (number of standard drinks per week) • Urine toxicology screening • Breathalyser reading to verify self-report
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	No details provided.
Allocation concealment?	Unclear risk	Method of concealment not described.
Blinding? Objective outcomes	High risk	Control condition consisted of no medication. Study does not report any procedure to prevent investigators and participants from knowing the allocated intervention.
Blinding? Subjective outcomes	High risk	Control condition consisted of no medication. Study does not report any procedure to prevent investigators and participants from knowing the allocated intervention.
Blinding of outcome assessor Subjective outcomes	High risk	Control condition consisted of no medication. Study does not report any procedure to prevent investigators and participants from knowing the allocated intervention.
Blinding of outcome assessor Objective outcomes	Low risk	Outcomes unlikely to be biased by lack of blinding.

Incomplete outcome data addressed?	Low risk	Attrition was described by medication condition. All participants who initiated treatment were included in the analysis (modified intention-to-treat analysis).
Free of selective reporting?	Unclear risk	Study protocol not available.

Carroll 1998 comparison b

Study characteristics		
Methods	See Carroll 1998 comparison a.	
Participants	See Carroll 1998 comparison a.	
Interventions	See Carroll 1998 comparison a.	
Outcomes	See Carroll 1998 comparison a.	
Notes	See Carroll 1998 comparison a.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	No details provided.
Allocation concealment?	Unclear risk	Method of concealment not described.
Blinding? Objective outcomes	High risk	Control condition consisted of no medication. Study does not report any procedure to prevent investigators and participants from knowing the allocated intervention.
Blinding? Subjective outcomes	High risk	Control condition consisted of no medication. Study does not report any procedure to prevent investigators and participants from knowing the allocated intervention.
Blinding of outcome assessor Subjective outcomes	High risk	The study does not report any procedure to prevent investigators and participants from knowing the allocated intervention.
Blinding of outcome assessor Objective outcomes	Low risk	Outcomes unlikely to be influenced by lack of blinding.
Incomplete outcome data addressed?	Low risk	Attrition was described by medication condition. All participants who initiated treatment were included in the analysis (modified intention-to-treat analysis).
Free of selective reporting?	Unclear risk	Study protocol not available.

Carroll 2004 comparison a

Study characteristics		
Methods	Randomized, placebo-controlled, double-masked (for medication condition) trial.	
Participants	60 subjects seeking treatment for substance abuse; mean age 34.6 years; male 74%; white 63%; single or divorced 76%; working 55%; average baseline alcohol use, 9.4 days in the past 28 days; average baseline cocaine use 13.0 days in the past 28 days. Inclusion criteria: fulfilling DSM-IV criteria for current cocaine dependence. Exclusion criteria: currently physically dependent on opiates or barbiturates, or whose principal drug of dependence was not cocaine; meeting lifetime DSM-IV criteria for a psychotic or bipolar disorder, or expressing significant suicidal or homicidal ideation; having a current medical condition contraindication use of disulfiram; having been treated for substance use during the previous two months. Individuals who were physically dependent on alcohol were eligible for the protocol after they completed alcohol detoxification.	
Interventions	(1) Cognitive Behavioral Therapy (CBT) plus disulfiram, 30 participants; (2) CBT plus placebo, 30 participants. Disulfiram dose : 250 mg/day. Outpatient. Duration 12 weeks. Country of origin: USA.	
Outcomes	Primary outcomes: (1) frequency of cocaine use (operational as number of days per week the subjects reported using cocaine); (2) results of urine screen (operational as likelihood of submitting a positive sample each week).	
Notes	In the primary study participants were divided into 4 sugroups that received the following treatments: (1) CBT plus disulfiram, 30 participants; (2) CBT plus placebo, 30 participants; (3) IPT plus disulfiram, 30 participants; (4) IPT plus placebo, 31 participants. In the present SR, the results of participants who received CBT plus disulfiram (30 participants) were compared to those who received CBT plus placebo (30 participants) (arm a), and the results of participants who received IPT plus disulfiram (30 participants) were compared to those of participants who received IPT plus placebo (31 participants) (arm B). Arm a: (1) CBT plus disulfiram (30 participants) vs (2) CBT plus placebo (30 participants); Arm b: (1) IPT plus disulfiram (30 participants) vs (2) IPT plus placebo (31 participants).	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Urn randomisation used to balance treatment groups with respect to baseline severity of cocaine dependence, sex, and race (Stout 1994).
Allocation concealment?	Unclear risk	Method of concealment not described.
Blinding? Objective outcomes	Low risk	Study described as double-blind. Placebo was similar in appearance to active medication.

Blinding? Subjective outcomes	Low risk	Study described as double-blind. Placebo was similar in appearance to active medication.
Blinding of outcome assessor Subjective outcomes	Low risk	Participants and clinical evaluators were blind.
Blinding of outcome assessor Objective outcomes	Low risk	Participants and clinical evaluators were blind.
Incomplete outcome data addressed?	Low risk	Attrition/exclusion described by medication condition. Analysis included all randomised participants (intention to treat).
Free of selective reporting?	Unclear risk	Study protocol not available.

Carroll 2004 comparison b

Study characteristics	
Methods	Randomized, placebo-controlled, double-masked (for medication condition), factorial (2 x 2) trial.
Participants	61 subjects seeking treatment for substance abuse; mean age 34.6 years; male 74%; white 63%; single or divorced 76%; working 55%; average baseline alcohol use, 9.4 days in the past 28 days; average baseline cocaine use 13.0 days in the past 28 days. Inclusion criteria: fulfilling DSM-IV criteria for current cocaine dependence. Exclusion criteria: currently physically dependent on opiates or barbiturates, or whose principal drug of dependence was not cocaine; meeting lifetime DSM-IV criteria for a psychotic or bipolar disorder, or expressing significant suicidal or homicidal ideation; having a current medical condition contraindicating use of disulfiram; having been treated for substance use during the previous two months. Individuals who were physically dependent on alcohol were eligible for the protocol after they completed alcohol detoxification.
Interventions	(1) Interpersonal PsychoTherapy (IPT) plus disulfiram, 30 participants; (2) IPT plus placebo, 31 participants. Disulfiram dose : 250 mg/day. Outpatient. Duration 12 weeks. Country of origin: USA.
Outcomes	Primary outcomes: (1) frequency of cocaine use (operational as number of days per week the subjects reported using cocaine); (2) results of urine screen (operational as likelihood of submitting a positive sample each week).
Notes	In the primary study participants were divided into 4 sugroups that received the following treatments: (1) CBT plus disulfiram, 30 participants; (2) CBT plus placebo, 30 participants; (3) IPT plus disulfiram, 30 participants; (4) IPT plus placebo, 31 participants. In the present SR, the results of participants who received CBT plus disulfiram (30 participants) were compared to those who received CBT plus placebo (30 participants) (arm a), and the results of participants who received IPT plus disulfiram (30 participants) were compared to those of participants who received IPT plus placebo (31 participants) (arm B). Arm a: (1) CBT plus disulfiram (30 participants) vs (2) CBT plus placebo (30 participants); Arm b: (1) IPT plus disulfiram (30 participants) vs (2) IPT plus placebo (31 participants).

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Urn randomisation used to balance treatment groups with respect to baseline severity of cocaine dependence, sex, and race (Stout 1994).
Allocation concealment?	Unclear risk	Method of concealment not described.
Blinding? Objective outcomes	Low risk	Study described as double-blind. Placebo was similar in appearance to active medication.
Blinding? Subjective outcomes	Low risk	Study described as double-blind. Placebo was similar in appearance to active medication.
Blinding of outcome assessor Subjective outcomes	Low risk	Participants and clinical evaluators were blind.
Blinding of outcome assessor Objective outcomes	Low risk	Participants and clinical evaluators were blind.
Incomplete outcome data addressed?	Low risk	Attrition/exclusion described by medication condition. Analysis included all randomised participants (intention to treat).
Free of selective reporting?	Unclear risk	No protocol available.

Carroll 2012 comparison a

Study characteristics		
Methods	double-blind, randomized, placebo-controlled trial	
Participants	Cocaine-dependent individuals maintained on methadone. Methadone maintenance patients were included as participants if they met DSM-IV criteria for current cocaine dependence. Individuals were excluded if they (1) had current use of barbiturates or whose principal illicit drug used was not cocaine, (2) met lifetime DSM-IV criteria for a psychotic or bipolar disorder, or expressed significant current suicidal or homicidal ideation, or (3) had a current medical condition which would contraindicate disulfiram treatment (e.g., hepatic or cardiac issues, hypertension, pregnancy). Individuals who were physically dependent on alcohol were eligible for the protocol after they completed alcohol detoxification. The mean age of the sample was 38.25 years and 56.25% of the participants were male.	
Interventions	Disulfiram (DIS) 250 mg/day and/or placebo and/or Twelve Step Facilitation (TSF) and Methadone. Outpatient. Duration 12 weeks.	
Outcomes	Frequency of self-reported cocaine use and results of urine toxicology screens.	
Notes	In the primary study participants were divided into 4 sugroups that received the following treatments: (1) disulfiram plus TSF, 29 participants; (2) placebo plus TSF, 27 participants; (3) disulfiram plus no TSF, 30 participants; (4) placebo plus no TSF, 26 participants. In the present SR, the results of participants who received TSF plus disulfiram (29 participants) were compared to those who received placebo plus TSF (27 participants) (arm a), and the results of participants who disulfiram plus no TSF (30 participants) were compared to those of participants who placebo plus no TSF (26 participants) (arm B).	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	A computerised urn randomisation program was used to balance groups with respect to baseline severity of cocaine dependence, alcohol use, gender, and race.
Allocation concealment?	Unclear risk	No information provided.
Blinding? Objective outcomes	Low risk	The study reports that the design was a double-blind for medication intervention. Quote: "Participants assigned to placebo received methadone formulated to appear identical to the disulfiram plus methadone combination. All participants were cautioned not to drink alcohol."
Blinding? Subjective outcomes	Low risk	The study reports that the design was a double-blind for medication intervention. Quote: "Participants assigned to placebo received methadone formulated to appear identical to the disulfiram plus methadone combination. All participants were cautioned not to drink alcohol."
Blinding of outcome assessor Subjective outcomes	Low risk	Participants and outcome assessors were blind to treatment assignment.
Blinding of outcome assessor Objective outcomes	Low risk	Participants and outcome assessors were blind to treatment assignment.
Incomplete outcome data addressed?	Low risk	Analysis conducted on all randomised participants (intention to treat).
Free of selective reporting?	Low risk	Study protocol is available. All prespecified outcomes were reported in the final publication.

Carroll 2012 comparison b

Study characteristics	
Methods	double-blind, randomized, placebo-controlled trial
Participants	Cocaine-dependent individuals maintained on methadone. Methadone maintenance patients were included as participants if they met DSM-IV criteria for current cocaine dependence. Individuals were excluded if they (1) had current use of barbiturates or whose principal illicit drug used was not cocaine, (2) met lifetime DSM-IV criteria for a psychotic or bipolar disorder, or expressed significant current suicidal or homicidal ideation, or (3) had a current medical condition which would contraindicate disulfiram treatment (e.g., hepatic or cardiac issues, hypertension, pregnancy). Individuals who were physically dependent on alcohol were eligible for the protocol after they completed alcohol detoxification. The mean age of the sample was 38.4 years and 60.5% of the participants were male.
Interventions	Disulfiram (DIS) 250 mg/day and/or placebo (PLA) and/or Twelve Step Facilitation (TSF) and Methadone. Outpatient. Duration 12 weeks.
Outcomes	Frequency of self-reported cocaine use and results of urine toxicology screens.
Notes	In the primary study participants were divided into 4 sugroups that received the following treatments: (1) disulfiram plus TSF, 29 participants; (2) placebo plus TSF, 27 participants; (3) disulfiram plus no TSF, 30 participants; (4) placebo plus no TSF, 26 participants. In the present SR, the results of participants who received TSF plus disulfiram (29 participants) were compared to those who received placebo plus TSF (27 participants) (arm a), and the results of participants who disulfiram plus no TSF (30 participants) were compared to those of participants who placebo plus no TSF (26 participants) (arm B).
Risk of bias	

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	A computerised urn randomisation program was used to balance groups with respect to baseline severity of cocaine dependence, alcohol use, gender, and race.
Allocation concealment?	Unclear risk	No information provided.
Blinding? Objective outcomes	Low risk	The study reports that the design was a double-blind for medication intervention. Quote: "Participants assigned to placebo received methadone formulated to appear identical to the disulfiram plus methadone combination. All participants were cautioned not to drink alcohol."
Blinding? Subjective outcomes	Low risk	The study reports that the design was a double-blind for medication intervention. Quote: "Participants assigned to placebo received methadone formulated to appear identical to the disulfiram plus methadone combination. All participants were cautioned not to drink alcohol."
Blinding of outcome assessor Subjective outcomes	Low risk	Participants and outcome assessors blind to treatment allocation.
Blinding of outcome assessor Objective outcomes	Low risk	Participants and outcome assessors blind to treatment allocation.
Incomplete outcome data addressed?	Low risk	Analysis conducted on all randomised participants (intention to treat).
Free of selective reporting?	Low risk	Study protocol is available. All prespecified outcomes reported in the final publication.

Carroll 2016 comparison a

Study characteristics	
Methods	Double blind, randomized, placebo-controlled study
Participants	Mean age: 38.9 years, Males: 38.9%, Caucasian: 39.4%; African American: 49.5%, Latino or Hispanic American: 7.1%, High school graduates: 85.9%, Never been married or living alone: 71.7%, Unemployed: 45%; full time job: 66.7% *Inclusion criteria:* 18 years or older and met current DSM-IV criteria for current cocaine dependence, as assessed by the Structured Clinical Interview for DSM-IV(SCID) interviews at baseline *Exclusion criteria*: they (1) were currently dependent on another drug (except tobacco) or whose principal drug use was not cocaine, (2) met lifetime DSM-IVcriteria for a non-substance-induced psychotic or bipolar disorder,(3) had a current medical condition which would contraindicatedisulfiram treatment (e.g. hepatic or cardiac issues, hypertension,pregnancy), as assessed by baseline physical examination (includ-ing EKG, urinalysis and blood work), or (4) were not sufficientlystable for outpatient treatment and had not received addiction treatment in the past 90 days.
Interventions	Disulfiram (DIS) 250 mg/day and/or placebo (PLA) plus cognitive behavioral therapy (CBT) and/or contingency management (CM). Outpatient. Duration 12 weeks.
Outcomes	Frequency of self-reported cocaine use and results of urine toxicology screens.
Notes	In the primary study participants were divided into 4 sugroups that received the following treatments: (1) disulfiram plus CM, 23 participants; (2) placebo plus CM, 22 participants; (3) disulfiram plus no CM, 28 participants; (4) placebo plus no CM, 26 participants. In the present SR, the results of participants who received disulfiram plus CM (23 participants) were compared to those who received placebo plus CM (22 participants) (arm a), and the results of participants who disulfiram plus no CM (28 participants) were compared to those of participants who received placebo plus no CM (26 participants) (arm B). Arm a: (1) Disulfiram (250 mg/day) plus CM, 23 participants; (2) Placebo plus CM, 22 participants; Arm b: (1) Disulfiram (250 mg/day) no CM, 28 participants; (2) Placebo no CM, 26 participants.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	A computerised urn randomisation program was used to produce equivalent group size and balance groups with respect to baseline level of cocaine use (more or less than 11 days per month), presence of alcohol dependence (yes/no), gender, and ethnicity (ethnic minority/non-minority).
Allocation concealment?	Unclear risk	No information provided.
Blinding? Objective outcomes	Low risk	The study reports that the design was a double-blind for medication intervention. Quote: "Participants assigned to placebo received identical capsules in order to maintain the blind. All study medication capsules contained a riboflavin tracer."
Blinding? Subjective outcomes	Low risk	The study reports that the design was a double-blind for medication intervention. Quote: "Participants assigned to placebo received identical capsules in order to maintain the blind. All study medication capsules contained a riboflavin tracer."
Blinding of outcome assessor Subjective outcomes	Low risk	Participants and outcome assessors blind to treatment allocation.

Blinding of outcome assessor Objective outcomes	Low risk	Participants and outcome assessors blind to treatment allocation.
Incomplete outcome data addressed?	Low risk	Analysis conducted on all randomised participants (intention to treat).
Free of selective reporting?	Low risk	Study protocol is available. All prespecified outcomes reported in the final publication.

Carroll 2016 comparison b

Study characteristics	
Methods	Double blind, randomized, placebo-controlled study
Participants	Mean age: 39.7 years, Males: 76.7%, Caucasian: 39.4%; African American: 49.5%, Latino or Hispanic American: 7.1%, High school graduates: 85.9%, Never been married or living alone: 71.7%, Unemployed: 45%; full time job: 66.7% *Inclusion criteria:* 18 years or older and met current DSM-IV criteria for current cocaine dependence, as assessed by the Structured Clinical Interview for DSM-IV(SCID) interviews at baseline *Exclusion criteria*: they (1) were currently dependent on another drug (except tobacco) or whose principal drug use was not cocaine, (2) met lifetime DSM-IVcriteria for a non-substance-induced psychotic or bipolar disorder,(3) had a current medical condition which would contraindicatedisulfiram treatment (e.g. hepatic or cardiac issues, hypertension,pregnancy), as assessed by baseline physical examination (includ-ing EKG, urinalysis and blood work), or (4) were not sufficientlystable for outpatient treatment and had not received addiction treatment in the past 90 days.
Interventions	Disulfiram (DIS) 250 mg/day and/or placebo (PLA) plus cognitive behavioral therapy (CBT) and/or contingency management (CM). Outpatient. Duration 12 weeks.
Outcomes	Frequency of self-reported cocaine use and results of urine toxicology screens.
Notes	In the primary study participants were divided into 4 sugroups that received the following treatments: (1) disulfiram plus CM, 23 participants; (2) placebo plus CM, 22 participants; (3) disulfiram plus no CM, 28 participants; (4) placebo plus no CM, 26 participants. In the present SR, the results of participants who received disulfiram plus CM (23 participants) were compared to those who received placebo plus CM (22 participants) (arm a), and the results of participants who received disulfiram plus no CM (28 participants) were compared to those of participants who received placebo plus no CM (26 participants) (arm B). Arm a: (1) Disulfiram (250 mg/day) plus CM, 23 participants; (2) Placebo plus CM, 22 participants; Arm b: (1) Disulfiram (250 mg/day) no CM, 28 participants; (2) Placebo no CM, 26 participants.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	A computerised urn randomisation program was used to produce equivalent group size and balance groups with respect to baseline level of cocaine use (more or less than 11 days per month), presence of alcohol dependence (yes/no), gender, and ethnicity (ethnic minority/non-minority).
Allocation concealment?	Unclear risk	No information provided.
Blinding? Objective outcomes	Low risk	The study reports that the design was a double-blind for medication intervention. Quote: "Participants assigned to placebo received identical capsules in order to maintain the blind. All study medication capsules contained a riboflavin tracer."
Blinding? Subjective outcomes	Low risk	The study reports that the design was a double-blind for medication intervention. Quote: "Participants assigned to placebo received identical capsules in order to maintain the blind. All study medication capsules contained a riboflavin tracer."
Blinding of outcome assessor Subjective outcomes	Low risk	Participants and outcome assessors blind to treatment allocation.
Blinding of outcome assessor Objective outcomes	Low risk	Participants and outcome assessors blind to treatment allocation.
Incomplete outcome data addressed?	Low risk	All randomised participants included in the analysis (intention to treat).
Free of selective reporting?	Low risk	Study protocol is available. All prespecified outcomes reported in the final publication.

George 2000

Study characteristics	
Methods	Randomized, placebo-controlled, double blind trial.
Participants	20 opiate dependent subjects with concurrent cocaine dependence induced onto buprenorphine maintenance; mean age: 36.8 years for disulfiram treated subjects and 39.3 years for placebo-treated subjects; male: 63.6% in disulfiram treated subjects and 55.6% in placebo-treated subjects; white 63.6% in disulfiram treated subjects and 88.9% in

	placebo-treated subjects; not married: 90.9% in disulfiram treated subjects and 77.8% in placebo-treated subjects; working: none in either (both) groups; iv users 63.6% in disulfiram treated subjects and 44.4 in placebo-treated subjects; alcohol use: 0.06 drinks/week in disulfiram-treated subjects and 0.18 in placebo-treated subjects. Inclusion criteria: opiate dependence with concurrent cocaine dependence. Exclusion criteria: having a current medical condition contraindicating use of disulfiram; using metronidazole, which is known to have disulfiram like effects in the presence of alcohol use; fulfilling DSM-IV criteria for alcohol or sedative hypnotic dependence (unless detoxified before study entry); current psychosis or idea of suicide; use of psychotropic drugs such as antidepressants, mood stabilizers, antipsychotic drugs; pregnancy.
Interventions	(1) disulfiram plus buprenorphine, 11 participants; (2) placebo plus buprenorphine, 9 participants. Partecipants were involved in weekly group drug counselling sessions. Drug dose: disulfiram 250 mg/day; buprenorphine 8 mg/day. Outpatient. Duration 12 weeks. Country of origin: USA.
Outcomes	Primary outcomes: abstinence from cocaine measured as (1) mean number of weeks of abstinence, (2) number of days to achieving three weeks of abstinence, (3) number of cocaine negative test during the 12 week trial. Secondary outcomes: (1) Treatment retention, (2) self reported cocaine, heroin and alcohol use.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	No details provided.
Allocation concealment?	Unclear risk	Method of concealment not described.
Blinding? Objective outcomes	Unclear risk	Quote: "subjects and the research staff were blind to medication assignment." Comment: no further details.
Blinding? Subjective outcomes	Unclear risk	Quote: "subjects and the research staff were blind to medication assignment." Comment: no further details.
Blinding of outcome assessor Subjective outcomes	Unclear risk	Quote: "subjects and the research staff were blind to medication assignment." Comment: no further details.
Blinding of outcome assessor Objective outcomes	Low risk	Quote: "subjects and the research staff were blind to medication assignment." Comment: no further details; however, objective outcomes are unlikely to be biased by lack of blinding.
Incomplete outcome data addressed?	Low risk	Attrition/exclusion described by medication condition. Analysis conducted on all randomised participants (intention to treat).
Free of selective reporting?	Unclear risk	No study protocol available.

Grassi 2007 comparison a

Study characteristics	
Methods	Randomized controlled study
Participants	8 subjects dependent on both alcohol and cocaine as measured by the Severity of Dependence Scale (SDS); mean age: 37.3 years for disulfiram plus CBT treated subjects and 29.3 years for only CBT treated subjects; married or cohabitant: 50.0% for disulfiram plus CBT treated subjects and 50.0% for only CBT treated subjects; working: 100% for disulfiram plus CBT treated subjects and 75.0% for only CBT treated subjects; average baseline alcohol use: 24.8 days in the pas 30 days for disulfiram plus CBT treated subjects and 20.5 days in the past 30 days for CBT treated subjects; average baseline cocaine use: 18.5 days in the pas 30 days for disulfiram plus CBT treated subjects and 18.8 days in the past 30 days for CBT treated subjects. Inclusion criteria: alcohol and cocaine dependence; presence of positive urinalyses for both cocaine and cocaethylene; being at least 18-year old. Exclusion criteria: having a concurrent opiate dependence; major medical or psychiatric disorders; pregnancy; hypersensitivity to disulfiram or naltrexone.
Interventions	In the primary study participants were divided into 3 sugroups that received the following treatments: (1) disulfiram plus CBT, 4 participants; (2) CBT, 4 participants; (3) naltrexone plus CBT, 4 participants. In the present SR, the results of participants who received disulfiram plus CBT (4 participants) were compared to those who received only CBT (4 participants) (arm a; included in Comparsin 1 (vs placebo or no pharmacological treatment)), and the results of participants who received disulfiram plus CBT (4 participants) were compared to those of participants who received naltrexone plus CBT (4 participants) (arm b, included in Comparison 2, Disulfiram vs naltrexone)). Arm a (Comparison 1): (1) Disulfiram (400 mg/day) plus CBT (4 participants); (2) CBT (4 participants); Arm b (Comparison 2): (1) Disulfiram (400 mg/day) plus CBT (4 participants); (2) Naltrexone (50 mg/day) plus CBT (4 participants). Outpatient. Duration 12 weeks. Country of origin: Italy.
Outcomes	(1) Retention in treatment; (2) rate of urines positive for cocaine or cocaethylene; (3) reduction in craving for cocaine and alcohol as measured by the Visual Analogue Scales.

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	No details provided.
Allocation concealment?	Unclear risk	<method of concealment not described.
Blinding? Objective outcomes	High risk	Open-label study. Control condition consisted of no medication. Study does not report any procedure to prevent investigators and participants from knowing the allocated intervention.
Blinding? Subjective outcomes	High risk	Open-label study. Control condition consisted of no medication. Study does not report any procedure to prevent investigators and participants from knowing the allocated intervention.
Blinding of outcome assessor Subjective outcomes	High risk	Open-label study. Control condition consisted of no medication. Study does not report any procedure to prevent investigators and participants from knowing the allocated intervention.
Blinding of outcome assessor Objective outcomes	Low risk	Open-label study. Control condition consisted of no medication. Study does not report any procedure to prevent investigators and participants from knowing the allocated intervention. However, objective outcomes unlikely to be influenced by lack of blinding.
Incomplete outcome data addressed?	Low risk	Attrition/exclusion described by medication condition. Data analysis on craving and urine positive for cocaine or cocaethylene was restricted to the first 4 weeks of treatment, when all the enroled subjects were still available for examination.
Free of selective reporting?	Unclear risk	No study protocol available.

Grassi 2007 comparison b

Study characteristics	
Methods	Randomized open study
Participants	8 subjects dependent on both alcohol and cocaine as measured by the Severity of Dependence Scale (SDS); mean age: 37.3 years for disulfiram plus CBT treated subjects and 32.0 years for naltrexone plus CBT treated subjects; married or cohabitant: 50.0% for disulfiram plus CBT treated subjects and 100% for naltrexone plus CBT treated subjects; working: 100% for disulfiram plus CBT treated subjects and 75.0% for naltrexone plus CBT treated subjects; average baseline alcohol use: 24.8 days in the pas 30 days for disulfiram plus CBT treated subjects and 23.5 days in the past 30 days for naltrexone plus CBT treated subjects; average baseline cocaine use: 18.5 days in the pas 30 days for disulfiram plus CBT treated subjects and 16.5 days in the past 30 days for naltrexone plus CBT treated subjects. Inclusion criteria: alcohol and cocaine dependence; presence of positive urinalyses for both cocaine and cocaethylene; being at least 18-year old. Exclusion criteria: having a concurrent opiate dependence; major medical or psychiatric disorders; pregnancy; hypersensitivity to disulfiram or naltrexone.
Interventions	In the primary study participants were divided into 3 sugroups that received the following treatments: (1) disulfiram plus CBT, 4 participants; (2) CBT, 4 participants; (3) naltrexone plus CBT, 4 participants. In the present SR, the results of participants who received disulfiram plus CBT (4 participants) were compared to those who received only CBT (4 participants) (arm a; included in Comparsin 1 (vs placebo or no pharmacological treatment)), and the results of participants who received disulfiram plus CBT (4 participants) were compared to those of participants who received naltrexone plus CBT (4 participants) (arm b, included in Comparison 2, Disulfiram vs naltrexone)). Arm a (Comparison 1): (1) Disulfiram (400 mg/day) plus CBT (4 participants); (2) CBT (4 participants); Arm b (Comparison 2): (1) Disulfiram (400 mg/day) plus CBT (4 participants); (2) Naltrexone (50 mg/day) plus CBT (4 participants). Outpatient. Duration 12 weeks. Country of origin: Italy.
Outcomes	(1) Retention in treatment (2); rate of urine positive for cocaine or cocaethylene; (3) reduction in craving for cocaine and alcohol as measured by the Visual Analogue Scales.
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	No details provided.
Allocation concealment?	Unclear risk	Method of concealment not described.
Blinding? Objective outcomes	High risk	Open-label study. Control condition consisted of no medication. Study does not report any procedure to prevent investigators and participants from knowing the allocated intervention.
Blinding? Subjective outcomes	High risk	Open-label study. Control condition consisted of no medication. Study does not report any procedure to prevent investigators and participants from knowing the allocated intervention.

Blinding of outcome assessor Subjective outcomes	High risk	Open-label study. Control condition consisted of no medication. Study does not report any procedure to prevent investigators and participants from knowing the allocated intervention.
Blinding of outcome assessor Objective outcomes	Low risk	Open-label study. Control condition consisted of no medication. Study does not report any procedure to prevent investigators and participants from knowing the allocated intervention. However, objective outcomes unlikely to be influenced by lack of blinding.
Incomplete outcome data addressed?	Low risk	Attrition/exclusion described by medication condition. Data analysis on craving and urine positive for cocaine or cocaethylene was restricted to the first 4 weeks of treatment, when all the enroled subjects were still available for examination.
Free of selective reporting?	Unclear risk	No study protocol available.

Kosten 2013

Study characteristics		
Methods	Double blind, randomized, placebo-controlled study	
Participants	74 cocaine and opioid-dependent patients. (10 African-American, 8 Hispanic, 56 Caucasian) The patients were mostly Caucasian men (64.5%) with a mean age of 38.75 years and 13 years of opiate abuse. Forty (54%) patients had been previously treated with methadone maintenance. They used cocaine for a mean of 12 years and for 19 days in the month before entering the study. Only 29 patients (39%) reported any alcohol abuse history reflecting our exclusion criteria, and 39 patients (53%) reported marijuana use. ***Inclusion criteria:*** *DSM-IV criteria for opioid and cocaine dependence and* at least one cocaine-positive urine sample during the 2-week period with methadone ***Exclusion criteria*****:** *Current diagnosis of other drug or alcohol physical dependence (other than tobacco), current major medical illness unstabilized on medications, a history of major psychiatric disorder (psychosis, schizophrenia and bipolar), current suicidality and an inability to read and understand the consent form, woman of childbearing age were included provided they had a negative urine pregnancy test, agreed to use adequate contraception to prevent pregnancy during the study and agreed to monthly pregnancy tests.*	
Interventions	(1) disulfiram (250 mg/day) plus methadone (60 mg/day) and cognitive behavioral therapy, 34 participants; (2) placebo plus methadone (60 mg/day) and cognitive behavioral therapy, 40 participants) Duration: 2 weeks with methadone and 10 weeks with disulfiram/placebo.	
Outcomes	Treatment adherence (number of subjects who received treatment for the full 60 days); Secondary outcomes: (ii) frequency of drug use (mean of number of days per week that crack cocaine was used); (iii) drug dose (daily mean dose of crack cocaine used; in grams); and (iv) drug-free rate (number of subjects that stopped crack cocaine use after 60 days, confirmed by urinalysis); (v) side-effects.	
Notes	NCT00149630	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	No information provided.
Allocation concealment?	Unclear risk	No information provided.
Blinding? Objective outcomes	Low risk	Quote: "Double blinding of patients, providers and clinical staff, and treatment assignment was maintained through the research pharmacy, and the individual patient's bottles of liquid methadone looked and tasted identical with lactose added to both the active disulfiram and placebo doses."
Blinding? Subjective outcomes	Low risk	Quote: "Double blinding of patients, providers and clinical staff, and treatment assignment was maintained through the research pharmacy, and the individual patient's bottles of liquid methadone looked and tasted identical with lactose added to both the active disulfiram and placebo doses."
Blinding of outcome assessor Subjective outcomes	Low risk	Participants and outcome assessors blinded to treatment allocation.
Blinding of outcome assessor Objective outcomes	Low risk	Participants and outcome assessors blinded to treatment allocation.
Incomplete outcome data addressed?	Low risk	All randomised participants included in the analysis (intention to treat).
Free of selective reporting?	Unclear risk	Study protocol available, but outcomes not clearly defined.

Oliveto 2011 comparison a

Study characteristics	
Methods	Double-blind, randomized, placebo-controlled study
Participants	Cocaine- and opioid-dependent individuals seeking opioid maintenance treatment; age: 18-65 years currently used cocaine with at least weekly self-reported use during the month preceding study entry, and had either laboratory

	confirmation of opioid use during the month prior to study entry or manifested opioid withdrawal. Inclusion criteria: DSM-IV criteria for opioid and cocaine dependence; current use of cocaine and opioid use during the month prior to study entry Exclusion criteria: Current alcohol physical dependence, abnormal liver function (with laboratory enzyme levels greater than three times normal), active hepatitis, hypertension, a current cardiac condition, occult coronary artery disease, high risk of cardiovascular disease, seizure disorders, other significant medical condition contraindicating disulfiram or methadone treatment, history of schizophrenia, bipolar disorder, other psychotic disorders, current suicidality or homicidality, current use of a prescribed psychotropic medication that could not be discontinued, current use of metronidazole or clotrimazole, benzodiazepine-positive urine toxicology screen, and pregnancy or breastfeeding.
Interventions	Methadone-stabilized (weeks 1–2) then disulfiram (0, 62.5, 125 or 250 mg daily) per 12 weeks (during weeks 3–14). All participants received weekly, manual-driven, individual cognitive behavioral therapy.
Outcomes	The primary outcome of interest was cocaine use, as determined by urine toxicology results and self reports. Secondary outcomes included retention, opioid use and adverse events.
Notes	In the primary study participants were divided into 4 sugroups that received the following treatments: (1) disulfiram 62.5 mg/day, 37 participants; (2) disulfiram 125 mg/day, 39 participants; (3) disulfiram 250 mg/day, 40 participants; (4) placebo, 39 participants. In the present SR, the number of participants of the control group were divided into the three comparisons of participants who received disulfiram: (1) disulfiram 62.5 mg/day (37 participants) were compared to those who received placebo (13 participants) (arm a), (2) the results of participants who received disulfiram 125 mg/day (39 participants) were comapred to those who received placebo (13 participants) (arm b); the results of participants who received disulfiram 250 mg/day (40 participants) were comapred to those who received placebo (12 participants). Arm a: (1) Placebo, 13 participants; (2) DIS 62.5 mg/day, 37 participants; Arm b: (1) Placebo, 13 participants; (2) DIS 125 mg/day, 38 participants Arm c: (1) Placebo, 12 participants; (2) DIS 250 mg/day, 39 participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Quote: "The data manager performed the randomization using a computerized urn randomization program, balancing groups on age, sex, race and Cocaine Selective Severity Assessment score (CSSA). Only the research pharmacist and data manager were aware of the medication condition."
Allocation concealment?	Low risk	Quote: "The data manager performed the randomization using a computerized urn randomization program, balancing groups on age, sex, race and Cocaine Selective Severity Assessment score (CSSA). Only the research pharmacist and data manager were aware of the medication condition."
Blinding? Objective outcomes	Low risk	Quote: "Only the research pharmacist and data manager were aware of the medication condition." Quote: "crushed disulfiram tablets or placebo (i.e., 300mg of microcrystalline cellulose) was suspended in the methadone solution."
Blinding? Subjective outcomes	Low risk	Quote: "Only the research pharmacist and data manager were aware of the medication condition." Quote: "crushed disulfiram tablets or placebo (i.e., 300mg of microcrystalline cellulose) was suspended in the methadone solution."
Blinding of outcome assessor Subjective outcomes	Low risk	Participants and outcome assessors blind to treatment allocation.
Blinding of outcome assessor Objective outcomes	Low risk	Participants and outcome assessors blind to treatment allocation.
Incomplete outcome data addressed?	Low risk	All randomised participants who received the allocated intervention were included in the analysis (modified intention to treat).
Free of selective reporting?	Unclear risk	Study protocol available but outcomes not clearly described.

Oliveto 2011 comparison b

Study characteristics	
Methods	Double-blind, radomized, placebo-controlled study
Participants	Cocaine- and opioid-dependent individuals seeking opioid maintenance treatment; age: 18-65 years currently used cocaine with at least weekly self-reported use during the month preceding study entry, and had either laboratory confirmation of opioid use during the month prior to study entry or manifested opioid withdrawal. Inclusion criteria: DSM-IV criteria for opioid and cocaine dependence; current use of cocaine and opioid use during the month prior to study entry Exclusion criteria: Current alcohol physical dependence, abnormal liver function (with laboratory enzyme levels greater than three times normal), active hepatitis, hypertension, a current cardiac condition, occult coronary artery disease, high risk of cardiovascular disease, seizure disorders, other significant medical condition contraindicating disulfiram or methadone treatment, history of schizophrenia, bipolar disorder, other psychotic disorders, current suicidality or homicidality, current use of a prescribed psychotropic medication that could not be discontinued, current use of metronidazole or clotrimazole, benzodiazepine-positive urine toxicology screen, and pregnancy or breastfeeding.
Interventions	Methadone-stabilized (weeks 1–2) then disulfiram (0, 62.5, 125 or 250 mg daily) per 12 weeks (during weeks 3–14). All participants received weekly, manual-driven, individual cognitive behavioral therapy.
Outcomes	

	The primary outcome of interest was cocaine use, as determined by urine toxicology results and self reports. Secondary outcomes included retention, opioid use and adverse events.
Notes	In the primary study participants were divided into 4 sugroups that received the following treatments: (1) disulfiram 62.5 mg/day, 37 participants; (2) disulfiram 125 mg/day, 39 participants; (3) disulfiram 250 mg/day, 40 participants; (4) placebo, 39 participants. In the present SR, the number of participants of the control group were divided into the three comparisons of participants who received disulfiram: (1) disulfiram 62.5 mg/day (37 participants) were compared to those who received placebo (13 participants) (arm a), (2) the results of participants who received disulfiram 125 mg/day (39 participants) were comapred to those who received placebo (13 participants) (arm b); the results of participants who received disulfiram 250 mg/day (40 participants) were comapred to those who received placebo (12 participants). Arm a: (1) Placebo, 13 participants; (2) DIS 62.5 mg/day, 37 participants; Arm b: (1) Placebo, 13 participants; (2) DIS 125 mg/day, 38 participants Arm c: (1) Placebo, 12 participants; (2) DIS 250 mg/day, 39 participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Quote: "The data manager performed the randomization using a computerized urn randomization program, balancing groups on age, sex, race and Cocaine Selective Severity Assessment score (CSSA). Only the research pharmacist and data manager were aware of the medication condition."
Allocation concealment?	Low risk	Quote: "The data manager performed the randomization using a computerized urn randomization program, balancing groups on age, sex, race and Cocaine Selective Severity Assessment score (CSSA). Only the research pharmacist and data manager were aware of the medication condition."
Blinding? Objective outcomes	Low risk	Quote: "Only the research pharmacist and data manager were aware of the medication condition." Quote: "crushed disulfiram tablets or placebo (i.e., 300mg of microcrystalline cellulose) was suspended in the methadone solution."
Blinding? Subjective outcomes	Low risk	Quote: "Only the research pharmacist and data manager were aware of the medication condition." Quote: "crushed disulfiram tablets or placebo (i.e., 300mg of microcrystalline cellulose) was suspended in the methadone solution."
Blinding of outcome assessor Subjective outcomes	Low risk	Participants and outcome assessors blind to treatment allocation.
Blinding of outcome assessor Objective outcomes	Low risk	Participants and outcome assessors blind to treatment allocation.
Incomplete outcome data addressed?	Low risk	All randomised participants who received the allocated intervention were included in the analysis (modified intention to treat).
Free of selective reporting?	Unclear risk	Study protocol available but outcomes not clearly described.

Oliveto 2011 comparison c

Study characteristics

Methods	Double-bind, randomized, placebo-controlled study
Participants	Cocaine- and opioid-dependent individuals seeking opioid maintenance treatment; age: 18-65 years currently used cocaine with at least weekly self-reported use during the month preceding study entry, and had either laboratory confirmation of opioid use during the month prior to study entry or manifested opioid withdrawal. Inclusion criteria: DSM-IV criteria for opioid and cocaine dependence; current use of cocaine and opioid use during the month prior to study entry Exclusion criteria: Current alcohol physical dependence, abnormal liver function (with laboratory enzyme levels greater than three times normal), active hepatitis, hypertension, a current cardiac condition, occult coronary artery disease, high risk of cardiovascular disease, seizure disorders, other significant medical condition contraindicating disulfiram or methadone treatment, history of schizophrenia, bipolar disorder, other psychotic disorders, current suicidality or homicidality, current use of a prescribed psychotropic medication that could not be discontinued, current use of metronidazole or clotrimazole, benzodiazepine-positive urine toxicology screen, and pregnancy or breastfeeding.
Interventions	Methadone-stabilized (weeks 1–2) then disulfiram (0, 62.5, 125 or 250 mg daily) per 12 weeks (during weeks 3–14). All participants received weekly, manual-driven, individual cognitive behavioral therapy.
Outcomes	The primary outcome of interest was cocaine use, as determined by urine toxicology results and self reports. Secondary outcomes included retention, opioid use and adverse events.
Notes	In the primary study participants were divided into 4 sugroups that received the following treatments: (1) disulfiram 62.5 mg/day, 37 participants; (2) disulfiram 125 mg/day, 39 participants; (3) disulfiram 250 mg/day, 40 participants; (4) placebo, 39 participants. In the present SR, the number of participants of the control group were divided into the three comparisons of participants who received disulfiram: (1) disulfiram 62.5 mg/day (37 participants) were compared to those who received placebo (13 participants) (arm a), (2) the results of participants who received disulfiram 125 mg/day (39 participants) were comapred to those who received placebo (13 participants) (arm b); the results of participants who received disulfiram 250 mg/day (40 participants) were comapred to those who received placebo (12 participants). Arm a: (1) Placebo, 13 participants; (2) DIS 62.5 mg/day, 37 participants; Arm b: (1) Placebo, 13 participants; (2) DIS 125 mg/day, 38 participants

	Arm c: (1) Placebo, 12 participants; (2) DIS 250 mg/day, 39 participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Quote: "The data manager performed the randomization using a computerized urn randomization program, balancing groups on age, sex, race and Cocaine Selective Severity Assessment score (CSSA). Only the research pharmacist and data manager were aware of the medication condition."
Allocation concealment?	Low risk	Quote: "The data manager performed the randomization using a computerized urn randomization program, balancing groups on age, sex, race and Cocaine Selective Severity Assessment score (CSSA). Only the research pharmacist and data manager were aware of the medication condition."
Blinding? Objective outcomes	Low risk	Quote: "Only the research pharmacist and data manager were aware of the medication condition." Quote: "crushed disulfiram tablets or placebo (i.e., 300mg of microcrystalline cellulose) was suspended in the methadone solution."
Blinding? Subjective outcomes	Low risk	Quote: "Only the research pharmacist and data manager were aware of the medication condition." Quote: "crushed disulfiram tablets or placebo (i.e., 300mg of microcrystalline cellulose) was suspended in the methadone solution."
Blinding of outcome assessor Subjective outcomes	Low risk	Participants and outcome assessors blind to treatment allocation.
Blinding of outcome assessor Objective outcomes	Low risk	Participants and outcome assessors blind to treatment allocation.
Incomplete outcome data addressed?	Low risk	All randomised participants who received the allocated intervention were included in the analysis (modified intention to treat).
Free of selective reporting?	Unclear risk	Study protocol available but outcomes not clearly described.

Petrakis 2000

Study characteristics

Methods	Randomized, placebo-controlled, double blind trial.
Participants	67 cocaine dependent (DSM-III-R criteria) methadone maintained subjects; male 48%; Caucasian 73%; unmarried 75%; working 21%; dependent on alcohol 23%; average days of cocaine in the previous 30 days was 18.4 days; average days of alcohol use in the previous 30 days was 4.1 days; route of cocaine ingestion: smoking free-base 62%, intranasal 11%, intravenously or subcutaneously 27%. Inclusion criteria: being in methadone maintenance for opioid addiction; fulfilling DSM-III-R criteria for current cocaine dependence; having at least three of four urine toxicology screens positive for cocaine in the month prior to study entry. Exclusion criteria: having psychotic or bipolar disorder according with DSM-II-R criteria (SCID) or psychiatric interview (ILP or EMK); having current suicidal or homicidal ideation; having a current medical condition contraindicating use of disulfiram.
Interventions	(1) disulfiram plus methadone, 36 participants; (2) placebo plus methadone, 31 participants. Partecipants were involved in weekly individual and group counselling sessions. Drug dose: disulfiram 250 mg/day; methadone dose reported as "highest tolerated dose". Outpatient. Duration 12 weeks. Country of origin: USA.
Outcomes	Primary: Frequency and quantity of cocaine and alcohol use, self reported and verified trough urine screen/breathalyzer. Olter outcomes: Severity of substance use and substance-related problems measured through the Addiction Severity Index (ASI).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	No details provided.
Allocation concealment?	Unclear risk	Method of concealment not described.
Blinding? Objective outcomes	Low risk	Study described as double-blind. Quote: "The study medication was dissolved directly in the methadone to ensure compliance. To maintain the blind, subjects assigned to the placebo group received methadone with cornstarch, an inert ingredient that made a suspension that resembled the methadone with disulfiram in appearance and taste."
Blinding? Subjective outcomes	Low risk	Study described as double-blind. Quote: "The study medication was dissolved directly in the methadone to ensure compliance. To maintain the blind, subjects assigned to the placebo group received methadone with cornstarch, an inert ingredient that made a suspension that resembled the methadone with disulfiram in appearance and taste."

Blinding of outcome assessor Subjective outcomes	Low risk	Participants and outcome assessors blind to treatment.
Blinding of outcome assessor Objective outcomes	Low risk	Participants and outcome assessors blind to treatment.
Incomplete outcome data addressed?	Low risk	22% of participants dropped out from the study; balanced between groups; detailed reasons for dropout provided.
Free of selective reporting?	High risk	No results provided for the previously stated assessment of the severity of substance use and substance-related problems measured by Addiction Severity Index.

Pettinati 2008 comparison a

Study characteristics		
Methods	Randomized, placebo-controlled, double blind trial.	
Participants	107 individuals who met DSM-IV criteria for both current cocaine and alcohol dependence; mean age 42 years; male 69%; African American 90%; mean education 12.1 years; use of cocaine in the previous month: 44.% of the days in the average; use of alcohol (heavy drinking) in the previous month: 49.6% of the days on the average. Inclusion criteria: current cocaine and alcohol dependence according with DSM-IV; age between 18 and 65 years; having used a minimum of $ 100 worth of cocaine and drank an average of 12 standard alcoholic drinks a week during the month before treatment; Exclusion criteria: subjects with dependence on substances other than cocaine and alcohol, except nicotine addiction; having an active psychosis, mania, dementia, or the need for treatment with psychiatric medications; being pregnant, breastfeeding; having active hepatitis and significant hepatocellular injury; if indicated, complete outpatient alcohol detoxification.	
Interventions	Interventions: (1) disulfiram, 53 participants; (2) placebo, 54 participants. Partecipants were involved in twice a week individual Cognitive Behavioural Therapy sessions. Drug dose: disulfiram 250 mg/day. Outpatient. Duration 11 weeks. Country of origin: USA.	
Outcomes	(1) Abstinence from cocaine and alcohol measured through self report; (2) value in dollars of cocaine used daily; (3) urine analysis for cocaine three times a week (if one or more resulted positive for cocaine the week was considered non abstinent); (4) proportion of patients with 3 consecutive weeks abstinent for cocaine; (5) number and types of size effects using the systematic assessment for treatment emergent effects.	
Notes	In the primary study participants were divided into 4 sugroups that received the following treatments: (1) disulfiram, 53 participants; (2) placebo, 54 participants; (3) disulfiram plus naltrexone, 49 participants; (4) naltrexone, 52 participants. In the present SR, the results of participants who received disulfiram (53 participants) were compared to those who received placebo (54 participants) (arm a), and the results of participants who received disulfiram (53 participants) were compared to those of participants who received naltrexone (52 participants) (arm b, Comparison 2 versus naltrexone). Arm a (Comparison 1): (1) disulfiram (53 participants) vs (2) placebo (54 participants); Arm b (Comparison 2): (1) disulfiram (53 participants) vs (2) naltrexone (52 participants).	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	No details provided.
Allocation concealment?	Unclear risk	Method of concealment not described.
Blinding? Objective outcomes	Low risk	Study described as double-blind. Quote: "All patients received the same number of pills (active medication and/or placebo pills), regardless of group or week of treatment. Study medication was dispensed in clearly labeled blister cards at a once-a-week medical evaluation visit."
Blinding? Subjective outcomes	Low risk	Study described as double-blind. Quote: "All patients received the same number of pills (active medication and/or placebo pills), regardless of group or week of treatment. Study medication was dispensed in clearly labeled blister cards at a once-a-week medical evaluation visit."
Blinding of outcome assessor Subjective outcomes	Low risk	Participants and outcome assessors blinded to treatment assignment.
Blinding of outcome assessor Objective outcomes	Low risk	Participants and outcome assessors blinded to treatment assignment.
Incomplete outcome data addressed?	Low risk	Attrition/exclusion described by medication condition. Main analyses in this paper were by intention to treat.

Free of selective reporting?	Unclear risk	No protocol available.

Pettinati 2008 comparison b

Study characteristics		
Methods	Randomized, placebo-controlled, double blind trial.	
Participants	105 individuals who met DSM-IV criteria for both current cocaine and alcohol dependence; mean age 41.6 years; male 70%; African American 87.9%; mean education 12.2 years; use of cocaine in the previous month: 47.0% of the days in the average; use of alcohol (heavy drinking) in the previous month: 48.8% of the days on the average. Inclusion criteria: current cocaine and alcohol dependence according with DSM-IV; age between 18 and 65 years; having used a minimum of $ 100 worth of cocaine and drank an average of 12 standard alcoholic drinks a week during the month before treatment; Exclusion criteria: subjects with dependence on substances other than cocaine and alcohol, except nicotine addiction; having an active psychosis, mania, dementia, or the need for treatment with psychiatric medications; being pregnant, breastfeeding; having active hepatitis and significant hepatocellular injury; if indicated, complete outpatient alcohol detoxification.	
Interventions	Interventions: (1) disulfiram, 53 participants; (2) naltrexone, 52 participants. Partecipants were involved in twice a week individual Cognitive Behavioural Therapy sessions. Drug dose: disulfiram 250 mg/day; naltrexone 100 mg/day. Outpatient. Duration 11 weeks. Country of origin: USA.	
Outcomes	(1) Abstinence from cocaine and alcohol measured through self report; (2) value in dollars of cocaine used daily; (3) urine analysis for cocaine three times a week (if one or more resulted positive for cocaine the week was considered non abstinent); (4) proportion of patients with 3 consecutive weeks abstinent for cocaine; (5) number and types of size effects using the the systematic assessment for treatment emergent effects.	
Notes	In the primary study participants were divided into 4 sugroups that received the following treatments: (1) disulfiram, 53 participants; (2) placebo, 54 participants; (3) disulfiram plus naltrexone, 49 participants; (4) naltrexone, 52 participants. In the present SR, the results of participants who received disulfiram (53 participants) were compared to those who received placebo (54 participants) (arm a), and the results of participants who received disulfiram (53 participants) were compared to those of participants who received naltrexone (52 participants) (arm b, Comparison 2 versus naltrexone). Arm a (Comparison 1): (1) disulfiram (53 participants) vs (2) placebo (54 participants); Arm b (Comparison 2): (1) disulfiram (53 participants) vs (2) naltrexone (52 participants).	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	No details provided.
Allocation concealment?	Unclear risk	Method of concealment not described.
Blinding? Objective outcomes	Low risk	Study described as double-blind. Quote: "All patients received the same number of pills (active medication and/or placebo pills), regardless of group or week of treatment. Study medication was dispensed in clearly labeled blister cards at a once-a-week medical evaluation visit."
Blinding? Subjective outcomes	Low risk	Study described as double-blind. Quote: "All patients received the same number of pills (active medication and/or placebo pills), regardless of group or week of treatment. Study medication was dispensed in clearly labeled blister cards at a once-a-week medical evaluation visit."
Blinding of outcome assessor Subjective outcomes	Low risk	Participant and outcome assessors blind to treatment allocation.
Blinding of outcome assessor Objective outcomes	Low risk	Participant and outcome assessors blind to treatment allocation.
Incomplete outcome data addressed?	Low risk	Attrition/exclusion described by medication condition. Main analyses in this paper were by intention to treat.
Free of selective reporting?	Unclear risk	No protocol available.

Pettinati 2008 comparison c

Study characteristics	
Methods	Randomized, placebo-controlled, double blind trial
Participants	105 individuals who met DSM-IV criteria for both current cocaine and alcohol dependence; mean age 41.6 years; male 70%; African American 87.9%; mean education 12.2 years; use of cocaine in the previous month: 47.0% of the days in the average; use of alcohol (heavy drinking) in the previous month: 48.80% of the days on the average.

	Inclusion criteria: current cocaine and alcohol dependence according with DSM-IV; age between 18 and 65 years; having used a minimum of $ 100 worth of cocaine and drank an average of 12 standard alcoholic drinks a week during the month before treatment; Exclusion criteria: subjects with dependence on substances other than cocaine and alcohol, except nicotine addiction; having an active psychosis, mania, dementia, or the need for treatment with psychiatric medications; being pregnant, breastfeeding; having active hepatitis and significant hepatocellular injury; if indicated, complete outpatient alcohol detoxification.
Interventions	Interventions: (1) disulfiram plus naltrexone, 49 participants; (2) naltrexone, 52 participants. Partecipants were involved in twice a week individual Cognitive Behavioural Therapy sessions. Drug dose: disulfiram 250 mg/day; naltrexone 100 mg/day. Outpatient. Duration 11 weeks. Country of origin: USA.
Outcomes	(1) Abstinence from cocaine and alcohol measured through self report; (2) value in dollars of cocaine used daily; (3) urine analysis for cocaine three times a week (if one or more resulted positive for cocaine the week was considered non abstinent); (4) proportion of patients with 3 consecutive weeks abstinent for cocaine; (5) number and types of size effects using the the systematic assessment for treatment emergent effects.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	No information provided.
Allocation concealment?	Unclear risk	Method of concealment not described.
Blinding? Objective outcomes	Low risk	Study described as double-blind. Quote: "All patients received the same number of pills (active medication and/or placebo pills), regardless of group or week of treatment. Study medication was dispensed in clearly labeled blister cards at a once-a-week medical evaluation visit."
Blinding? Subjective outcomes	Low risk	Study described as double-blind. Quote: "All patients received the same number of pills (active medication and/or placebo pills), regardless of group or week of treatment. Study medication was dispensed in clearly labeled blister cards at a once-a-week medical evaluation visit."
Blinding of outcome assessor Subjective outcomes	Low risk	Participants and outcome assessors blind to treatment allocation.
Blinding of outcome assessor Objective outcomes	Low risk	Participants and outcome assessors blind to treatment allocation.
Incomplete outcome data addressed?	Low risk	Attrition/exclusion described by medication condition. Main analyses in this paper were by intention-to-treat.
Free of selective reporting?	Unclear risk	No protocol available.

Schottenfeld 2013

Study characteristics	
Methods	Doble-bind, randomized, placebo-controlled study
Participants	N=177 mean age= 18-45 years; PLA (n = 86): Age = 31.3 (6.8); % Females = 27/86 (31.4%); % White = 56/86 (65.1%); Years of cocaine use = 8.1 (5.1); Days of cocaine use in the past 30 = 12.4 (8.8); % IV drug use = 36.6%; DIS (n=91): Age = 31.7 (7.3); % Females = 23/91 (25.3%); % White = 67/91 (73.6%); Years of cocaine use = 9.3 (6.8); Days of cocaine use in the past 30 = 11.9 (8.4); % IV drug use = 32.1% Inclusion criteria: current opioid dependence and cocaine abuse or dependence. Women were included if they agreed to adequate contraception and to monthly pregnancy testing. Exclusion criteria: currently physiologically dependent on alcohol; using metronidazole or clotrimazole; experiencing significant cardiovascular, renal, hepatic or neurologic illness or had liver enzymes (alkaline phosphatase or alanine transaminase) greater than three times the upper limit of normal; dangerous to themselves or others; psychotic; or considered at risk for suicide or violence. First degree family member with a history of myocardial infarction prior to age 60, a past history of myocardial infarction, hypertension (systolic blood pressure > 140 or diastolic blood pressure > 90), or EKG evidence of myocardial infarction or ischemia.
Interventions	(1) DIS (250 mg/day) plus buprenorphine (24 mg SL daily) (91 participants) (2) PLA plus buprenorphine (24 mg SL daily) (86 participants) Duration: 2 weeks to stabilize buprenorphine and then 12 weeks of treatment with disulfiram
Outcomes	Primary outcomes: frequency (the number of days per week) of cocaine use and the number of cocaine-negative urine tests in successive two-week intervals, and the maximum consecutive weeks of abstinence from cocaine, documented by urine toxicology testing. Secondary outcomes: frequency (the number of days per week) of opioid use and the number of opioid-negative urine tests in successive two-week intervals, and the maximum consecutive weeks abstinent from illicit opioids, documented by urine toxicology testing
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Quote: "A research pharmacist who had no direct contact with participants used a computer-generated simple randomization list to allocate participants to active or placebo disulfiram."
Allocation concealment?	Low risk	Quote: "With the exception of the research pharmacist, none of the other research personnel or care providers had access to the randomization list, which was kept in the locked pharmacy office."
Blinding? Objective outcomes	Low risk	Quote: "With the exception of the research pharmacist, none of the other research personnel or care providers had access to the randomization list, which was kept in the locked pharmacy office."; "The research pharmacist prepared active disulfiram 250 mg and matching placebo capsules by filling identical blue 00 capsules with Avicel (microcrystalline cellulose, NF) only or Avicel mixed with pulverized disulfiram 250 mg tablets, purchased from a local pharmacy, and dispensed the medications in individual medication bottles prepared for each participant."
Blinding? Subjective outcomes	Low risk	Quote: "With the exception of the research pharmacist, none of the other research personnel or care providers had access to the randomization list, which was kept in the locked pharmacy office."; "The research pharmacist prepared active disulfiram 250 mg and matching placebo capsules by filling identical blue 00 capsules with Avicel (microcrystalline cellulose, NF) only or Avicel mixed with pulverized disulfiram 250 mg tablets, purchased from a local pharmacy, and dispensed the medications in individual medication bottles prepared for each participant."
Blinding of outcome assessor Subjective outcomes	Low risk	Participants and outcome assessors blind to treatment allocation.
Blinding of outcome assessor Objective outcomes	Low risk	Participants and outcome assessors blind to treatment allocation.
Incomplete outcome data addressed?	Low risk	Quote: "Data analyses, planned a priori, were based on an intention-to-treat sample of all randomized participants."
Free of selective reporting?	Unclear risk	Study protocol available but posted after study initiation; outcomes not clearly described.

CBT: cognitive behavioural therapy; CG: control group; DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition Revised; EG: experimental group; ICD-10: International Classification of Diseases, 10th Edition; IV: intravenous; n = number of participants; RCT: randomised controlled trial; TSF: twelve-step facilitation.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Assistance Publique - Hôpitaux de Paris 2014	Recruitment status: withdrawn (no eligible patients).
Baker 2007	Ineligible study design.
Carroll 2000	Ineligible study design (follow-up study using 80% of subjects enrolled in a previous trial).
DeVito 2014	An aggregate sample comprised of data from 5 randomised clinical trials of treatment for cocaine dependence (n = 434) was evaluated for gender differences in clinical outcomes.
Easton 2007	Ineligible study design: uses data from 2 previous study to carry out secondary analysis.
Haile 2012	Cross-over design.
Jofre-Bonet 2004	Ineligible study design.
McCance 1996	Ineligible study design (inpatient setting).
McCance 1998a	Ineligible study design (inpatient setting).
McCance 1998b	Ineligible study design.
Milligan 2004	Ineligible study design: analyses results from 2 previous studies to investigate predictivity of ethnic differences in relation to treatment.
Nahata 2015	Ineligible study design: reports on secondary analyses examining the prognostic relevance of dopamine beta-hydroxylase levels in a clinical trial of disulfiram at higher doses for treating cocaine dependence in methadone-stabilised participants.
Pantalon 2002	Ineligible study design.

Characteristics of ongoing studies [ordered by study ID]

NCT00000278

Study name	Disulfiram for cocaine-alcohol abuse
Methods	Information not available
Participants	Either sex, aged 18–50 years
Interventions	Disulfiram; no other information available
Outcomes	Side effects, cocaine effects

Starting date	September 1999
Contact information	Thomas Kosten, MD, Baylor College of Medicine, One Baylor Plaza, BCM 350, Houston, TX 77030. kosten@bcm.edu [mailto:kosten%40bcm.edu?subject=NCT00149630, NIDA-18197-2, Pharmacogenetics of Disulfiram for Cocaine]
Notes	ClinicalTrials.gov identifier: NCT00000278

NCT00094289

Study name	Interactions between cocaine and ethanol and disulfiram - 1
Methods	2-site, double-blind, placebo-controlled inpatient study
Participants	People with cocaine abuse or dependence who are not seeking treatment
Interventions	Disulfiram
Outcomes	Cardiovascular and psychiatric safety of alcohol use in cocaine-dependent subjects who had used cocaine after treatment with disulfiram
Starting date	
Contact information	John Roache, Ph.D., University of Texas Health Science Center, San Antonio (TX)
Notes	ClinicalTrials.gov identifier: NCT00094289

NCT00580827

Study name	Clinical efficacy of disulfiram in LAAM-maintained cocaine abusers
Methods	Treatment, randomised, double-blind (subject, caregiver, investigator, outcomes assessor), placebo-controlled, factorial assignment, efficacy study
Participants	Cocaine-dependent opioid addicts, aged 18-65 years
Interventions	Placebo or disulfiram at 62.5 mg/day, 125 mg/day, or 250 mg/day, while concurrently receiving LAAM (levomethadyl acetate hydrochloride)
Outcomes	Primary: reductions in cocaine use as measured by urine toxicology and self-report Secondary: predictors of treatment efficacy using DBH (dopamine beta-hydroxylase) genotyping
Starting date	September 2003
Contact information	James Poling, Ph.D., Yale University, West Haven, CT, 06516, james.poling@yale.edu
Notes	ClinicalTrials.gov identifier: NCT00580827

Appendices

Appendix 1. CDAG Specialised Register search strategy

#1 (Disulfiram or Antabuse or Antabus or Etiltox) AND INREGISTER
#2 cocaine* or crack* AND INREGISTER
#3 #2 AND #1
#4 2009 TO 2022:YR AND INREGISTER
#5 #3 AND #4

Appendix 2. Cochrane Central Register of Controlled Trials search strategy

#1 MeSH descriptor: [Cocaine-Related Disorders] explode all trees
#2 ((drug* or substance) near/2 (abuse* or misuse* or addict* or dependen*)):ti,ab
#3 ((cocaine* or crack*) near/2 (abuse* or addict* or dependen*)):ti,ab
#4 ((stimulant* or psychostimulant* or psycho-stimulant*) near/5 (abstain* or abstinence or abstinent or abuse* or addict* or chronic* or detox* or disorder* or depend* or habitual* or misuse* or overuse or reduce* or reducing or reduction or retain* or retention or users or withdrawal)):ti,ab
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Cocaine] explode all trees
#7 (cocaine* or crack):ti,ab
#8 #6 or #7
#9 #5 and #8
#10 MeSH descriptor: [Disulfiram] explode all trees
#11 (Disulfiram or Antabuse or Antabus or Etiltox):ti,ab
#12 #10 or #11
#13 #9 and #12 with Publication Year from 2009 to present, in Trials

Appendix 3. Ovid MEDLINE search strategy

1. exp Cocaine-Related Disorders/
2. ((cocaine* or crack-cocaine*) adj5 (abuse* or addict* or chronic* or disorder* or depend* or habitual* or misuse* or overuse or users)).tw,kf.

3. ((stimulant* or psychostimulant* or psycho-stimulant*) adj5 (abstain* or abstinence or abstinent or abuse* or addict* or chronic* or detox* or disorder* or depend* or habitual* or misuse* or overuse or reduce* or reducing or reduction or retain* or retention or users or withdrawal)).tw,hw,id.
4. ((drug or polydrug* or substance or stimulant* or psychostimulant* or psycho-stimulant*) and (abuse* or addict* or disorder* or depend* or misuse* or overuse or users)).tw,kf.
5. 1 or 2 or 3 or 4
6. cocaine.mp. or exp Cocaine/
7. 5 and 6
8. Disulfiram/
9. (Disulfiram or Antabuse or Antabus or Etiltox).mp.
10. 8 or 9
11. 7 and 10
12. randomized controlled trial.pt.
13. controlled clinical trial.pt.
14. random*.ab.
15. placebo.ab.
16. clinical trials as topic.sh.
17. random allocation.sh.
18. trial.ti.
19. 12 or 13 or 14 or 15 or 16 or 17 or 18
20. exp animals/ not humans.sh.
21. 19 not 20
22. 11 and 21
23. limit 22 to yr="2009 -Current"

Appendix 4. Ovid Embase search strategy

1. exp cocaine dependence/
2. ((cocaine* or crack-cocaine*) adj5 (abuse* or addict* or chronic* or disorder* or depend* or habitual* or misuse* or overuse or users)).tw,kf.
3. ((drug or polydrug* or substance or stimulant* or psychostimulant* or psycho-stimulant*) and (abuse* or addict* or disorder* or depend* or misuse* or overuse or users)).tw,kf.
4. 1 or 2 or 3
5. cocaine.mp. or exp Cocaine/
6. 4 and 5
7. Disulfiram/
8. (Disulfiram or Antabuse or Antabus or Etiltox).mp.
9. 7 or 8
10. 6 and 9
11. Clinical-Trial/ or Randomized-Controlled-Trial/ or Randomization/ or Single-Blind-Procedure/ or Double-Blind-Procedure/ or Crossover-Procedure/ or Prospective-Study/ or Placebo/
12. (((clinical or control or controlled) adj (study or trial)) or ((single or double or triple) adj (blind$3 or mask$3)) or (random$ adj (assign$ or allocat$ or group or grouped or patients or study or trial or distribut$)) or (crossover adj (design or study or trial)) or placebo or placebos).ti,ab.
13. 11 or 12
14. 10 and 13
15. limit 14 to yr="2009 -Current"

Appendix 5. PsycINFO search strategy

1. exp Drug Addiction/ or exp "Substance Use Disorder"/
2. ((cocaine* or crack-cocaine*) adj5 (abuse* or addict* or chronic* or disorder* or depend* or habitual* or misuse* or overuse or users)).tw.

3. ((drug or polydrug* or substance or stimulant* or psychostimulant* or psycho-stimulant*) and (abuse* or addict* or disorder* or depend* or misuse* or overuse or users)).tw.
4. 1 or 2 or 3
5. cocaine.mp. or exp Cocaine/
6. 4 and 5
7. Disulfiram/
8. (Disulfiram or Antabuse or Antabus or Etiltox).mp.
9. 7 or 8
10. 6 and 9
11. exp Clinical Trials/
12. (random* or (clinical adj3 trial*) or (reserch adj3 design*) or (evaluat adj3 stud*) or (prospective* adj3 stud*)).tw.
13. ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*)).tw.
14. 11 or 12 or 13
15. 10 and 14
16. limit 15 to yr="2009 -Current"

Appendix 6. CINAHL (EBSCOhost) search strategy

S27 S10 AND S26

S26 S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25

S25 AB (cluster W3 RCT)

S24 MH (crossover design) OR MH (comparative studies)

S23 AB (control W5 group)

S22 PT (randomized controlled trial)

S21 MH (placebos)

S20 MH (sample size) AND AB (assigned OR allocated OR control)

S19 TI (trial)

S18 AB (random*)

S17 TI (randomised OR randomized)

S16 MH cluster sample

S15 MH pretest-posttest design

S14 MH random assignment

S13 MH single-blind studies

S12 MH double-blind studies

S11 MH randomized controlled trials

S10 S6 AND S9

S9 S7 OR S8

S8 TX(Disulfiram or Antabuse or Antabus or Etiltox)

S7 (MH "Disulfiram") OR "Disulfiram"

S6 S4 AND S5

S5 TX cocaine or MH cocaine

S4 S1 OR S2 OR S3

S3 TX ((stimulant* or psychostimulant* or psycho-stimulant*) and (abuse* or addict* or disorder* or depend* or misuse* or overuse or users))

S2 TX ((cocaine* or crack-cocaine*) AND (abuse* or addict* or chronic* or disorder* or depend* or habitual* or misuse* or overuse or users))

S1 (MH "Substance Use Disorders+")

Appendix 7. Criteria for risk of bias assessment

Item	Judgement	Description
1. Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process such as: • random number table; • computer random number generator; • coin tossing; • shuffling cards or envelopes; • throwing dice; or • drawing of lots, minimisation.
	High risk	The investigators describe a non-random component in the sequence generation process such as: • odd or even date of birth; • date (or day) of admission; • hospital or clinic record number; • alternation; • judgement of the clinician; • results of a laboratory test or a series of tests; or • availability of the intervention.
	Unclear risk	Insufficient information about the sequence generation process to permit judgement of low or high risk.
2. Allocation concealment (selection bias)	Low risk	Investigators enroling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: • central allocation (including telephone, web-based, and pharmacy-controlled randomisation); • sequentially numbered drug containers of identical appearance; or • sequentially numbered, opaque, sealed envelopes.
	High risk	Investigators enroling participants could possibly foresee assignments because one of the following methods was used: • open random allocation schedule (e.g. a list of random numbers); • assignment envelopes without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); • alternation or rotation; • date of birth; • case record number; or • any other explicitly unconcealed procedure.
	Unclear risk	Insufficient information to permit judgement of low or high risk. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement.
3. Blinding of participants and providers (performance bias) **Objective outcomes**	Low risk	• No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; or • blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk	• No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; or • blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit judgement of low or high risk.
4. Blinding of participants and providers (performance bias) **Subjective outcomes**	Low risk	Blinding of participants and providers ensured and unlikely that the blinding could have been broken.
	High risk	• No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; or • blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit judgement of low or high risk.
5. Blinding of outcome assessor (detection bias) **Objective outcomes**	Low risk	• No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; or • blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.

	High risk	• No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; or • blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit judgement of low or high risk.
6. Blinding of outcome assessor (detection bias) **Subjective outcomes**	Low risk	Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk	• No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; or • blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit judgement of low or high risk.
7. Incomplete outcome data (attrition bias) **All outcomes except dropout**	Low risk	• No missing outcome data; or • reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); or • missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; or, • for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; or • for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; or • missing data have been imputed using appropriate methods; or • all randomised participants are reported/analysed in the group they were allocated to by randomisation irrespective of non-compliance and co-interventions (intention to treat).
	High risk	• Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; or • for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; or • for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; or • 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation.
	Unclear risk	Insufficient information to permit judgement of low or high risk (e.g. number randomised not stated, no reasons for missing data provided; number of dropouts not reported for each group).
8. Selective reporting (reporting bias)	Low risk	• Study protocol is available and all prespecified (primary and secondary) outcomes that are of interest in the review have been reported as prespecified; or • the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon).
	High risk	• Not all of the study's prespecified primary outcomes have been reported; or • one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified; or • one or more reported primary outcomes were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); or • one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; or • the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear risk	Insufficient information to permit judgement of low or high risk.

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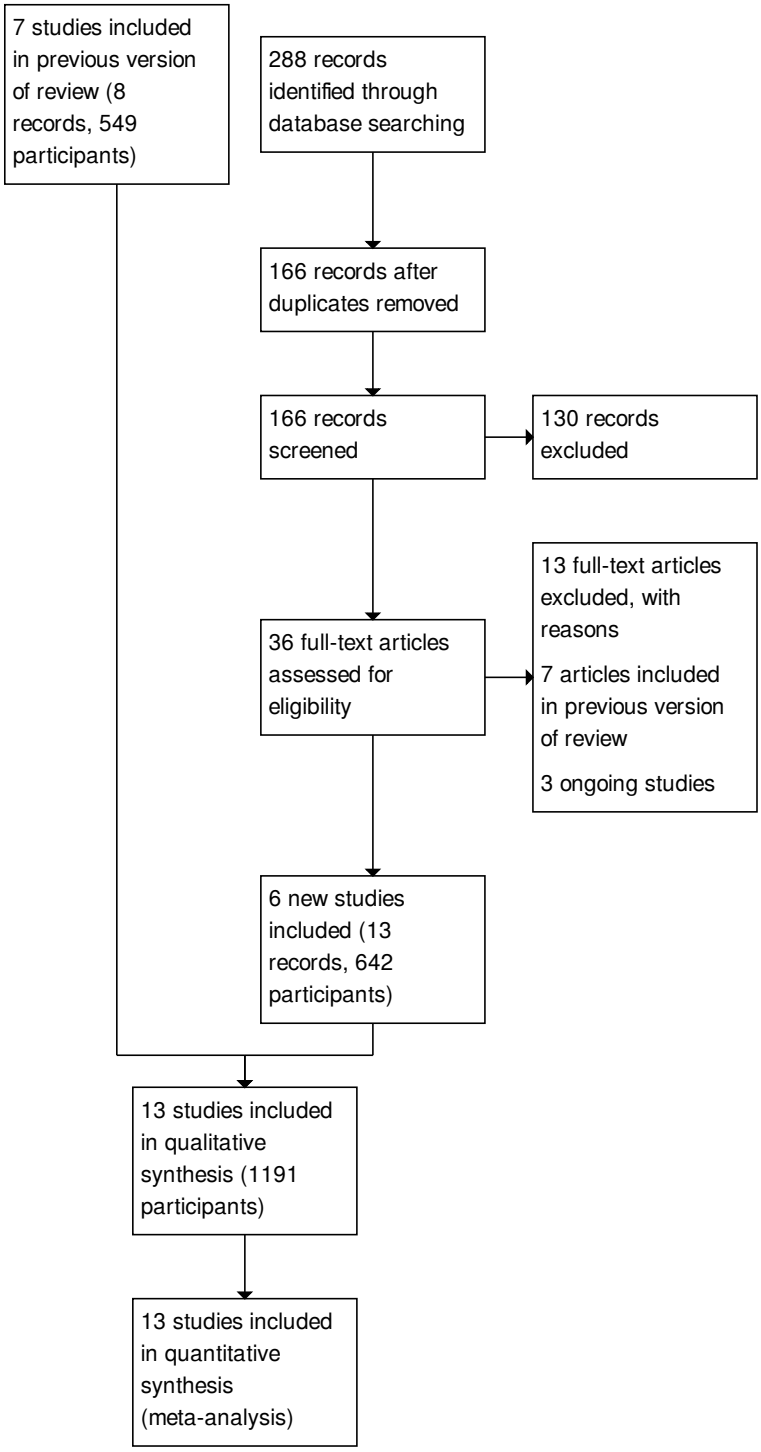
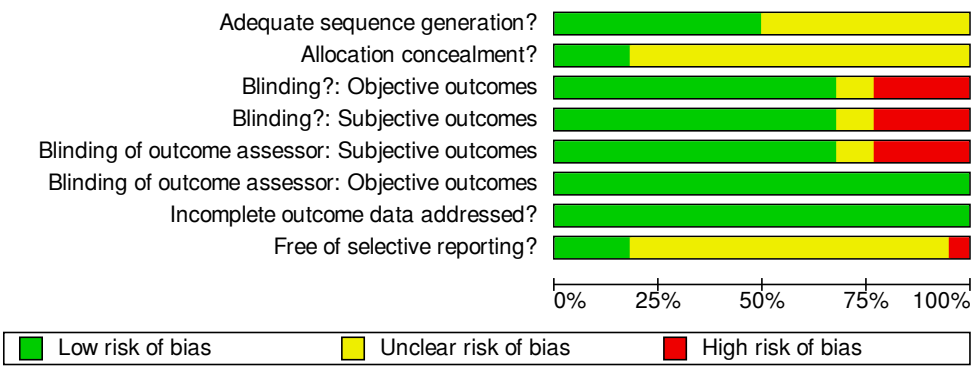
Figure 1



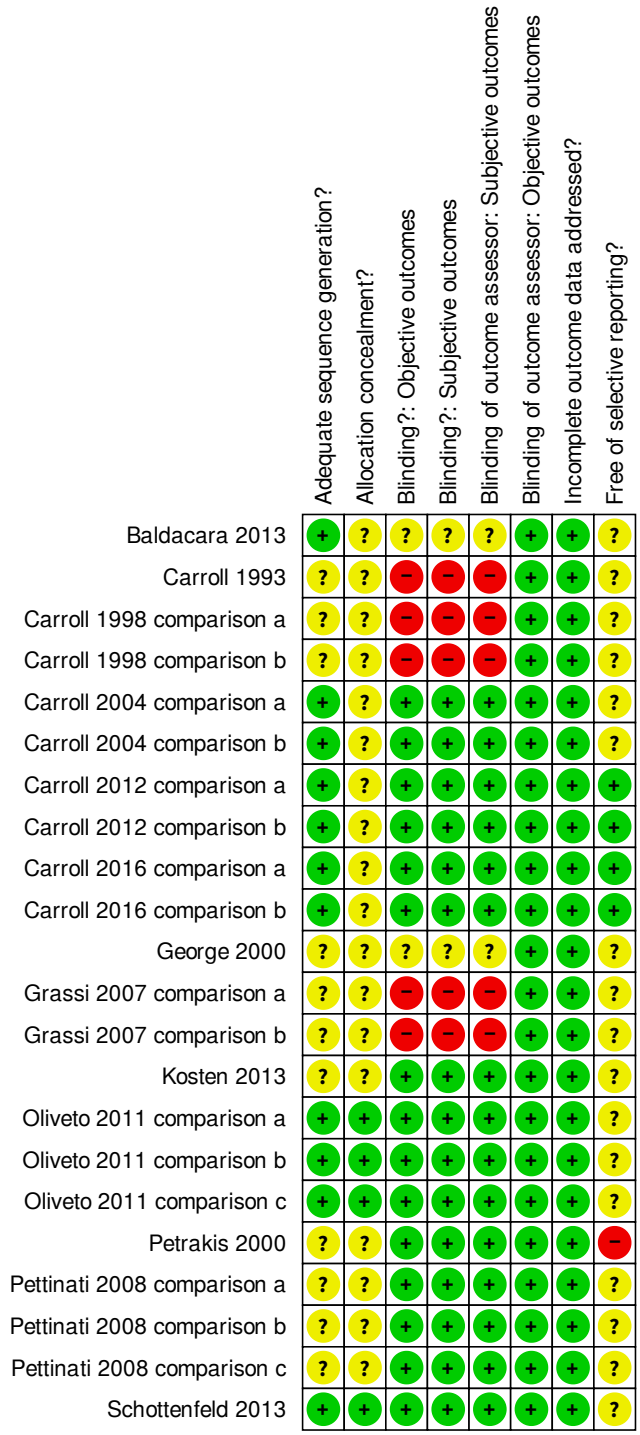
PRISMA flow diagram illustrating the study selection process.

Figure 2



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

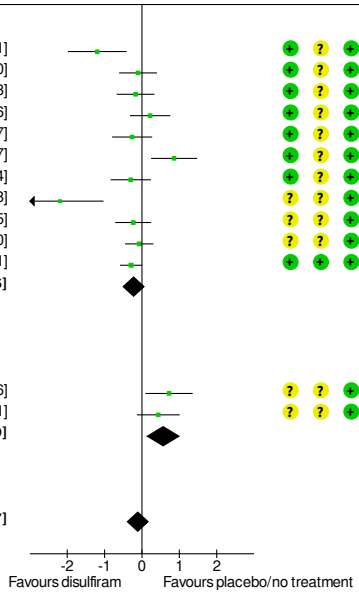
Figure 3



Risk of bias summary: review authors' judgements about each methodological quality item presented as percentages across all included studies.

Figure 4

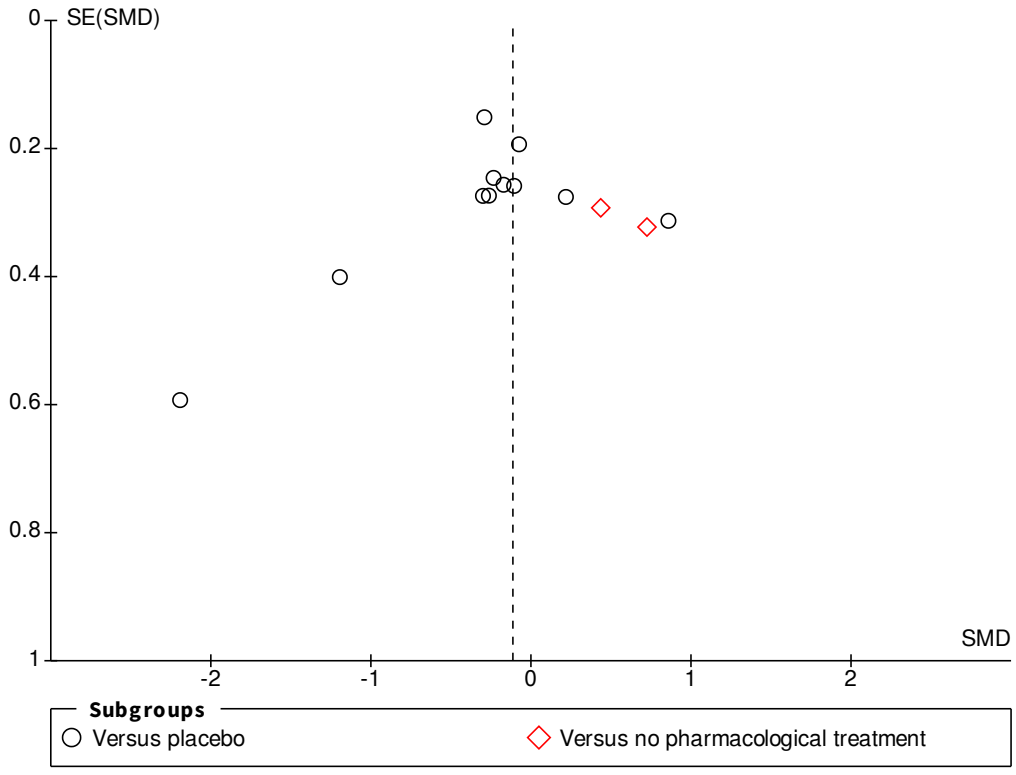
Study or Subgroup	Disulfiram Mean	SD	Total	Placebo/no treatment Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Risk of Bias A	B	C	D
1.1.1 Versus placebo												
Baldacara 2013	0.6	0.2	15	1.4	0.9	15	5.9%	-1.19 [-1.98 , -0.41]	+	?	+	?
Carroll 2004 comparison a	0.3	6.885	30	1	6.27	30	8.2%	-0.10 [-0.61 , 0.40]	+	?	+	?
Carroll 2004 comparison b	0.4	6.885	30	1.54	6.27	31	8.3%	-0.17 [-0.67 , 0.33]	+	?	+	?
Carroll 2012 comparison a	31.7	22.9	27	26.6	23.1	26	7.9%	0.22 [-0.32 , 0.76]	+	?	+	+
Carroll 2012 comparison b	39.7	22.7	28	45.7	22.3	26	8.0%	-0.26 [-0.80 , 0.27]	+	?	+	+
Carroll 2016 comparison a	25.54	26.63	23	7.48	11.42	22	7.3%	0.86 [0.25 , 1.47]	+	?	+	+
Carroll 2016 comparison b	17.48	15.2	28	23.35	22.93	26	8.0%	-0.30 [-0.84 , 0.24]	+	?	+	+
George 2000	29.4	18.2	11	60.9	3.5	9	3.8%	-2.19 [-3.35 , -1.03]	?	?	+	?
Petrakis 2000	4.96	7.5	36	6.68	7.03	31	8.4%	-0.23 [-0.72 , 0.25]	?	?	+	−
Pettinati 2008 comparison a	6.025	1.87	53	6.17	2	54	9.3%	-0.07 [-0.45 , 0.30]	?	?	+	?
Schottenfeld 2013	0.66	1.144727	91	0.99	1.112834	86	10.0%	-0.29 [-0.59 , 0.01]	+	+	+	?
Subtotal (95% CI)			**372**			**356**	**85.2%**	**-0.22 [-0.50 , 0.06]**				
Heterogeneity: Tau² = 0.15; Chi² = 32.28, df = 10 (P = 0.0004); I² = 69%												
Test for overall effect: Z = 1.56 (P = 0.12)												
1.1.2 Versus no pharmacological treatment												
Carroll 1998 comparison a	4.54	4.51	24	1.83	2.03	18	7.1%	0.73 [0.09 , 1.36]	?	?	+	?
Carroll 1998 comparison b	3.76	3.84	25	2.22	3.02	23	7.6%	0.44 [-0.14 , 1.01]	?	?	+	?
Subtotal (95% CI)			**49**			**41**	**14.8%**	**0.57 [0.14 , 0.99]**				
Heterogeneity: Tau² = 0.00; Chi² = 0.44, df = 1 (P = 0.51); I² = 0%												
Test for overall effect: Z = 2.61 (P = 0.009)												
Total (95% CI)			**421**			**397**	**100.0%**	**-0.11 [-0.39 , 0.17]**				
Heterogeneity: Tau² = 0.18; Chi² = 43.39, df = 12 (P < 0.0001); I² = 72%												
Test for overall effect: Z = 0.79 (P = 0.43)												
Test for subgroup differences: Chi² = 9.26, df = 1 (P = 0.002), I² = 89.2%												



Risk of bias legend
(A) Adequate sequence generation?
(B) Allocation concealment?
(C) Incomplete outcome data addressed?
(D) Free of selective reporting?

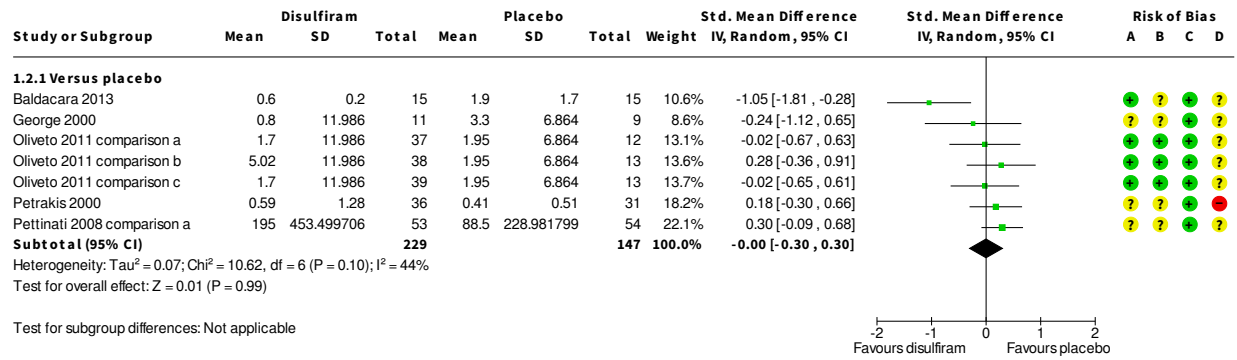
Forest plot of comparison: 1 Disulfiram versus placebo or no pharmacological treatment; outcome: 1 Frequency of cocaine use.

Figure 5



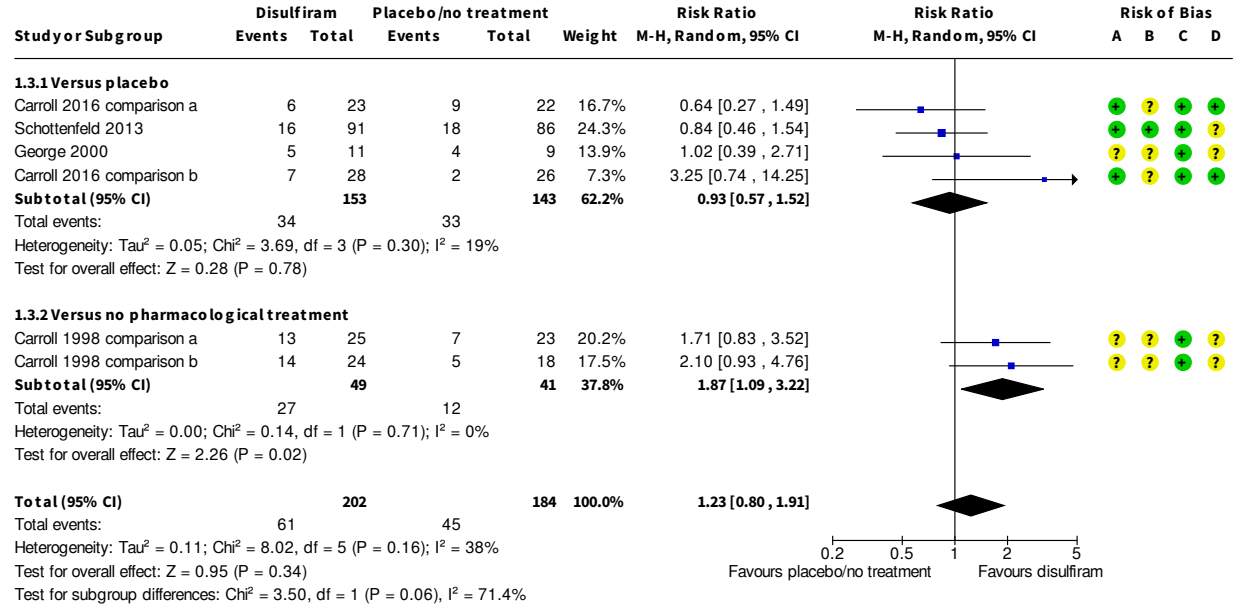
Funnel plot for comparison: 1 Disulfiram versus placebo or no pharmacological treatment; outcome: 1 Frequency of cocaine use.

Figure 6



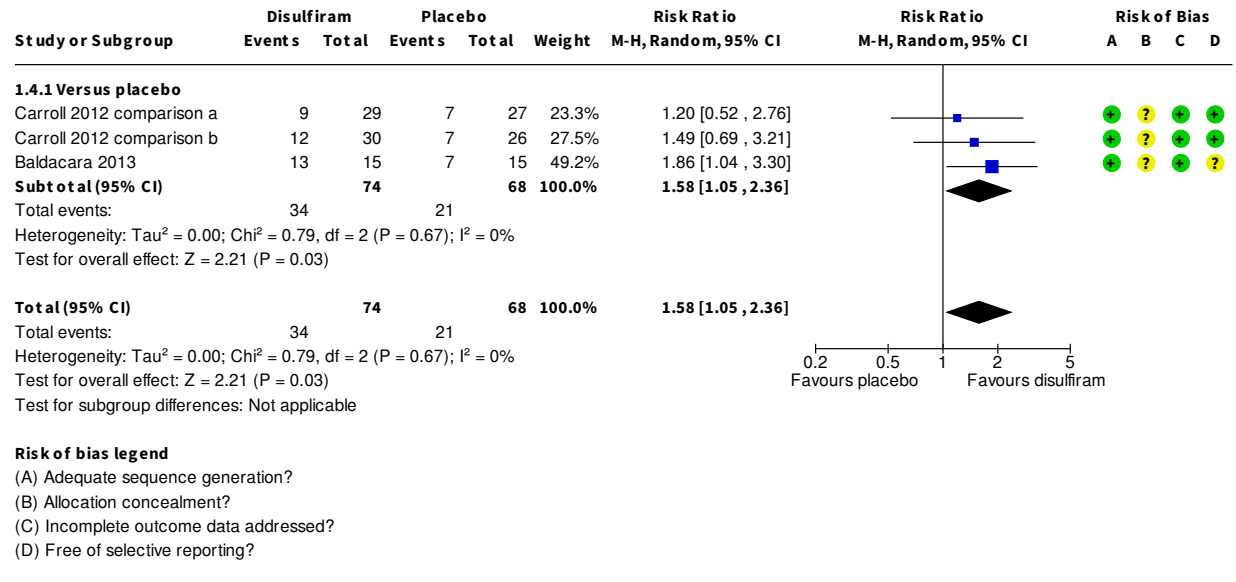
Forest plot of comparison: 1 Disulfiram versus placebo or no pharmacological treatment; outcome: 2 Amount of cocaine use.

Figure 7



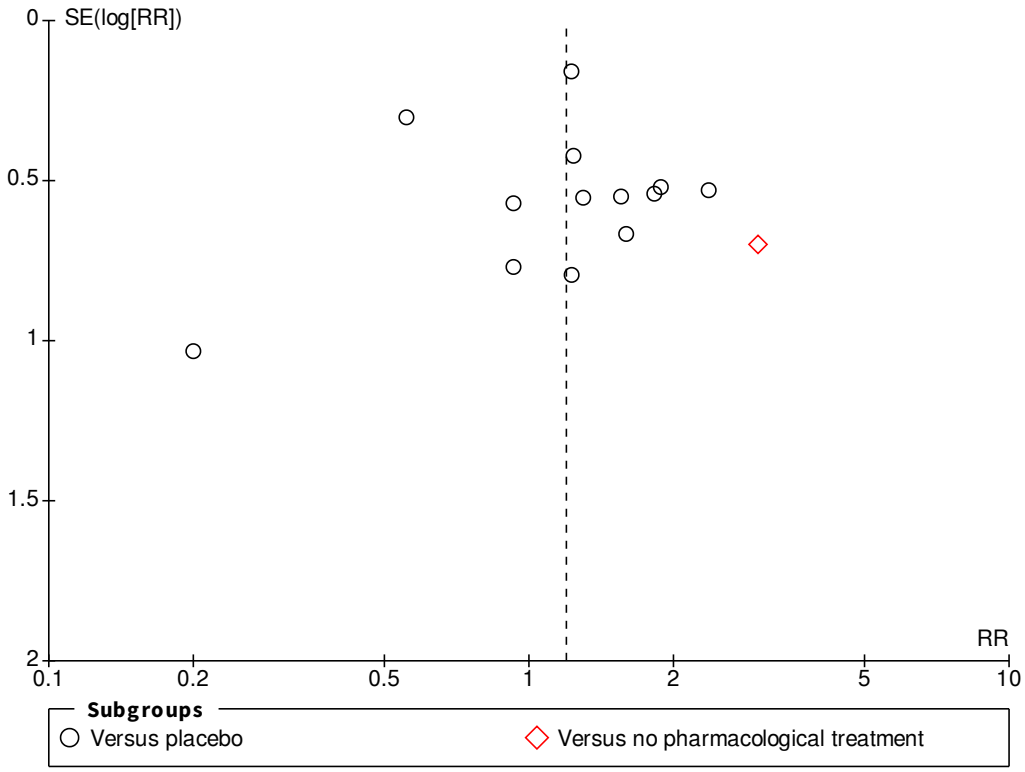
Forest plot of comparison: 1 Disulfiram versus placebo or no pharmacological treatment; outcome: 3 Continuous abstinence.

Figure 8



Forest plot of comparison: 1 Disulfiram versus placebo or no pharmacological treatment; outcome: 4 Point abstinence.

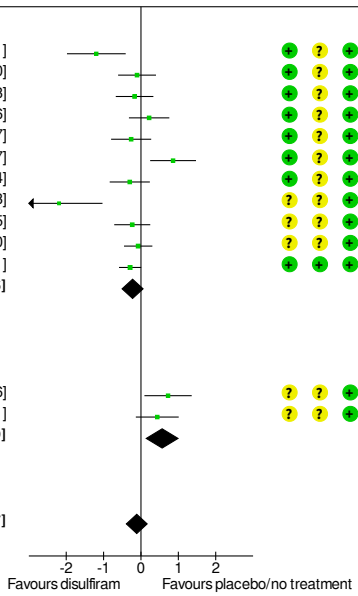
Figure 9



Funnel plot for comparison: 1 Disulfiram versus placebo or no pharmacological treatment; outcome: 5 Dropout for any reason

Analysis 1.1

Study or Subgroup	Disulfiram Mean	SD	Total	Placebo/no treatment Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Versus placebo								
Baldacara 2013	0.6	0.2	15	1.4	0.9	15	5.9%	-1.19 [-1.98 , -0.41]
Carroll 2004 comparison a	0.3	6.885	30	1	6.27	30	8.2%	-0.10 [-0.61 , 0.40]
Carroll 2004 comparison b	0.4	6.885	30	1.54	6.27	31	8.3%	-0.17 [-0.67 , 0.33]
Carroll 2012 comparison a	31.7	22.9	27	26.6	23.1	26	7.9%	0.22 [-0.32 , 0.76]
Carroll 2012 comparison b	39.7	22.7	28	45.7	22.3	26	8.0%	-0.26 [-0.80 , 0.27]
Carroll 2016 comparison a	25.54	26.63	23	7.48	11.42	22	7.3%	0.86 [0.25 , 1.47]
Carroll 2016 comparison b	17.48	15.2	28	23.35	22.93	26	8.0%	-0.30 [-0.84 , 0.24]
George 2000	29.4	18.2	11	60.9	3.5	9	3.8%	-2.19 [-3.35 , -1.03]
Petrakis 2000	4.96	7.5	36	6.68	7.03	31	8.4%	-0.23 [-0.72 , 0.25]
Pettinati 2008 comparison a	6.025	1.87	53	6.17	2	54	9.3%	-0.07 [-0.45 , 0.30]
Schottenfeld 2013	0.66	1.144727	91	0.99	1.112834	86	10.0%	-0.29 [-0.59 , 0.01]
Subtotal (95% CI)			**372**			**356**	**85.2%**	**-0.22 [-0.50 , 0.06]**
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 32.28$, df = 10 (P = 0.0004); $I^2 = 69\%$								
Test for overall effect: Z = 1.56 (P = 0.12)								
1.1.2 Versus no pharmacological treatment								
Carroll 1998 comparison a	4.54	4.51	24	1.83	2.03	18	7.1%	0.73 [0.09 , 1.36]
Carroll 1998 comparison b	3.76	3.84	25	2.22	3.02	23	7.6%	0.44 [-0.14 , 1.01]
Subtotal (95% CI)			**49**			**41**	**14.8%**	**0.57 [0.14 , 0.99]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.44$, df = 1 (P = 0.51); $I^2 = 0\%$								
Test for overall effect: Z = 2.61 (P = 0.009)								
Total (95% CI)			**421**			**397**	**100.0%**	**-0.11 [-0.39 , 0.17]**
Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 43.39$, df = 12 (P < 0.0001); $I^2 = 72\%$								
Test for overall effect: Z = 0.79 (P = 0.43)								
Test for subgroup differences: $Chi^2 = 9.26$, df = 1 (P = 0.002), $I^2 = 89.2\%$								



Risk of bias legend
(A) Adequate sequence generation?
(B) Allocation concealment?
(C) Incomplete outcome data addressed?
(D) Free of selective reporting?

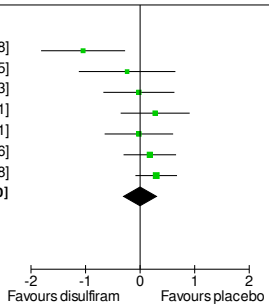
Comparison 1: Disulfiram versus placebo or no pharmacological treatment, Outcome 1: Frequency of cocaine use

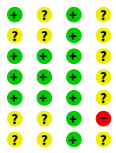
Analysis 1.2

Study or Subgroup	Disulfiram Mean	Disulfiram SD	Disulfiram Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.2.1 Versus placebo								
Baldacara 2013	0.6	0.2	15	1.9	1.7	15	10.6%	-1.05 [-1.81 , -0.28]
George 2000	0.8	11.986	11	3.3	6.864	9	8.6%	-0.24 [-1.12 , 0.65]
Oliveto 2011 comparison a	1.7	11.986	37	1.95	6.864	12	13.1%	-0.02 [-0.67 , 0.63]
Oliveto 2011 comparison b	5.02	11.986	38	1.95	6.864	13	13.6%	0.28 [-0.36 , 0.91]
Oliveto 2011 comparison c	1.7	11.986	39	1.95	6.864	13	13.7%	-0.02 [-0.65 , 0.61]
Petrakis 2000	0.59	1.28	36	0.41	0.51	31	18.2%	0.18 [-0.30 , 0.66]
Pettinati 2008 comparison a	195	453.499706	53	88.5	228.981799	54	22.1%	0.30 [-0.09 , 0.68]
Subtotal (95% CI)			**229**			**147**	**100.0%**	**-0.00 [-0.30 , 0.30]**

Heterogeneity: Tau² = 0.07; Chi² = 10.62, df = 6 (P = 0.10); I² = 44%
Test for overall effect: Z = 0.01 (P = 0.99)

Test for subgroup differences: Not applicable





Risk of bias legend
(A) Adequate sequence generation?
(B) Allocation concealment?
(C) Incomplete outcome data addressed?
(D) Free of selective reporting?

Comparison 1: Disulfiram versus placebo or no pharmacological treatment, Outcome 2: Amount of cocaine use

Analysis 1.3

Study or Subgroup	Disulfiram Events	Disulfiram Total	Placebo/no treatment Events	Placebo/no treatment Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Versus placebo						
Carroll 2016 comparison a	6	23	9	22	16.7%	0.64 [0.27 , 1.49]
Schottenfeld 2013	16	91	18	86	24.3%	0.84 [0.46 , 1.54]
George 2000	5	11	4	9	13.9%	1.02 [0.39 , 2.71]
Carroll 2016 comparison b	7	28	2	26	7.3%	3.25 [0.74 , 14.25]
Subtotal (95% CI)		**153**		**143**	**62.2%**	**0.93 [0.57 , 1.52]**
Total events:	34		33			

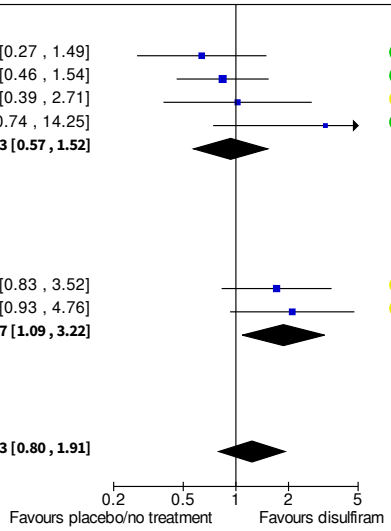
Heterogeneity: Tau² = 0.05; Chi² = 3.69, df = 3 (P = 0.30); I² = 19%
Test for overall effect: Z = 0.28 (P = 0.78)

1.3.2 Versus no pharmacological treatment						
Carroll 1998 comparison a	13	25	7	23	20.2%	1.71 [0.83 , 3.52]
Carroll 1998 comparison b	14	24	5	18	17.5%	2.10 [0.93 , 4.76]
Subtotal (95% CI)		**49**		**41**	**37.8%**	**1.87 [1.09 , 3.22]**
Total events:	27		12			

Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 2.26 (P = 0.02)

Total (95% CI)		**202**		**184**	**100.0%**	**1.23 [0.80 , 1.91]**
Total events:	61		45			

Heterogeneity: Tau² = 0.11; Chi² = 8.02, df = 5 (P = 0.16); I² = 38%
Test for overall effect: Z = 0.95 (P = 0.34)
Test for subgroup differences: Chi² = 3.50, df = 1 (P = 0.06), I² = 71.4%



Risk of bias legend
(A) Adequate sequence generation?
(B) Allocation concealment?
(C) Incomplete outcome data addressed?
(D) Free of selective reporting?

Comparison 1: Disulfiram versus placebo or no pharmacological treatment, Outcome 3: Continuous abstinence

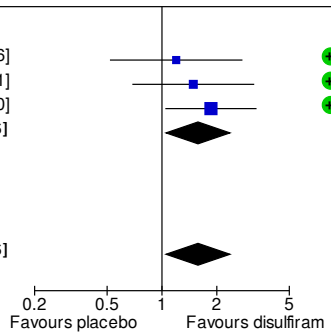
Analysis 1.4

Study or Subgroup	Disulfiram Events	Disulfiram Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Versus placebo						
Carroll 2012 comparison a	9	29	7	27	23.3%	1.20 [0.52 , 2.76]
Carroll 2012 comparison b	12	30	7	26	27.5%	1.49 [0.69 , 3.21]
Baldacara 2013	13	15	7	15	49.2%	1.86 [1.04 , 3.30]
Subtotal (95% CI)		**74**		**68**	**100.0%**	**1.58 [1.05 , 2.36]**
Total events:	34		21			

Heterogeneity: Tau² = 0.00; Chi² = 0.79, df = 2 (P = 0.67); I² = 0%
Test for overall effect: Z = 2.21 (P = 0.03)

Total (95% CI)		**74**		**68**	**100.0%**	**1.58 [1.05 , 2.36]**
Total events:	34		21			

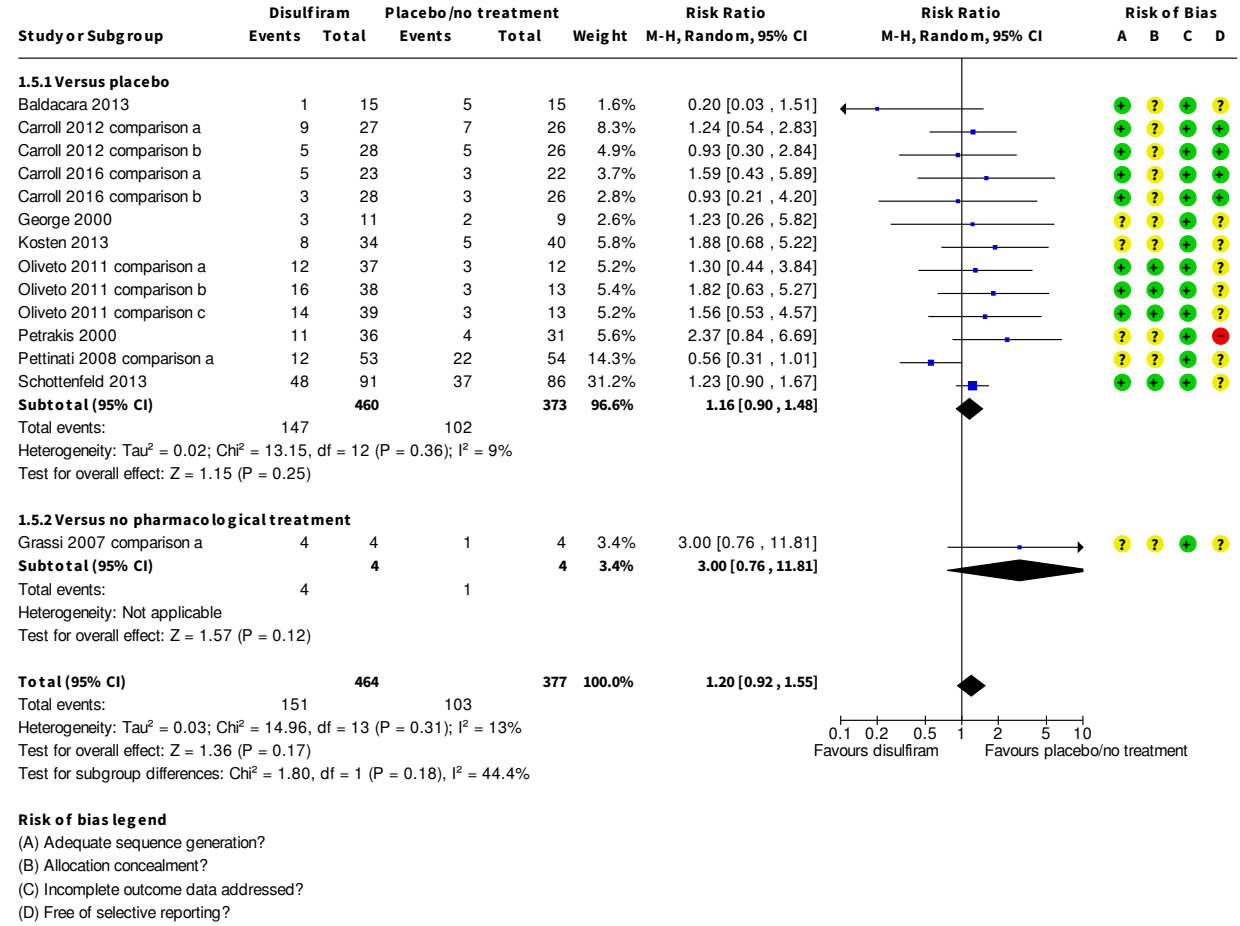
Heterogeneity: Tau² = 0.00; Chi² = 0.79, df = 2 (P = 0.67); I² = 0%
Test for overall effect: Z = 2.21 (P = 0.03)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Adequate sequence generation?
(B) Allocation concealment?
(C) Incomplete outcome data addressed?
(D) Free of selective reporting?

Comparison 1: Disulfiram versus placebo or no pharmacological treatment, Outcome 4: Point abstinence

Analysis 1.5

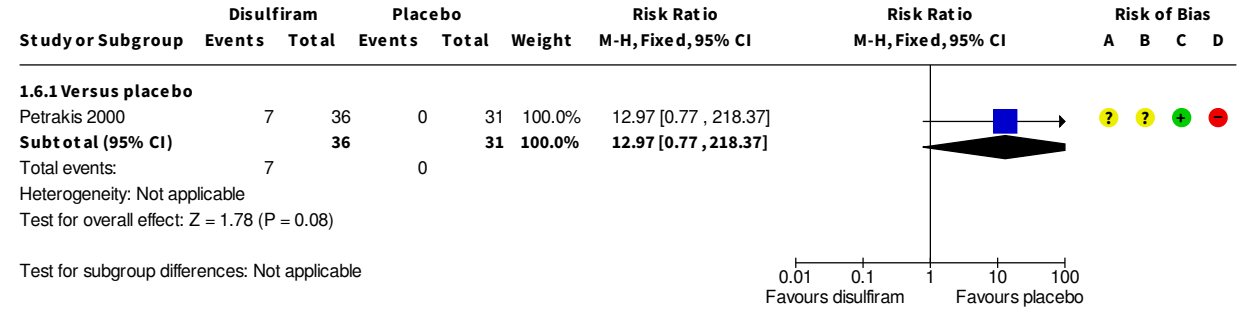


Risk of bias legend

(A) Adequate sequence generation?
(B) Allocation concealment?
(C) Incomplete outcome data addressed?
(D) Free of selective reporting?

Comparison 1: Disulfiram versus placebo or no pharmacological treatment, Outcome 5: Dropout for any reason

Analysis 1.6

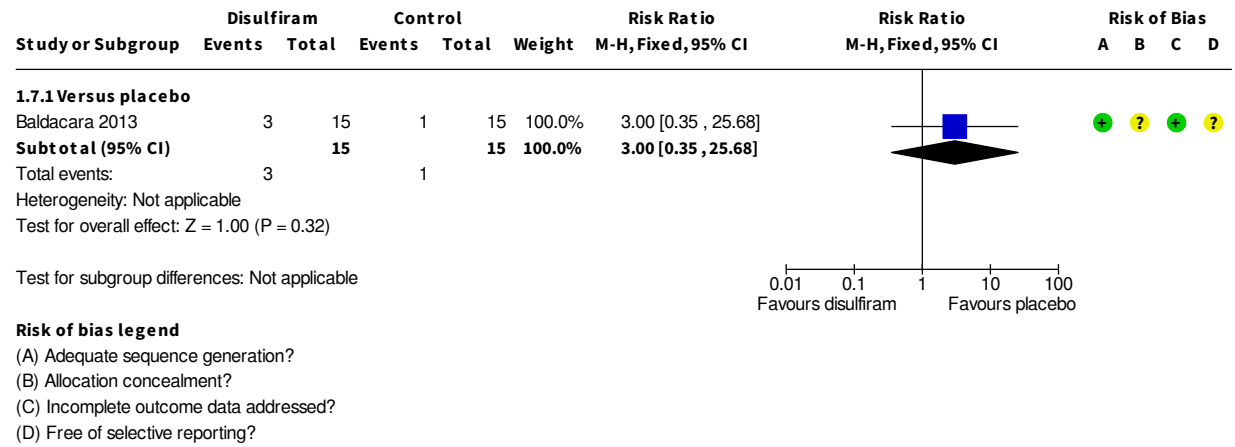


Risk of bias legend

(A) Adequate sequence generation?
(B) Allocation concealment?
(C) Incomplete outcome data addressed?
(D) Free of selective reporting?

Comparison 1: Disulfiram versus placebo or no pharmacological treatment, Outcome 6: Dropout due to adverse events

Analysis 1.7

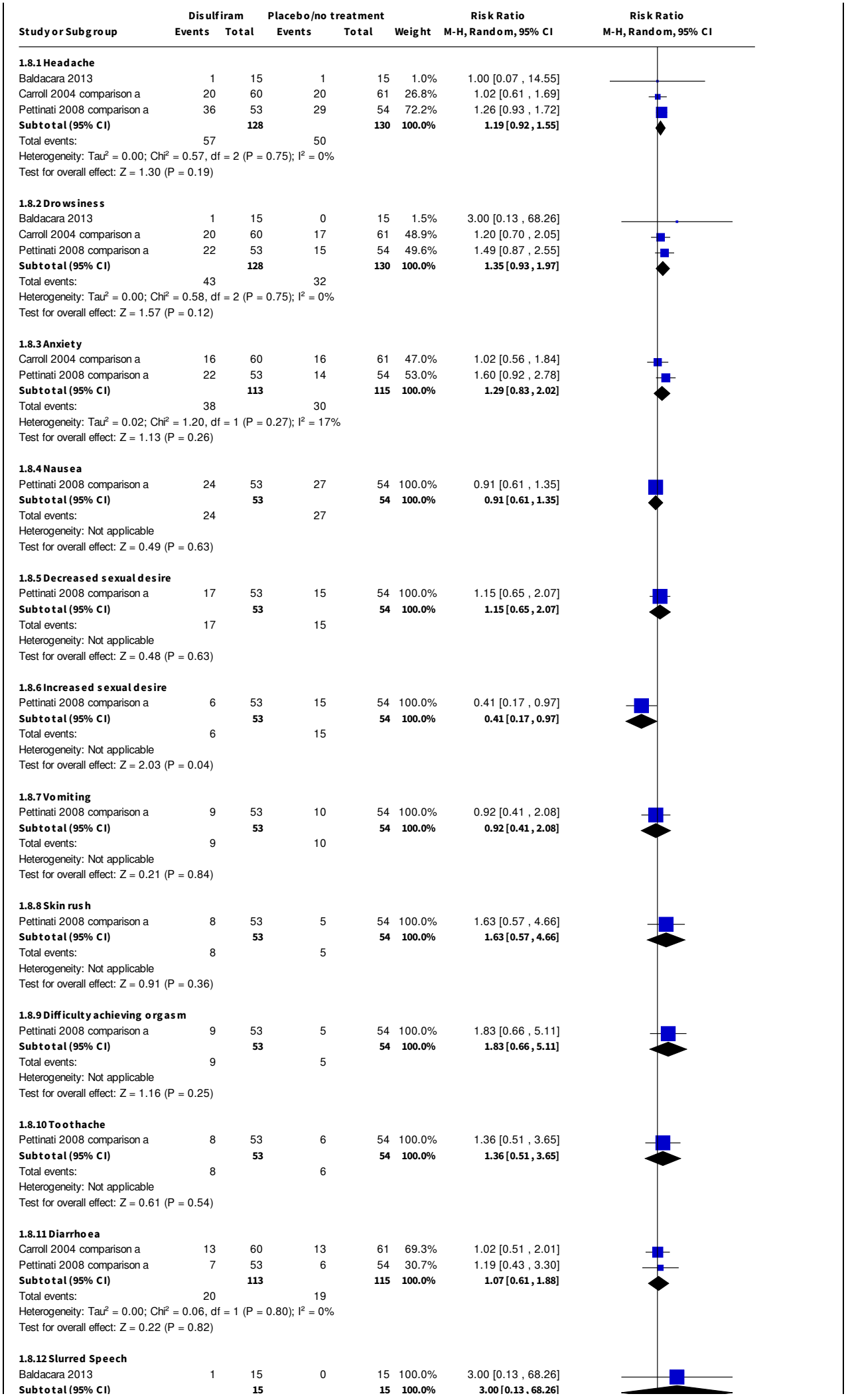


Risk of bias legend

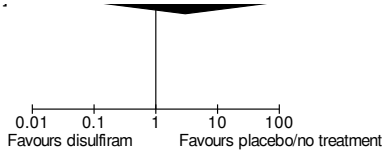
(A) Adequate sequence generation?
(B) Allocation concealment?
(C) Incomplete outcome data addressed?
(D) Free of selective reporting?

Comparison 1: Disulfiram versus placebo or no pharmacological treatment, Outcome 7: Any adverse events

Analysis 1.8


Disulfiram
Placebo/no treatment
Risk Ratio
Risk Ratio
Study or Subgroup
Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.8.1 Headache
Baldacara 2013 1 15 1 15 1.0% 1.00 [0.07 , 14.55]
Carroll 2004 comparison a 20 60 20 61 26.8% 1.02 [0.61 , 1.69]
Pettinati 2008 comparison a 36 53 29 54 72.2% 1.26 [0.93 , 1.72]
Subtotal (95% CI) 128 130 100.0% 1.19 [0.92 , 1.55]
Total events: 57 50
Heterogeneity: Tau² = 0.00; Chi² = 0.57, df = 2 (P = 0.75); I² = 0%
Test for overall effect: Z = 1.30 (P = 0.19)
1.8.2 Drowsiness
Baldacara 2013 1 15 0 15 1.5% 3.00 [0.13 , 68.26]
Carroll 2004 comparison a 20 60 17 61 48.9% 1.20 [0.70 , 2.05]
Pettinati 2008 comparison a 22 53 15 54 49.6% 1.49 [0.87 , 2.55]
Subtotal (95% CI) 128 130 100.0% 1.35 [0.93 , 1.97]
Total events: 43 32
Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 2 (P = 0.75); I² = 0%
Test for overall effect: Z = 1.57 (P = 0.12)
1.8.3 Anxiety
Carroll 2004 comparison a 16 60 16 61 47.0% 1.02 [0.56 , 1.84]
Pettinati 2008 comparison a 22 53 14 54 53.0% 1.60 [0.92 , 2.78]
Subtotal (95% CI) 113 115 100.0% 1.29 [0.83 , 2.02]
Total events: 38 30
Heterogeneity: Tau² = 0.02; Chi² = 1.20, df = 1 (P = 0.27); I² = 17%
Test for overall effect: Z = 1.13 (P = 0.26)
1.8.4 Nausea
Pettinati 2008 comparison a 24 53 27 54 100.0% 0.91 [0.61 , 1.35]
Subtotal (95% CI) 53 54 100.0% 0.91 [0.61 , 1.35]
Total events: 24 27
Heterogeneity: Not applicable
Test for overall effect: Z = 0.49 (P = 0.63)
1.8.5 Decreased sexual desire
Pettinati 2008 comparison a 17 53 15 54 100.0% 1.15 [0.65 , 2.07]
Subtotal (95% CI) 53 54 100.0% 1.15 [0.65 , 2.07]
Total events: 17 15
Heterogeneity: Not applicable
Test for overall effect: Z = 0.48 (P = 0.63)
1.8.6 Increased sexual desire
Pettinati 2008 comparison a 6 53 15 54 100.0% 0.41 [0.17 , 0.97]
Subtotal (95% CI) 53 54 100.0% 0.41 [0.17 , 0.97]
Total events: 6 15
Heterogeneity: Not applicable
Test for overall effect: Z = 2.03 (P = 0.04)
1.8.7 Vomiting
Pettinati 2008 comparison a 9 53 10 54 100.0% 0.92 [0.41 , 2.08]
Subtotal (95% CI) 53 54 100.0% 0.92 [0.41 , 2.08]
Total events: 9 10
Heterogeneity: Not applicable
Test for overall effect: Z = 0.21 (P = 0.84)
1.8.8 Skin rush
Pettinati 2008 comparison a 8 53 5 54 100.0% 1.63 [0.57 , 4.66]
Subtotal (95% CI) 53 54 100.0% 1.63 [0.57 , 4.66]
Total events: 8 5
Heterogeneity: Not applicable
Test for overall effect: Z = 0.91 (P = 0.36)
1.8.9 Difficulty achieving orgasm
Pettinati 2008 comparison a 9 53 5 54 100.0% 1.83 [0.66 , 5.11]
Subtotal (95% CI) 53 54 100.0% 1.83 [0.66 , 5.11]
Total events: 9 5
Heterogeneity: Not applicable
Test for overall effect: Z = 1.16 (P = 0.25)
1.8.10 Toothache
Pettinati 2008 comparison a 8 53 6 54 100.0% 1.36 [0.51 , 3.65]
Subtotal (95% CI) 53 54 100.0% 1.36 [0.51 , 3.65]
Total events: 8 6
Heterogeneity: Not applicable
Test for overall effect: Z = 0.61 (P = 0.54)
1.8.11 Diarrhoea
Carroll 2004 comparison a 13 60 13 61 69.3% 1.02 [0.51 , 2.01]
Pettinati 2008 comparison a 7 53 6 54 30.7% 1.19 [0.43 , 3.30]
Subtotal (95% CI) 113 115 100.0% 1.07 [0.61 , 1.88]
Total events: 20 19
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.22 (P = 0.82)
1.8.12 Slurred Speech
Baldacara 2013 1 15 0 15 100.0% 3.00 [0.13 , 68.26]
Subtotal (95% CI) 15 15 100.0% 3.00 [0.13 , 68.26]

Total events: 1 0
Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)



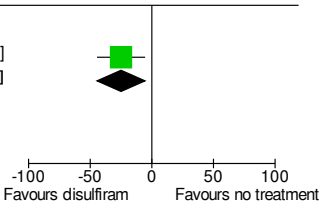
Comparison 1: Disulfiram versus placebo or no pharmacological treatment, Outcome 8: Individual adverse events

Analysis 1.9

Study or Subgroup	Disulfiram Mean	SD	Total	No treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.9.1 Versus no pharmacological treatment								
Grassi 2007 comparison a	38.01	12.76	4	63.01	15.3	4	100.0%	-25.00 [-44.52 , -5.48]
Subtotal (95% CI)			**4**			**4**	**100.0%**	**-25.00 [-44.52 , -5.48]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.51 (P = 0.01)

Test for subgroup differences: Not applicable



Comparison 1: Disulfiram versus placebo or no pharmacological treatment, Outcome 9: Craving (measured on a visual analogue scale of 0–100 points)

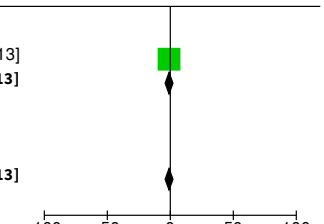
Analysis 1.10

Study or Subgroup	Disulfiram Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.10.1 Versus placebo								
Pettinati 2008 comparison a	3	7.255995	53	4	9.159272	54	100.0%	-1.00 [-4.13 , 2.13]
Subtotal (95% CI)			**53**			**54**	**100.0%**	**-1.00 [-4.13 , 2.13]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.63 (P = 0.53)

Total (95% CI)			**53**			**54**	**100.0%**	**-1.00 [-4.13 , 2.13]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.63 (P = 0.53)
Test for subgroup differences: Not applicable



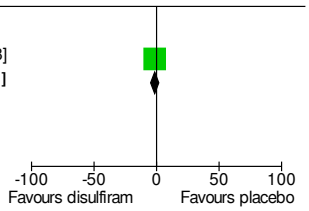
Comparison 1: Disulfiram versus placebo or no pharmacological treatment, Outcome 10: Depression (measured on a scale of 0–52 points)

Analysis 1.11

Study or Subgroup	Disulfiram Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.11.1 Versus placebo								
Pettinati 2008 comparison a	2	5.441996	53	3.5	10.991126	54	100.0%	-1.50 [-4.78 , 1.78]
Subtotal (95% CI)			**53**			**54**	**100.0%**	**-1.50 [-4.78 , 1.78]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.90 (P = 0.37)

Test for subgroup differences: Not applicable

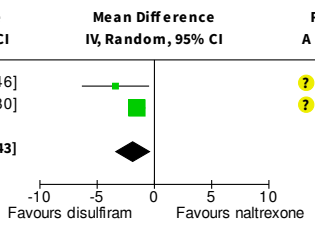


Comparison 1: Disulfiram versus placebo or no pharmacological treatment, Outcome 11: Anxiety (measured on a scale of 0–56 points)

Analysis 2.1

Study or Subgroup	Disulfiram Mean	SD	Total	Naltrexone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A	B	C	D
Carroll 1993	1.7	2.4	9	5.1	3.8	9	20.0%	-3.40 [-6.34 , -0.46]	?	?	+	?
Pettinati 2008 comparison b	6.025	1.87	53	7.55	1.94	52	80.0%	-1.52 [-2.25 , -0.80]	?	?	+	?
Total (95% CI)			**62**			**61**	**100.0%**	**-1.90 [-3.37 , -0.43]**				

Heterogeneity: Tau² = 0.57; Chi² = 1.48, df = 1 (P = 0.22); I² = 32%
Test for overall effect: Z = 2.53 (P = 0.01)
Test for subgroup differences: Not applicable



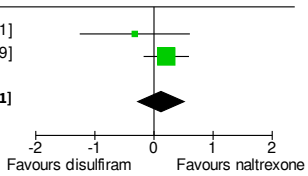
Risk of bias legend
(A) Adequate sequence generation?
(B) Allocation concealment?
(C) Incomplete outcome data addressed?
(D) Free of selective reporting?

Comparison 2: Disulfiram versus naltrexone, Outcome 1: Frequency of cocaine use

Analysis 2.2

Study or Subgroup	Disulfiram Mean	Disulfiram SD	Disulfiram Total	Naltrexone Mean	Naltrexone SD	Naltrexone Total	Weight	Std. Mean Difference IV, Random, 95% CI
Carroll 1993	1.3	2	9	2.4	4.1	9	17.0%	-0.32 [-1.26 , 0.61]
Pettinati 2008 comparison b	195	453.499706	53	107.5	377.152764	52	83.0%	0.21 [-0.18 , 0.59]
Total (95% CI)			**62**			**61**	**100.0%**	**0.12 [-0.27 , 0.51]**

Heterogeneity: Tau² = 0.01; Chi² = 1.07, df = 1 (P = 0.30); I² = 7%
Test for overall effect: Z = 0.59 (P = 0.56)
Test for subgroup differences: Not applicable

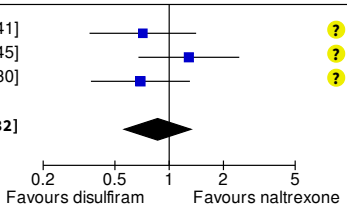


Comparison 2: Disulfiram versus naltrexone, Outcome 2: Amount of cocaine use

Analysis 2.3

Study or Subgroup	Disulfiram Events	Disulfiram Total	Naltrexone Events	Naltrexone Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D
Carroll 1993	5	9	7	9	31.1%	0.71 [0.36 , 1.41]	?	?	+	?
Grassi 2007 comparison b	4	4	3	4	34.0%	1.29 [0.68 , 2.45]	?	?	+	?
Pettinati 2008 comparison b	12	53	17	52	34.9%	0.69 [0.37 , 1.30]	?	?	+	?
Total (95% CI)		**66**		**65**	**100.0%**	**0.86 [0.56 , 1.32]**				
Total events:	21		27							

Heterogeneity: Tau² = 0.03; Chi² = 2.57, df = 2 (P = 0.28); I² = 22%
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable



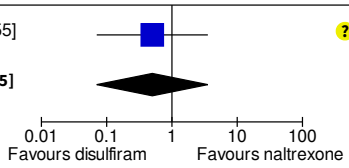
Risk of bias legend
(A) Adequate sequence generation?
(B) Allocation concealment?
(C) Incomplete outcome data addressed?
(D) Free of selective reporting?

Comparison 2: Disulfiram versus naltrexone, Outcome 3: Dropout for any reason

Analysis 2.4

Study or Subgroup	Disulfiram Events	Disulfiram Total	Naltrexone Events	Naltrexone Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D
Grassi 2007 comparison b	1	4	2	4	100.0%	0.50 [0.07 , 3.55]	?	?	+	?
Total (95% CI)		**4**		**4**	**100.0%**	**0.50 [0.07 , 3.55]**				
Total events:	1		2							

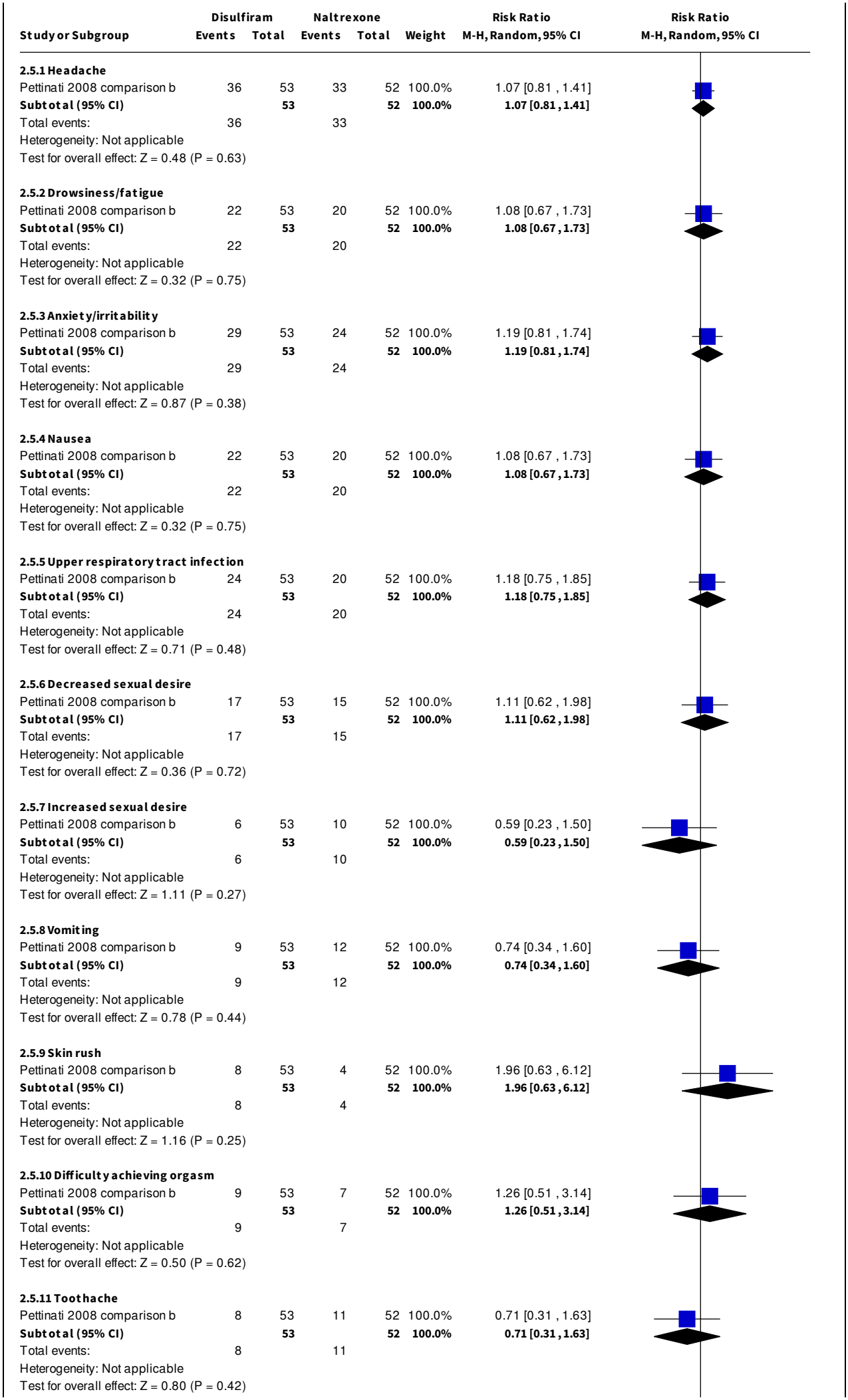
Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Adequate sequence generation?
(B) Allocation concealment?
(C) Incomplete outcome data addressed?
(D) Free of selective reporting?

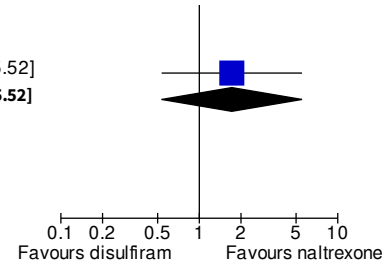
Comparison 2: Disulfiram versus naltrexone, Outcome 4: Dropout due to adverse events

Analysis 2.5


Disulfiram
Naltrexone
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
2.5.1 Headache
Pettinati 2008 comparison b 36 53 33 52 100.0% 1.07 [0.81 , 1.41]
Subtotal (95% CI) 53 52 100.0% 1.07 [0.81 , 1.41]
Total events: 36 33
Heterogeneity: Not applicable
Test for overall effect: Z = 0.48 (P = 0.63)
2.5.2 Drowsiness/fatigue
Pettinati 2008 comparison b 22 53 20 52 100.0% 1.08 [0.67 , 1.73]
Subtotal (95% CI) 53 52 100.0% 1.08 [0.67 , 1.73]
Total events: 22 20
Heterogeneity: Not applicable
Test for overall effect: Z = 0.32 (P = 0.75)
2.5.3 Anxiety/irritability
Pettinati 2008 comparison b 29 53 24 52 100.0% 1.19 [0.81 , 1.74]
Subtotal (95% CI) 53 52 100.0% 1.19 [0.81 , 1.74]
Total events: 29 24
Heterogeneity: Not applicable
Test for overall effect: Z = 0.87 (P = 0.38)
2.5.4 Nausea
Pettinati 2008 comparison b 22 53 20 52 100.0% 1.08 [0.67 , 1.73]
Subtotal (95% CI) 53 52 100.0% 1.08 [0.67 , 1.73]
Total events: 22 20
Heterogeneity: Not applicable
Test for overall effect: Z = 0.32 (P = 0.75)
2.5.5 Upper respiratory tract infection
Pettinati 2008 comparison b 24 53 20 52 100.0% 1.18 [0.75 , 1.85]
Subtotal (95% CI) 53 52 100.0% 1.18 [0.75 , 1.85]
Total events: 24 20
Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)
2.5.6 Decreased sexual desire
Pettinati 2008 comparison b 17 53 15 52 100.0% 1.11 [0.62 , 1.98]
Subtotal (95% CI) 53 52 100.0% 1.11 [0.62 , 1.98]
Total events: 17 15
Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)
2.5.7 Increased sexual desire
Pettinati 2008 comparison b 6 53 10 52 100.0% 0.59 [0.23 , 1.50]
Subtotal (95% CI) 53 52 100.0% 0.59 [0.23 , 1.50]
Total events: 6 10
Heterogeneity: Not applicable
Test for overall effect: Z = 1.11 (P = 0.27)
2.5.8 Vomiting
Pettinati 2008 comparison b 9 53 12 52 100.0% 0.74 [0.34 , 1.60]
Subtotal (95% CI) 53 52 100.0% 0.74 [0.34 , 1.60]
Total events: 9 12
Heterogeneity: Not applicable
Test for overall effect: Z = 0.78 (P = 0.44)
2.5.9 Skin rush
Pettinati 2008 comparison b 8 53 4 52 100.0% 1.96 [0.63 , 6.12]
Subtotal (95% CI) 53 52 100.0% 1.96 [0.63 , 6.12]
Total events: 8 4
Heterogeneity: Not applicable
Test for overall effect: Z = 1.16 (P = 0.25)
2.5.10 Difficulty achieving orgasm
Pettinati 2008 comparison b 9 53 7 52 100.0% 1.26 [0.51 , 3.14]
Subtotal (95% CI) 53 52 100.0% 1.26 [0.51 , 3.14]
Total events: 9 7
Heterogeneity: Not applicable
Test for overall effect: Z = 0.50 (P = 0.62)
2.5.11 Toothache
Pettinati 2008 comparison b 8 53 11 52 100.0% 0.71 [0.31 , 1.63]
Subtotal (95% CI) 53 52 100.0% 0.71 [0.31 , 1.63]
Total events: 8 11
Heterogeneity: Not applicable
Test for overall effect: Z = 0.80 (P = 0.42)

2.5.12 Diarrhoea						
Pettinati 2008 comparison b	7	53	4	52	100.0%	1.72 [0.53 , 5.52]
Subtotal (95% CI)		**53**		**52**	**100.0%**	**1.72 [0.53 , 5.52]**
Total events:	7		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.91 (P = 0.36)

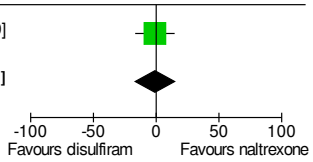


Comparison 2: Disulfiram versus naltrexone, Outcome 5: Individual adverse events

Analysis 2.6

Study or Subgroup	Disulfiram Mean	SD	Total	Naltrexone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Grassi 2007 comparison b	38.01	12.76	4	39.03	9.7	4	100.0%	-1.02 [-16.73 , 14.69]
Total (95% CI)			**4**			**4**	**100.0%**	**-1.02 [-16.73 , 14.69]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.13 (P = 0.90)
Test for subgroup differences: Not applicable

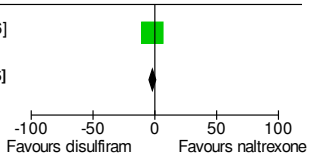


Comparison 2: Disulfiram versus naltrexone, Outcome 6: Craving (measured on a visual analogue scale of 0–100 points)

Analysis 2.7

Study or Subgroup	Disulfiram Mean	SD	Total	Naltrexone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Pettinati 2008 comparison b	3	7.255995	53	5	7.183862	52	100.0%	-2.00 [-4.76 , 0.76]
Total (95% CI)			**53**			**52**	**100.0%**	**-2.00 [-4.76 , 0.76]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.42 (P = 0.16)
Test for subgroup differences: Not applicable

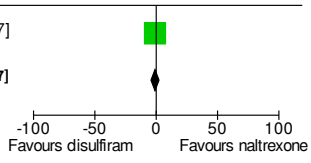


Comparison 2: Disulfiram versus naltrexone, Outcome 7: Depression (measured on a scale of 0–52 points)

Analysis 2.8

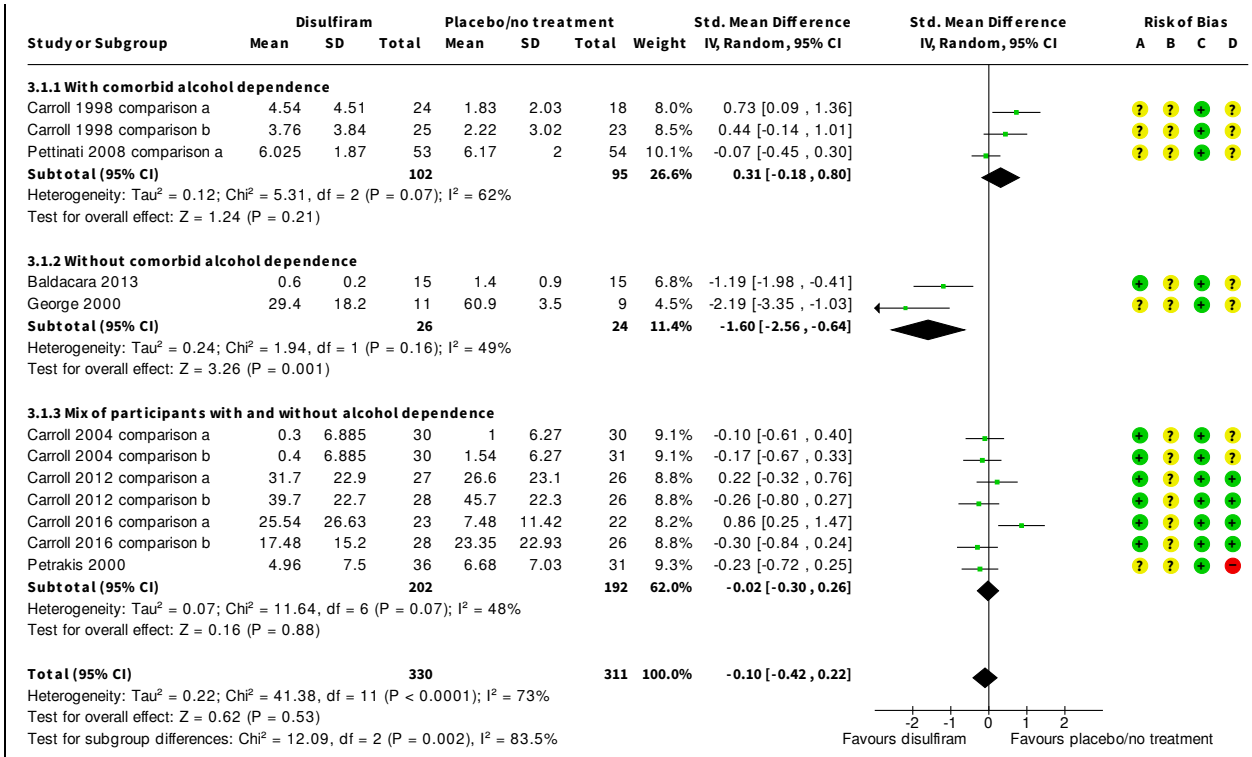
Study or Subgroup	Disulfiram Mean	SD	Total	Naltrexone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Pettinati 2008 comparison b	2	5.441996	53	3	10.775793	52	100.0%	-1.00 [-4.27 , 2.27]
Total (95% CI)			**53**			**52**	**100.0%**	**-1.00 [-4.27 , 2.27]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.60 (P = 0.55)
Test for subgroup differences: Not applicable



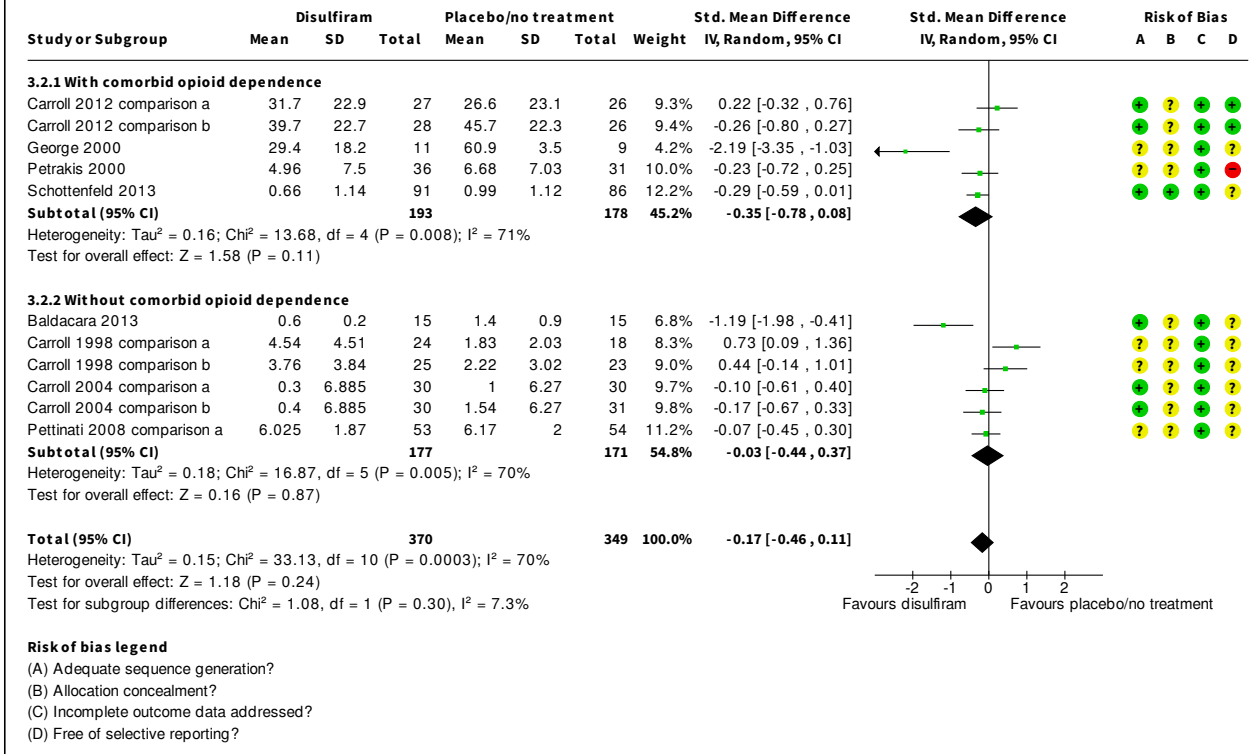
Comparison 2: Disulfiram versus naltrexone, Outcome 8: Anxiety (measured on a scale of 0–56 points)

Analysis 3.1



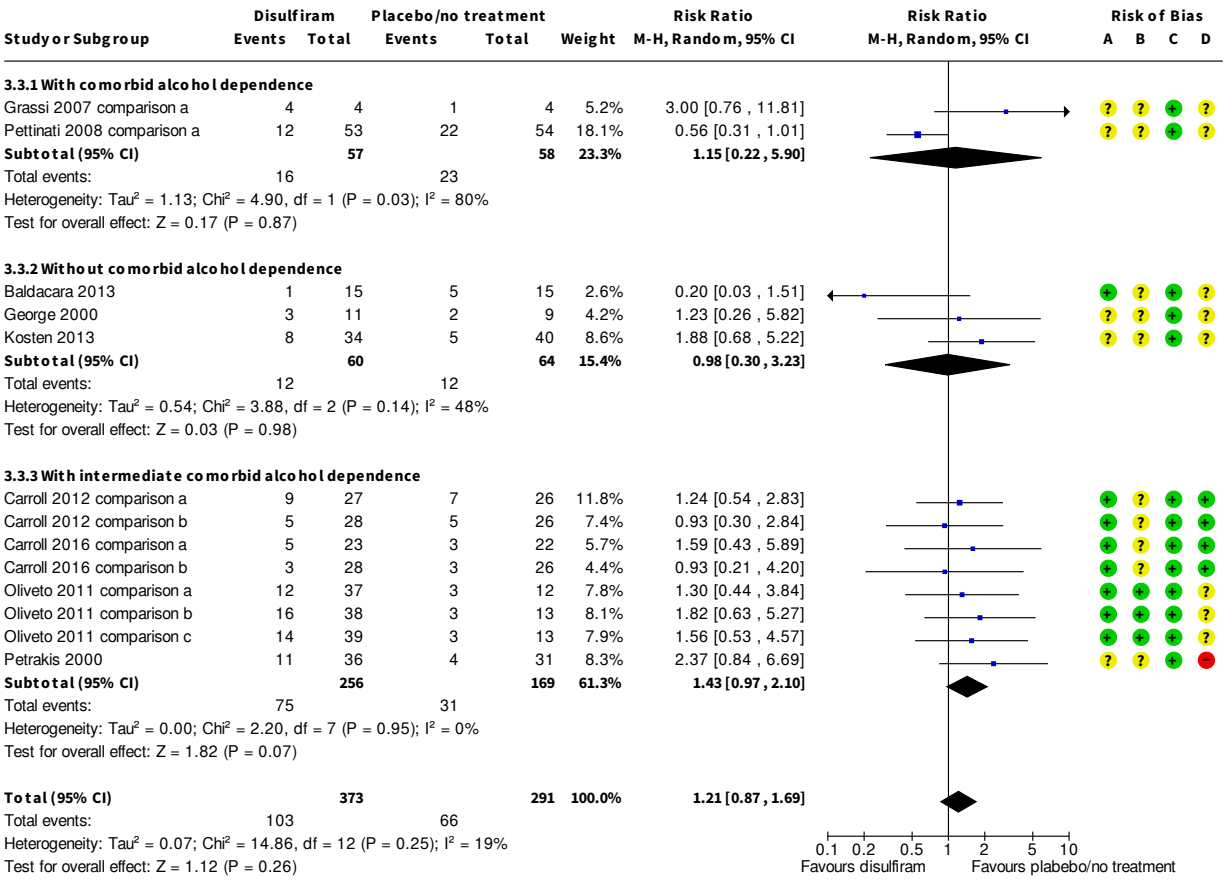
Comparison 3: Disulfiram versus placebo or no pharmacological treatment (subgroup analyses), Outcome 1: Frequency of cocaine use (according to the presence of alcohol dependence)

Analysis 3.2



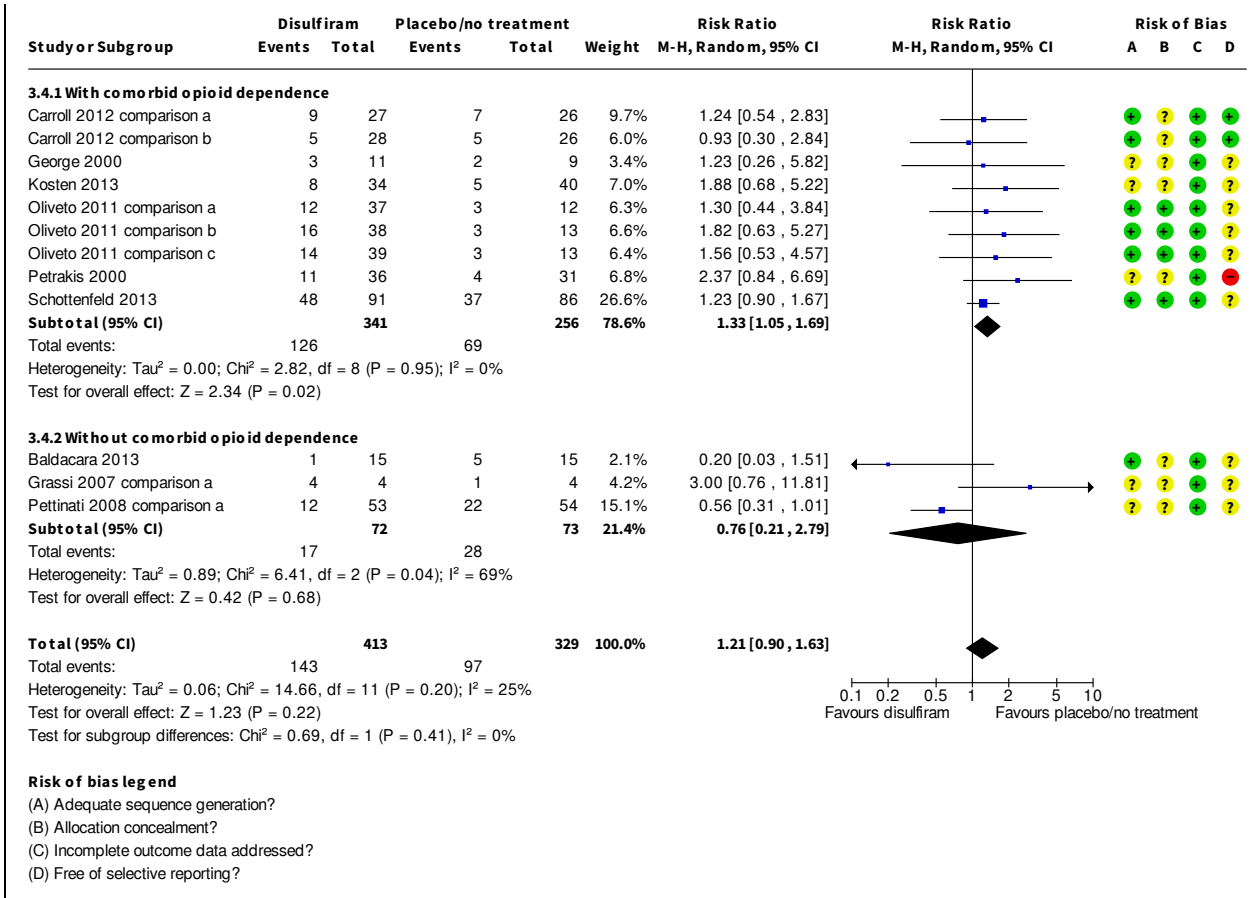
Comparison 3: Disulfiram versus placebo or no pharmacological treatment (subgroup analyses), Outcome 2: Frequency of cocaine use (according to the presence of opioid dependence in opioid agonist treatment)

Analysis 3.3



Comparison 3: Disulfiram versus placebo or no pharmacological treatment (subgroup analyses), Outcome 3: Dropout for any reason (according to the presence of comorbid alcohol dependence)

Analysis 3.4



Comparison 3: Disulfiram versus placebo or no pharmacological treatment (subgroup analyses), Outcome 4: Dropout for any reason (according to the presence of opioid dependence in opioid agonist treatment)