Disulfiram for cocaine dependence

Abstract

- Background

Cocaine dependence is a disorder for which no pharmacological treatment of proven efficacy exists, advances in the neurobiology could guide future medication development.

- Objectives

To evaluate the efficacy and the acceptability of disulfiram for cocaine dependence.

- Search methods

We searched: PubMed, EMBASE, CINAHL, PsycInfo (up to June 2011), the Cochrane Central Register of Controlled Trials (CENTRAL-The Cochrane Library, 7, 2011), reference lists of trials, main electronic sources of ongoing trials, conference proceedings and contacted researchers for unpublished trials.

- Selection criteria

Randomised and controlled clinical trials comparing disulfiram alone or associated with psychosocial intervention with no intervention, placebo, or other pharmacological intervention for the treatment of cocaine dependence.

- Data collection and analysis

Two authors independently assessed trial quality and extracted data.

- Results

Eight studies, 569 participants, met the inclusion criteria.

<u>Disulfiram versus placebo:</u> no statistically significant results for dropouts, three studies, 164 participants, RR 0.94 (95% CI 0.66 to 1.35). One more study, 107 participants, favouring disulfiram, was excluded from meta-analysis due to high heterogeneity, RR 0.34 (95% CI 0.20 to 0.58). For cocaine use, it was not possible to pool together primary studies, results from single studies showed that, one, out of four comparisons, was in favour of disulfiram (number of weeks abstinence, 20 participants, WMD 4.50 (95% CI 2.93 to 6.07).

<u>Disulfiram versus naltrexone:</u> no statistically significant results for dropouts but a trend favouring disulfiram, three studies, 131 participants, RR 0.67 (95% CI 0.45 to 1.01). No significant difference for cocaine use was seen in the only study that considered this outcome.

<u>Disulfiram versus no pharmacological treatment:</u> for cocaine use: a statistically significant difference in favour of disulfiram, one study, two comparisons, 90 participants: maximum weeks of consecutive abstinence, WMD 2.10 (95% CI 0.69 to 3.51); number of subjects achieving 3 or more weeks of consecutive abstinence, RR 1.88 (95% CI 1.09 to 3.23).

- Authors' conclusions

There is low evidence, at the present, supporting the clinical use of disulfiram for the treatment of cocaine dependence. Larger randomised investigations are needed investigating relevant outcomes and reporting data to allow comparisons of results between studies. Results from ongoing studies will be added as soon as their results will be available.

1. Background

- Description of the condition

Cocaine is an alkaloid derived from the leaf of erythroxylon coca, being commonly used as powder, for intranasal or intravenous use, or as crack, a free-base form which is smoked. Cocaine dependence is a major

public health problem that is characterized by recidivism and a host of medical and psychosocial complications (EMCDDA 2008).

There is a wide and well documented range of consequences associated to acute and chronic use of this drug, such as medical, psychological and social problems, including the spread of infectious diseases (e.g. AIDS, hepatitis and tuberculosis), crime, violence and neonatal drug exposure (Higgins 1994). Both injection and non injection cocaine use can increase the risk of HIV infection through high risk injecting and sexual behaviours (Sorensen 1991).

The illicit use of cocaine has become a persistent health problem worldwide. According to recent population surveys, between 0.1% and 16% of the adult population report having tried cocaine at least once (i.e. lifetime prevalence), with USA (16.2%), Colombia, Mexico, New Zealand, United Kingdom, Italy, and Spain (4.0% to 7.7%) being at the upper end of this range (Degenhardt 2008; SAMHSA 2007; EMCDDA 2008). Recent cocaine use (last 12 months) is, in general, reported by less than 1% of adults. In most countries, the range is between 0.3% and 1%. In Spain, United Kingdom, Italy and USA recent prevalence rates are higher than 2% (SAMHSA 2007; EMCDDA 2008). Although cocaine prevalence figures are much lower than comparable figures for cannabis, the prevalence of use among younger adults can be higher than the population average. In Europe, lifetime experience among 15- to 34-year-olds ranges from 0.7% to 12.7%, with the highest levels being found in Spain (9.6%) and the United Kingdom (12.7%); recent use ranges between 0.2% and 5.4%, with Spain and the United Kingdom having rates over 5% (EMCDDA 2008). In the USA, lifetime experience among 26- to 34-year-olds ranges from 21% to 24%, while recent use ranges from 4.2% to 5.2% (SAMHSA 2007). Recently an increase of cocaine use among addicts seeking treatment has been observed in USA (Craddok 1997; Karch 2006), Australia (Topp 2003), Italy (Davoli 2007; Siliquini 2005) and Spain (Suelves 2001).

- Description of the intervention

Cocaine dependence remains a disorder for which no pharmacological treatment of proved efficacy exists, although considerable advances in the neurobiology of this addiction could guide future medication development.

Cocaine effect seems to rely on its ability 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 is shared by cocaine with other drugs, like heroin, alcohol, cannabis and nicotine, has been involved in rewarding effect of drugs and self-administration behaviour in animal and human (Di Chiara 1988; Drevets 1999; Drevets 2001; Volkow 2003).

Recently, evidences have started to accumulate on the potential utility of some compounds already used in human for the treatment of other pathologies (Preti 2007; Sofuoglu 2006; Vocci 2005). In particular, the potential usefulness of disulfiram, a medication marketed for the treatment of alcoholism, is supported by preclinical and clinical observations (Baker 2007; Bourdelat-Parks 2005; Carroll 1998; Carroll 2000; Carroll 2004; George 2000; Haile 2003; McCance 1998b; Petrakis 2000; Schank 2006).

- How the intervention might work

The effect of disulfiram in alcoholism depends on the inhibition of the aldehyde dehydrogenase, an enzyme which is involved in the metabolism of alcohol. In the past, the observed reduction in cocaine use in subjects treated with disulfiram for their alcoholism was thought to be caused by the interruption of the alcohol-related disinhibition and impaired judgement (Carroll 1993). However, recent studies have indicated a more specific mechanism of action in support of disulfiram potential usefulness in cocaine addiction: being this compound a generalized enzyme inhibitor, its effect on cocaine addiction could be ascribed to its ability to interfere with enzymes involved in the metabolism of cerebral monoamines. Particularly the inhibition of dopamine-beta-hydroxylase, resulting in an excess of dopamine and decreased synthesis of norepinephrine, has been proposed to favourably influence the functioning of the meso-limbic circuits disrupted by cocaine addiction (Bourdelat-Parks 2005; Haile 2003; Petrakis 2000; Schank 2006).

- Why it is important to do this review

Although effective pharmacotherapy is available for alcohol and heroin dependence (Amato 2010; Faggiano 2003; Mattick 2003; Minozzi 2010; O'Brian 2001; Polycarpou 2005) none exists currently for cocaine dependence despite two decades of clinical trials primarily involving antidepressant, anticonvulsants and dopaminergic medications.

Four Cochrane reviews have been published on the efficacy of antidepressant (Lima 2003), antipsychotic (Amato 2007), anticonvulsants (Minozzi 2007), and dopamine agonists (Soares 2003) for the treatment of cocaine dependence but none of them found support for the efficacy of these treatments. One review has been published on the efficacy of psychosocial treatments for psychostimulants dependence (Knapp 2007) showing that existing treatments result in modest outcomes at best, leading to the conclusion there is still a need to develop and test different formats of existing treatment models and new psychosocial interventions. In the last years the interest in the use of disulfiram for the treatment of cocaine dependence has increased consistently. Both preclinical and clinical studies have investigated the potential efficacy of disulfiram for this substance use disorder, the neurobiological bases for its effect and related safety issues. In particular the relevance of the latter has to be considered in the ligth of the risk of adding to the known adverse effects of disulfiram and disulfiram-alcohol interaction (epathic, psychiatric, cardiovascular, etc.), those due to disulfiram-cocaine interaction (Malcolm 2008).

This review will assess the efficacy and safety of disulfiram for the treatment of cocaine dependence.

2. Objectives
To evaluate the efficacy and the acceptability of disulfiram for the treatment of cocaine dependence.

3. Methods
3.a.Criteria for considering studies for this review
Types of studies

All randomised controlled trials and controlled clinical trials which focus on the use of disulfiram for cocaine dependence.

Types of participants

Cocaine dependents as diagnosed by the Diagnostic and Statistical Manual of Mental Disorder (DSM-IV-R) or by specialists. Trials including participants with additional diagnoses of substance dependence were also eligible. People under 18 years of age and pregnant women were excluded for the substantially different approach and clinical management of these people. People with comorbid mental health conditions were included and considered in subgroup analysis.

Types of interventions

- Experimental intervention

Disulfiram alone or in combination with any psychosocial intervention.

- Control Intervention

Placebo; No intervention; Other pharmacological interventions; Any psychosocial intervention.

3.b Types of comparisons
1. disulfiram versus placebo or no intervention;
2. disulfiram versus other drugs;
3. disulfiram versus any psychosocial intervention.

Furthermore we considered different factors as confounders and take them into account in the analysis whenever possible:

-setting (inpatient or outpatient treatment);

-starting dose/rate and pattern of dose reduction;

-scheduled duration of treatment;
-severity of dependence (duration of use, route of administration, frequency of assumption);
-health status;
-psychiatric comorbidity;
-other treatment offered (psychosocial support);
-social status;
-number of previous treatment attempts and previous treatment outcomes.

3.c Types of outcome measures
- *Primary outcomes*
1. Dropouts from the treatment as number of participants who did not complete the treatment;
2. Acceptability of the treatment as number and type of side effects experienced during the treatment;
3. 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.
4. Results at follow-up as number of participants using cocaine at follow-up.

- *Secondary outcomes*
1. Compliance;
2. Craving as measured by validated scales e.g. Brief Substance Craving Scale (BSCS), Visual Analog Scale (VAS);
3. Severity of dependence as measured by validated scales e.g. Addiction Severity Index (ASI), Clinical Global Impression scale (CGI-S), Clinical Global Impression-Observer Scale (CGI-O), Severity of Dependence Scale (SDS);
4. Amount of cocaine use (as measured by grams used or money spent);
5. Psychiatric symptoms/psychological distress diagnosed using standard instruments e.g. Diagnostic and Statistical Manual of Mental Disorders (DSM) or measured by validated scales e.g. Hamilton Depression Rating Scale (HDRS), Profile of Mood States Scale (POMSS), Positive and Negative Syndrome Scale (PANSS).

4. Search methods for identification of studies
- *Electronic searches*
Relevant randomised trials were identified searching the following databases:
- The Cochrane Central Register of Controlled Trials (CENTRAL-The Cochrane Library, issue 7, 2011), which includes the Cochrane Drugs and Alcohol Groups specialised register;
- PubMed (from 1966 to June 2011);
- EMBASE (from 1980 to June 2011);
- CINAHL (1982 to June 2011).
- PsycInfo (1967 to June 2011)
We also searched ongoing trials via the following web sites:
Current Controlled Trials (http://www.controlled-trials.com/); Clinical Trials.gov; Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali (https://oss-sper-clin.agenziafarmaco.it/); Trialsjournal.com.
We compiled detailed search strategies for each database searched to take account of differences in controlled vocabulary and syntax rules.
- Databases: Embase, Pubmed via STN (Scientific & Technical Information Network) database; CINAHL (via EBSCO); PsycInfo (via DIALOG DATA STAR).

Cochrane Register of Controlled Trials:
1. MeSH descriptor cocaine-related disorders explode all trees
2. ((drug or substance) near2 (abuse* or misuse* or addict* or dependen*)):ti,ab

3.   #1 or #2
4.   MeSH descriptor Cocaine explode all trees
5.   Cocaine :ti,ab
6.   #4 OR #5
7.   MeSH descriptor Disulfiram explode all trees
8.   Disulfiram:ti,ab
9.   Antabuse:ti,ab
10. #7 or #8 or #9
11. #3 AND #6 AND #10

PubMed and EMBASE:
1.   COCAINE-RELATED DISORDER/CT
2.   COCAINE DEPENDENCE/CT
3.   (ADDICT? OR ABUSE? OR DEPENDEN? OR DISORDER?)/TI,AB
4.   (COCAINE/CT OR COCAINE/TI,AB)
5.   1 OR 2 OR 3
6.   4 AND 5
7.   DISULFIRAM/CT,TI,AB
8.   ANTABUSE/TI,AB
9.   6 AND (7 OR 8)
10. RANDOMIZED CONTROLLED TRIAL/DT
11. RANDOMIZED CONTROLLED TRIAL/CT
12. CONTROLLED CLINICAL TRIAL/DT
13. PHASE 2 CLINICAL TRIAL/CT
14. PHASE 3 CLINICAL TRIAL/CT
15. DOUBLE BLIND PROCEDURE/CT
16. SINGLE BLIND PROCEDURE/CT
17. CROSSOVER PROCEDURE/CT
18. LATIN SQUARE DESIGN/CT
19. PLACEBO/CT
20. MULTICENTER STUDY
21. DRUG THERAPY+NT/CT
22. RANDOM?/TI,AB
23. PLACEBO/TI,AB OR PLACEBOS/TI,AB
24. CROSSOVER?/TI,AB
25. (TRIAL# OR GROUP#)/TI,AB
26. (SINGL? OR DOUBL? OR TREBL? OR TRIPL?)/TI,AB(S) (BLIND? OR MASK?)/TI,AB
27. 9 AND (10-26)
28. 27/HUMAN

CINAHL:
1.   MH SUBSTANCE ABUSE
2.   ((DRUG OR SUBSTANCE OR COCAINE) AND (ABUSE* OR DEPENDEN* OR ADDICT* OR DISORDER*))
3.   1 OR 2
4.   TX COCAINE OR MH COCAINE
5.   3 AND 4
6.   EXP DISULFIRAM OR TX DISULFIRAM OR TX ANTABUSE
7.   5 AND 6
8.   TX RANDOM*
9.   TX (CLINICAL AND TRIAL*)
10. TX ((SINGL* OR DOUBL* OR TRIPL* OR TREBL*) AND (MASK* OR BLIND*))
11. TX (CROSSOVER* OR ALLOCAT* OR ASSIGN*)
12. MH RANDOM ASSIGNMENT/
13. MH CLINICAL TRIALS/
14. 8 OR 9 OR 10 OR 11 OR 12 OR 13
15. 7 AND 14

PsycInfo:
1.   COCAINE-DEPENDENCE.KW.
2.   COCAINE-RELATED-DISORDERS.KW.
3.   (ADDICT$4 OR DISORDER$1 OR DEPENDEN$3 OR ABUSE$1).TI,AB.

4. COCAINE.KW,TI,AB.
5. 4 AND (1 OR 2 OR 3)
6. MENTAL-HEALTH-PROGRAMME-EVALUATION.KW.
7. TREATMENT-EFFECTIVENESS-EVALUATION
8. PLACEBO.KW.
9. PLACEBO$1.TI,AB.
10. RANDOM$6.KW,TI,AB.
11. ((SINGL$2 OR DOUBL$3 OR TREVL$3 OR TRIPL$4) NEAR (BLIND$4 OR MASK$4 OR DUMMY)).TI,AB.
12. (FACTORIAL$1 OR ALLOCAT$5 OR ASSIGN$5 OR VOLUNTEER$1).TI,AB.
13. (CROSSOVER$).TI,AB. OR (CROSS ADJ OVER$1).TI,AB.
14. (QUASI ADJ EXPERIMENTAL).TI,AB.
15. ((CONTROL$5 NEAR (TRIAL$1 OR STUDY OR STUDIES OR GROUP$1))).TI,AB.
16. 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15
17. 5 AND 16
18. (DISULFIRAM.KW.)
19. DISULFIRAM.TI,AB.
20. ANTABUSE.KW, TI,AB.
21. 17 AND (18 OR 19 OR 20)

Legend:
*truncation symbol
adj Adjacent (i.e., terms are near/next to one another, any order)
ti Title
ab Abstract
MESH Medical Subject Heading
pt Publication type

- *Searching other resources*

We also searched: the reference lists of all relevant papers to identify further studies; conference proceedings likely to contain trials relevant to the review. We contacted investigators seeking information about unpublished or incomplete trials; some of the main electronic sources of ongoing 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.

5. Data collection and analysis

- *Selection of studies*

Two authors independently screened the titles and abstracts of all publications, obtained through the search strategy. All potentially eligible studies were obtained as full articles and two authors independently assessed these for inclusion. In doubtful or controversial cases, all identified discrepancies were discussed and reached consensus on all items.

- *Data extraction and management*

Two authors independently extracted data from published sources, where differences in data extracted occurred this was resolved through discussion. Where required additional information was obtained through collaboration with the original authors.

- *Assessment of risk of bias in included studies*

The risk of bias assessment for RCTs and CCTs (controlled clinical trials) in this review was performed using the criteria recommended by the Cochrane Handbook (Higgins 2011). The recommended approach for assessing risk of bias in studies included in Cochrane Review is a two-part tool, addressing specific domains, namely sequence generation and allocation concealment (selection bias), blinding of participants and providers (performance bias) blinding of outcome assessor (detection bias), incomplete outcome data (attrition bias) and selective outcome reporting (reporting bias). The first part of the tool involves describing what was reported to have happened in the study. The second part of the tool involves assigning a judgement relating to the risk of bias for that entry, in terms of low, high or unclear risk. To make these judgments we used the criteria indicated by the handbook adapted to the addiction field. See Table 1 for

details.

The domains of sequence generation and allocation concealment (avoidance of selection bias) were addressed in the tool by a single entry for each study.

Blinding of participants and outcome assessor (avoidance of performance and detection bias) were considered separately for objective outcomes (e.g. drop out, abstinence measured by urine-analysis, subjects relapsed at the end of follow up, subjects engaged in further treatments) and subjective outcomes (e.g. duration and severity of signs and symptoms of withdrawal, patient self-reported use of substance, side effects, social functioning as integration at school or at work, family relationship). For objective outcomes all the studies were considered as at low risk of detection bias.

Incomplete outcome data (avoidance of attrition bias) was considered for all outcomes except for the drop out from the treatment, which is very often the primary outcome measure in trials on addiction.

- *Measures of treatment effect*

Key findings were summarized narratively in the first instance and assessed for meta-analysis where possible. Dichotomous outcomes were analysed calculating the Relative risk (RR) for each trial with the uncertainty in each result being expressed by their confidence intervals. Continuous outcomes were analysed calculating the WMD or the SMD with 95% CI. In case of missing standard deviation of the differences from baseline to the end of treatment, the standard deviation were imputed using the standard deviation of the mean at the end of treatment for each group.

- *Assessment of heterogeneity*

The outcome measures from the individual trials were combined through meta-analysis where possible (comparability of intervention and outcomes between trials) using a fixed effect model unless there was significant heterogeneity, in which case a random effect model was used. A P-value of the Chi-square test less than 0.05 indicates a significant heterogeneity.

- *Assessment of reporting biases*

1) Random sequence generation (Selection bias)

<u>Low risk:</u> 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; drawing of lots; minimization.

<u>High risk:</u> 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; availability of the intervention.

<u>Unclear risk:</u> Insufficient information about the sequence generation process to permit judgement of low or high risk.

2) Allocation concealment (Selection bias)

<u>Low risk:</u> Investigators enrolling 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; sequentially numbered, opaque, sealed envelopes.

<u>High risk:</u> Investigators enrolling participants could possibly foresee assignments because one of the following method 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 non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

<u>Unclear risk:</u> 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 those providing and receiving the intervention (Performance bias)

<u>Low risk:</u> No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to

be influenced by lack of blinding; 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; 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 the outcome assessor (Detection bias)

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; 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; 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.

4) Incomplete outcome data (Attrition bias)

Low risk: No missing outcome data; Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; 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; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; Missing data have been imputed using appropriate methods; All randomised patients 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; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; '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 drop out not reported for each group).

5) Selective reporting (reporting bias)

Low risk: The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

High risk: Not all of the study's pre-specified primary outcomes have been reported; One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; 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.

- Grading of evidence

The quality of evidence was assessed according to GRADE method (Guyatt 2008), a method systematic and

explicit. In order to indicate the extent to which one can be confident that an estimate of effect is correct, judgments about the quality of evidence are made for each comparison and outcome. These judgments consider study design (RCT, quasi RCT or observational study), study quality (detailed study design and execution), consistency of results (similarity of estimates of effect across studies), precision of estimates, and directness (the extent to which people, interventions and outcome measures are similar to those of interest). The following definitions in grading the quality of evidence for each outcome are used: High: further research is very unlikely to change our confidence in the estimate of effect. Moderate: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low: further research is very likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Very low: any estimate of effect is very uncertain.

- *Data synthesis*

Dichotomous outcomes were analysed calculating the Relative Risk (RR) for each trial with the uncertainty in each result being expressed by their 95% confidence intervals. Continuous outcomes were analysed calculating the Weighted Mean Difference (WMD) with 95% CI comparing the post intervention mean score of the experimental and control group or the mean score differences from baseline to end of treatment in the experimental and control group. In case of missing standard deviation of the differences from baseline to the end of treatment, the standard deviation were imputed using the standard deviation of the mean score at the end of treatment for each group. The outcomes from the individual trials have been combined through meta-analysis where possible (comparability of intervention and outcomes between trials) using a fixed effect model unless there was significant heterogeneity, in which case a random effect model have been used. A P-value of the Chi-square test less than 0.05 indicates a significant heterogeneity.

If all arms in a multi-arm trial are to be included in the meta-analysis and one treatment arm is to be included in more than one of the treatment comparisons, then we divided the number of events and the number of participants in that arm by the number of treatment comparisons made. This method will avoid the multiple use of participants in the pooled estimate of treatment effect while retaining information from each arm of the trial. It will compromise the precision of the pooled estimate slightly.

Funnel plot (plot of the effect estimate from each study against the sample size or effect standard error) was not used to assess the potential for bias related to the size of the trials, because all the included studies had small sample size and not statistically significant results.

- *Sensitivity analysis*

The methodological quality were not used as inclusion criterion; in order to assess the effect of the low quality studies we intended to perform a sensitivity analysis, either including or excluding the classes C studies.

6. Results

1. Description of studies

- *Results of the search*

We identified 369 reports, including four ongoing trials that had insufficient information to be included in the analysis; of the remaining 365 studies, 324 were excluded on basis of title and abstract; 41 articles were retrieved for more detailed evaluation, 33 of which were excluded after reading the full text; the remaining 8 studies satisfied all the criteria to be included in the review. ***See Flow chart showing identification of studies***

Flow chart showing identification of included trials
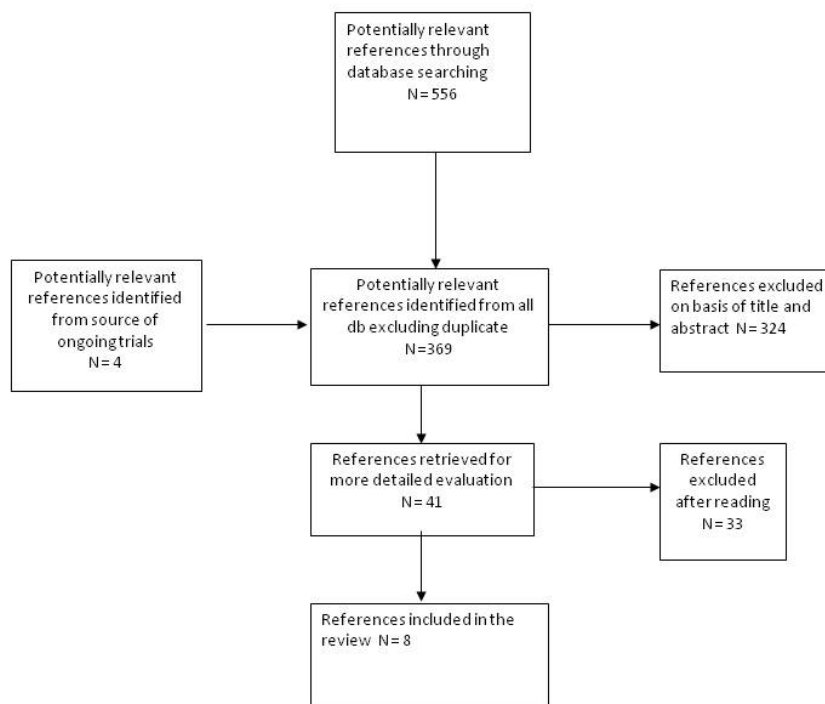
- *Included studies*
Eight studies with 569 participants met the inclusion criteria for this review, for details, ***See Table 1 "Characteristics of Included Studies"***
Country of origin of the included studies
All the studies, except one (Grassi 2007), were conducted in USA.
Number of studies per type of comparison
- Disulfiram versus placebo: five studies, 394 participants;
- Disulfiram versus naltrexone: three studies, 131 participants;
- Disulfiram versus no pharmacological treatment: two studies, 103 participants
The mean duration of the trials was 12 weeks (range 11 to 14 weeks)
The disulfiram dose was 250 mg/day in six studies; 250-500 mg/day in one study and 400 mg/day in another.
All trials but two clearly defined the psychosocial treatments concomitantly given with disulfiram: Cognitive Behavioral Psychotherapy, 3 studies; Counselling, 2 studies, Twelve Step Facilitation and Interpersonal Psychotherapy, 1 study each.
Five studies enrolled patients with cocaine dependence and alcohol abuse or dependence. Three enrolled patients with concurrent opioid addiction, in treatment with buprenorphine (1 study) or methadone (2 studies).
All the eight studies were conducted in outpatient setting.
- *Excluded studies*
33 studies did not meet the criteria for inclusion in this review. The grounds for exclusion were: study design not in the inclusion criteria: eighteen studies; type of intervention not in the inclusion criteria: seven

studies; outcomes measures not in the inclusion criteria: six studies: type of participants not in the inclusion criteria: two studies, *See Table 2 " Characteristics of Excluded Studies"*
- Quality assessment of included studies
All studies were randomised controlled trials. Of these, 5 were placebo controlled. Two studies were judged at low risk of selection bias for sequence generation, while the other studies were judged at unclear risk because details provided did not allow a specific evaluation on this criteria. Only one study was at low risk of selection bias for allocation concealment, all the others were judged at unclear risk since none of them reported the procedures adopted to prevent participants and investigators from foresee assignment. Four studies were double-blind controlled trials, therefore were judged at low risk of performance and detection bias. Three studies were not blinded and judged at high risk of performance and detection bias. All but one study used an intention to treat analysis. In all but two studies, missing data on patients were considered using appropriate methods; therefore all but three studies were judged at low risk of attrition bias. One study did not give the results on the previously stated assessment of the severity of substance use and substance-related problems measured by ASI and was judged at high risk of reporting bias; For the other studies information available does not allow to assess selective outcome reporting. *See Table 1 " Characteristics of Included Studies"*
This is a plot of the distribution of judgements (Low risk, High risk, Unclear risk) across studies for each risk of bias item.
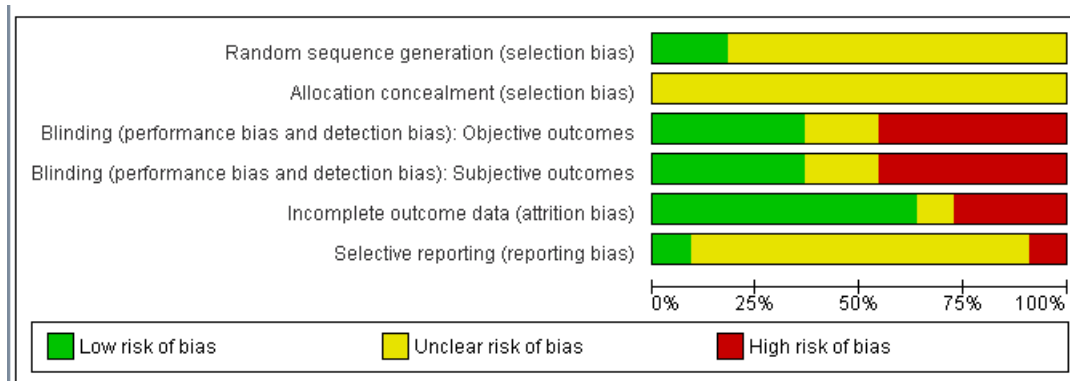
2. Effects of interventions
The results were summarized, with comparison of quantitative data where possible, first for disulfiram versus placebo and then for disulfiram versus naltrexone and for disulfiram versus no pharmacological treatment.
To see the forest plot of the comparisons *see Data and analyses graphs*
For some outcomes, it was not possible to pool results because either outcomes' measures were not comparable or part of required data were not available. For them, we reported results from single studies:
Comparison 1 Disulfiram versus placebo:
1.1 Dropouts from the treatment:
Four studies, 271 participants, RR 0.77 (95% CI 0.46 to 1.28), the result is not statistically significant. Since the test for heterogeneity was significant (I^2= 84%; P = 0.002), the analysis was repeated excluding the data of Pettinati 2008. This sensitivity analysis still showed a result not statistically significant, RR 0.94 (95% CI 0.66 to 1.35). On the other hand the comparison concerning the only study of Pettinati 2008 showed a significant difference in favour of disulfiram, RR 0.34 (95% CI 0.20 to 0.58).
1.2 Use of cocaine continuous measures:
1.2.1 Use of cocaine at the end of treatment as mean grams per week in past 30 days
One study, 43 participants, WMD 0.18 (95% CI -0.38 to 0.74), the result is not statistically significant. See

Analysis 1.2.

1.2.2 Frequency of cocaine use as mean number of days of cocaine use, past 30 days at end of treatment

One study, 53 participants, MD -1.72 (95% Cl -5.64 to 2.2), the result is not statistically significant.

1.2.3 Frequency of cocaine use as total number of weeks abstinent

One study, 20 participants, MD 4.50 (95% CI 2.93 to 6.07), the result is statistically significant in favour of disulfiram

1.3 Use of cocaine dichotomous measures:

1.3.1 Number of subjects achieving 3 weeks of abstinence

One study, 20 participants, RR 1.02 (95% CI 0.39 to 2.71), the result is not statistically significant

1.3.2 Number of subjects with positive urine at the end of the treatment

One study, 77 participants, RR 0.86 (95% CI 0.51 to 1.46), the result is not statistically significant. Furthermore, a study considers the median percentage of negative urine. The authors of this study, applying a generalized estimating equations model, failed in showing medication effects significant at the 5% level. Another study considered umbers of days per week of cocaine use, random-effects regression analysis applied by authors in this study showed a significantly higher reduction in cocaine use for participants assigned to disulfiram in comparison with those assigned to placebo (medication x time, Z -2.82; P< 0.01). This difference in favour of disulfiram is confirmed also by urinalyses specimens (medication x time , Z - 2.06; P= 0.04).

Data reported in these two articles do not allow further standardized Cochrane analyses.

1.4 Side effects:

No difference between disulfiram and placebo was seen besides the sexual desire which resulted higher in the placebo group.

Comparison 2 Disulfiram versus naltrexone:

2.1 Dropouts from the treatment:

Three studies, 131 participants, RR 0.67 (95% CI 0.45 to 1.01), the result is not statistically significant but is possible to observe a trend for a lower dropout in disulfiram treated patients.

2.2 Use of cocaine as percentage of urine screens positive for cocaine

One study, 18 participants, WMD -23.50 (95% CI -26.58 to -20.42), the result is statistically significant in favour of disulfiram.

Furthermore, one study, 105 participants considered median percentage of negative urine, the authors, applying a generalized estimating equations model, failed in showing disulfiram effects significant at the 5% level. Another study, 8 participants, investigated the percentage of positive urine during the first four weeks of treatment, the difference is reported in the article as statistically significant in favour of disulfiram (Chi square 27.220; P< 0.001).

Data reported in these two studies do not allow further standardized Cochrane analyses.

Comparison 3 Disulfiram versus no pharmacological tratment:

3.1 Use of cocaine as maximum weeks of consecutive abstinence

One study, 90 participants, WMD 2.10 (95% CI 0.69 to 3.51), the result is statistically significant in favour of disulfiram.

3.2 Use of cocaine as number of subjects achieving 3 or more weeks of consecutive abstinence during treatment

One study, 90 participants, RR 1.88 (95% CI 1.09 to 3.23), the result is statistically significant in favour of disulfiram.

No usable data were reported for Acceptability of the treatment as number and type of side effects in the two studies comparing disulfiram with no pharmacological treatment.

3. Summary of main results

- Overall completeness and applicability of evidence

Despite the systematic bibliographic search, only one of the included studies was conducted out of the USA and of the six studies conducted in USA, five were carried out at Yale University. This is another limit to the generalizability of the results, since: a) different social contests can influence differently the severity of dependence and the availability to enter an experimental design; b) different clinical contests can influence differently the selection of participants to the trials and the results of the treatment, acting as an effect modifier in the estimation of efficacy of treatment.

- Quality of the evidence

From a methodological perspective, the overall quality of the included studies was not good. Although all studies were randomised, all had unclear allocation concealment, only one had adequate sequence generation, only four were double blind, while three were open (Carroll 1993; Carroll 1998 arm a; Carroll 1998 arm b; Grassi 2007; Grassi 2007 arm b).

Moreover, it must be considered that, due the well known adversive disulfiram alcohol reaction, participants could easily test the study blindness. Finally, although pre-established outcomes were considered in (all) the included studies, the great heterogeneity of the scales used in the primary studies and the way in which results were reported made not possible to undertake a cumulative analysis.

7. Authors' conclusions

Implications for practice

Although caution is needed when assessing results from a limited number of clinical trials, there is low evidence, at the present, supporting the clinical use of disulfiram in the treatment of cocaine dependence. This results could not be considered conclusive due principally to the low quality of evidence, due to study design, small sample size and heterogeneity in terms of outcome operational definition of some of the included studies. Moreover, safety issues, particularly those related to the interaction between disulfiram and cocaine, should be deeply explored. This uncertainty requires that clinicians balance the possible benefits against the potential adverse effects of the treatment.

Implications for research

Aiming to answer the urgent demand of clinicians, patients, families, and the community as a whole for an adequate treatment for cocaine dependence, larger randomised investigations are needed investigating relevant outcomes and safety issues and reporting data to allow comparison of results between studies. Some of these studies are ongoing and will be added as soon as their results will be available.

8. Contributions of authors

Vecchi and Solimini performed the literature searches and organised papers collection; Vecchi and Solimini reviewed the papers, abstracted data from the papers for meta-analysis. Amato wrote abstract, introduction, discussion and conclusions sections and assessed methodological quality of included studies and results sections. Zuccaro supervised to all the process and all authors provided comments to the final version.

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10. Tables
- Table 1 Characteristics of included studies

Study	Participants	Interventions	Outcomes
Carroll 1993	N= 18; 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 Interview for DSM-III-R.	**Group A** (9) Disulfiram 250 mg/day plus individual psychotherapy **Group B** (9) naltrexone 50 mg/day plus individual psychotherapy Outpatient. Duration 12 weeks. Country of origin: USA.	Frequency and intensity of alcohol and cocaine use measured as self-reports and toxicological screens; retention in treatment
Carrol 1998 arm a and b	**Arm a:** N=45 subjects; **Arm b:** N=50 Subjects seeking treatment for substance abuse; mean age 30.8 years; male 73%; white 39%; single or divorced 59%; working 43%; average baseline alcohol use, 17.2 days in the past 30 days; average baseline cocaine use 14.1 days in the past 30 days; 20% were cocaine intranasal users and 3% iv users. 50 subjects seeking treatment for substance abuse; mean age 30.8 years; male 73%; white 39%; single or divorced 59%; working 43%; average baseline alcohol use, 17.2 days in the past 30 days; average baseline cocaine use 14.1 days in the past 30 days; 20% were cocaine intranasal users and 3% iv users. **Inclusion criteria:** fulfilling DSM-III-R criteria for current cocaine dependence and alcohol dependence or abuse. **Exclusion criteria:** currently physically dependent on opiates or barbiturates, or whose principal drug of	**Arm a:** **Group A** (26) Cognitive Behavioral Therapy (CBT) plus disulfiram **Group B** (19) CBT plus no medication **Arm b:** **Group A** (25) Facilitation (TSF) plus disulfiram **Group B** (25) TSF plus no medication Disulfiram dose range: 250 - 500 mg/day Outpatient. Duration 12 weeks. Country of origin: USA.	Duration of periods of abstinence from cocaine, alcohol and both substances simultaneously; frequency of cocaine use (number of days per week the subject reported cocaine use); quantity of cocaine use (grams per week); frequency of alcohol use (number of days per week the subject reported at least one standard drink per week); quantity of alcohol use (number of

	dependence was not cocaine; meeting lifetime DSM-III-R 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 or currently in psychotherapy or pharmacotherapy for any other psychiatric disorder; having condition of probation or parole requiring reports of drug use to officers of the court.		standard drinks per week); urine toxicology screening and breathalyzer reading to verify self report.
Carroll 2004 arm a and b	**Arm a:** N=60 subjects; **Arm b:** N=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 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.	**Arm a:** **Group A** (30) Cognitive Behavioral Therapy (CBT) plus disulfiram **Group B** (30) CBT plus no medication **Arm b:** **Group A** (30) Interpersonal PsychoTherapy (IPT) plus disulfiram **Group B** (31) IPT plus placebo Disulfiram dose: 250 mg/day Outpatient. Duration 12 weeks. Country of origin: USA.	Frequency of cocaine use (operational as number of days per week the subjects reported using cocaine); results of urine screen (operational as likelihood of submitting a positive sample each week).
George 2000	N=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.	**Group A** (30) disulfiram plus buprenorphine**, placebo plus** **Group B** (9) placebo plus buprenorphine Partecipants were involved in weekly group drug counselling sessions. disulfiram 250 mg/day; buprenorphine 8 mg/day. Outpatient. Duration 12 weeks. Country of origin: USA.	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; Treatment retention; self reported cocaine, heroin and alcohol use.
Grassi 2007	N=12 subjects 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	**Group A** (4) Cognitive Behavioral Therapy (CBT) plus disulfiram **Group B** (4) CBT alone **Group C** (4) naltrexone plus CBT	

	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.	disulfiram 400 mg/day; naltrexone 50 mg/day Outpatient. Duration 12 weeks. Country of origin: Italy.	
Oliveto 2011	N=77 Cocaine and opioid dependents **Inclusion criteria:** meet DSM IV criteria for opioid and cocaine dependence. Each participant (aged 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. **Exclusion criteria:** 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 disorder, current suicidality or homicidality, current use of prescribed psychotropic medication that could not be discontinued, current use of metronidazole,or clotrimazole, benzodiazerpine positive urine toxicology screen, and pregnancy or breastfeeding	**Group A** (39) Disulfiram 205mg **Group B** (38) Placebo All methadone stabilized (week 1-2) Outpatient. Duration 14 weeks. Country of origin: USA.	Retention in treatment; weekly percentage of participants retained in each treatment; use of cocaine
Petrakis 2000	N=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.	**Group A** (36) disulfiram plus methadone **Group B** (31) placebo plus methadone Partecipants were involved in weekly individual and group counselling sessions. disulfiram 250 mg/day; methadone dose reported as "highest tolerated dose". Outpatient. Duration 12 weeks. Country of origin: USA.	Frequency and quantity of cocaine and alcohol use, self reported and verified trough urine screen/breathalyzer; severity of substance use and substance-related problems measured through the Addiction Severity Index (ASI).
Pettinati 2008	N=159 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	**Group A** (53) Disulfiram **Group B** (54) Placebo **Group C** (52) naltrexone Participants were involved in twice a week individual Cognitive Behavioural	

| | | 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. | Therapy sessions.

disulfiram 250 mg/day; naltrexone 100 mg/day.

Outpatient. Duration 11 weeks. Country of origin: USA. | |

Results of the assessment of risk of bias

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants, personnel (performance bias)	Blinding of outcome assessor (detection bias)	Incomplete outcome data addressed (attrition bias)	selective reporting (reporting bias)
Carroll 1993	Unclear risk	Unclear risk	High risk	High risk	Unclear risk	Unclear risk
Carrol 1998 arm a and b	Unclear	Unclear risk	High risk	High risk	Low risk	Unclear risk
Carroll 2004 arm a and b	Low risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk
George 2000	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk
Grassi 2007	Unclear risk	Unclear risk	High risk	High risk	High risk	Unclear risk
Oliveto 2011	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Petrakis 2000	Unclear risk	Unclear risk	Low risk	Low risk	High risk	High risk
Pettinati 2008	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk

- Table 2 Characteristics of excluded studies

Study	Reason for exclusion
Altice 2010	Type of participants and type of interventions not in the inclusion criteria
Baker 2007	Study design and outcome measures not in the inclusion criteria
Barth 2010	Study design not in the inclusion criteria
Bruce 2010	Study design not in the inclusion criteria
Carroll 2000	Study design not in the inclusion criteria
Carroll 2007	Type of intervention not in the inclusion criteria
Easton 2007	Study design not in the inclusion criteria
Galligo 2010	Study design not in the inclusion criteria
Gaval-Cruz 2008	Study design not in the inclusion criteria
Gaval-Cruz 2009	Study design not in the inclusion criteria
Haile 2009	Study design not in the inclusion criteria
Higgins 2007	Type of intervention not in the inclusion criteria
Jofre-Bonet 2004	Outcome measures not in the inclusion criteria
Kampman 2009	Study design not in the inclusion criteria
Karila 2008	Type of intervention not in the inclusion criteria
Karila 2009	Study design not in the inclusion criteria

Kenna 2007	Study design not in the inclusion criteria
Laqueille 2009	Study design not in the inclusion criteria
Magill 2009	Type of intervention not in the inclusion criteria
Malcom 2008	Study design not in the inclusion criteria
McCance 1996	Outcome measures not in the inclusion criteria
McCance 1998 a	Outcome measures not in the inclusion criteria
McCance 1998 b	Outcome measures not in the inclusion criteria
Milligan 2004	Outcome measures not in the inclusion criteria
Olbrich 2007	Study design not in the inclusion criteria
Pantalon 2002	Outcome measures not in the inclusion criteria
Petry 2007	Type of intervention not in the inclusion criteria
Rosen 2007	Type of intervention not in the inclusion criteria
Ross 2009	Study design not in the inclusion criteria
Sofuoglu 2008	Type of participants not in the inclusion criteria
Sullivan 2008	Type of intervention not in the inclusion criteria
Walter 2009	Study design not in the inclusion criteria
Xu 2010	Study design not in the inclusion criteria

1. Data and analyses graphs

Comparison 1 Disulfiram versus Placebo

Comparison 1.1 Dropout from the treatment
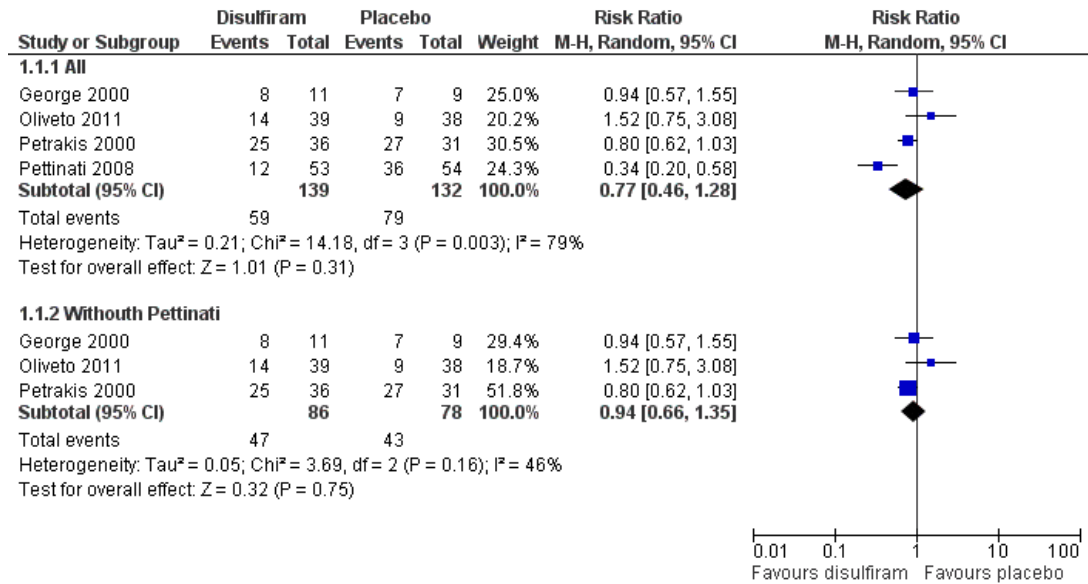
Comparison 1.2 Use of cocaine continuous measures
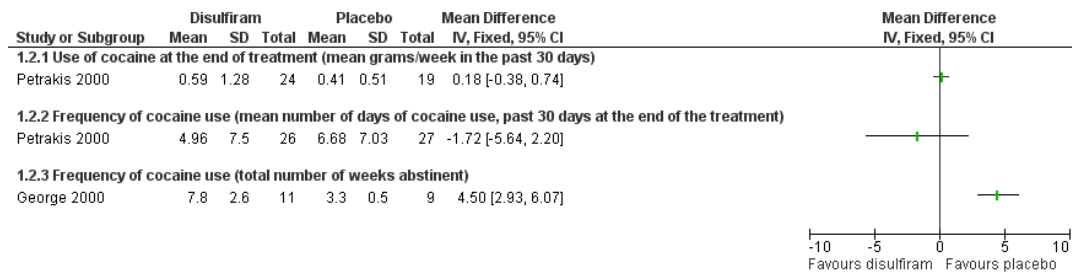
Comparison 1.3 Use of cocaine dichotomous measures
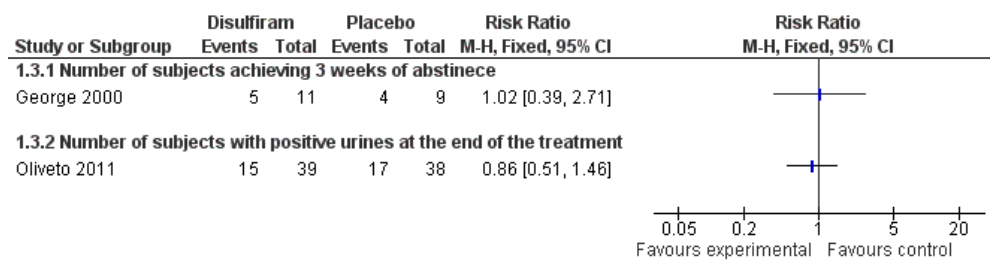
Comparison 1.4 Side effects

Study or Subgroup	Disulfiram Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Withdrawn for medical reasons					
Petrakis 2000	7	36	0	31	12.97 [0.77, 218.37]
1.4.2 Anxiety/irritability					
Pettinati 2008	29	53	28	54	1.06 [0.74, 1.51]
1.4.3 Costipation-bloody stools					
Oliveto 2011	1	39	0	38	2.92 [0.12, 69.64]
1.4.4 Decreased sexual desire					
Pettinati 2008	17	53	15	54	1.15 [0.65, 2.07]
1.4.5 Diarrhea					
Pettinati 2008	7	53	6	54	1.19 [0.43, 3.30]
1.4.6 Difficulty achieving orgasm					
Pettinati 2008	9	53	5	54	1.83 [0.66, 5.11]
1.4.7 Drowsiness/fatigue					
Pettinati 2008	22	53	15	54	1.49 [0.87, 2.55]
1.4.8 Headache					
Pettinati 2008	36	53	29	54	1.26 [0.93, 1.72]
1.4.9 Increased sexual desire					
Pettinati 2008	6	53	15	54	0.41 [0.17, 0.97]
1.4.10 Nausea					
Pettinati 2008	22	53	14	54	1.60 [0.92, 2.78]
1.4.11 Skin rush					
Oliveto 2011	1	39	0	38	2.92 [0.12, 69.64]
Pettinati 2008	8	53	5	54	1.63 [0.57, 4.66]
1.4.12 Toothache					
Pettinati 2008	8	53	6	54	1.36 [0.51, 3.65]
1.4.13 Upper respiratory tract intection					
Pettinati 2008	24	53	27	54	0.91 [0.61, 1.35]
1.4.14 Vomiting					
Pettinati 2008	9	53	10	54	0.92 [0.41, 2.08]

0.01   0.1   1   10   100
Favours disulfiram   Favours placebo

Comparison 2 Disulfiram versus Naltrexone

Comparison 2.1 Dropouts from the treatment

Study or Subgroup	Disulfiram Events	Total	Naltrexone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Carroll 1993	5	9	7	9	100.0%	0.71 [0.36, 1.41]
Total (95% CI)		9		9	100.0%	0.71 [0.36, 1.41]
Total events	5		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.97 (P = 0.33)						

0.01   0.1   1   10   100
Favours disulfiram   Favours naltrexone
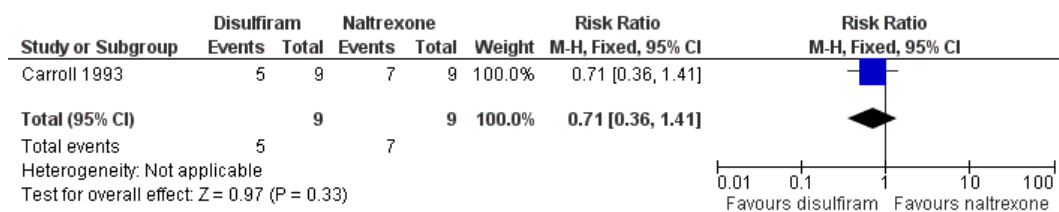
Comparison 2.2 Use of cocaine as percentage of urine screen positive for cocaine

| Study or Subgroup | Disulfiram | | | Naltrexone | | | Mean Difference | Mean Difference |
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Carroll 1993	10.8	1.4	9	34.3	4.5	9	-23.50 [-26.58, -20.42]	

-100 -50 0 50 100
Favours disulfiram Favours naltrexone
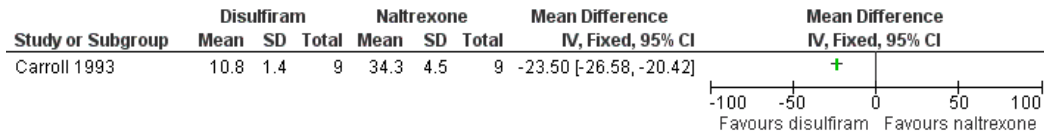
Comparison 3 Disulfiram versus no pharmacological treatment

Comparison 3.1 Use of cocaine as maximum weeks of consecutive absinence

| Study or Subgroup | Disulfiram | | | No pharmacological | | | Weight | Mean Difference | Mean Difference |
	Mean	SD	Total	Mean	SD	Total		IV, Random, 95% CI	IV, Random, 95% CI
Carroll 1998 arm a	4.54	4.51	24	1.83	2.03	18	47.8%	2.71 [0.68, 4.74]	
Carroll 1998 arm b	3.76	3.84	25	2.22	3.02	23	52.2%	1.54 [-0.41, 3.49]	
Total (95% CI)			49			41	100.0%	2.10 [0.69, 3.51]	

Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 2.93 (P = 0.003)

-10 -5 0 5 10
Favours no pharm Favours disulfiram

Comparison 3.2 Use of cocaine as number of subjects achieving 3 or more weeks of consecutive abstinence

| Study or Subgroup | Disulfiram | | Control | | Weight | Risk Ratio | Risk Ratio |
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Carroll 1998 arm a	13	25	7	23	56.1%	1.71 [0.83, 3.52]	
Carroll 1998 arm b	14	24	5	18	43.9%	2.10 [0.93, 4.76]	
Total (95% CI)		49		41	100.0%	1.88 [1.09, 3.23]	
Total events	27		12				

Heterogeneity: Chi² = 0.14, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 2.28 (P = 0.02)

0.01 0.1 1 10 100
Favours control Favours disulfiram