Antidepressants for cocaine dependence and problematic cocaine use (Review)

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[Intervention Review]

Antidepressants for cocaine dependence and problematic cocaine use

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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 investigate the efficacy and acceptability of antidepressants alone or in combination with any psychosocial intervention for the treatment of cocaine dependence and problematic cocaine use.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, EMBASE and CINAHL in July 2011 and researchers for unpublished trials.

Selection criteria

Randomised clinical trials comparing antidepressants alone or associated with psychosocial intervention with placebo, no treatment, other pharmacological or psychosocial interventions.

Data collection and analysis

Two authors independently assessed trial quality and extracted data.

Main results

37 studies were included in the review (3551 participants).

Antidepressants versus placebo: results for dropouts did not show evidence of difference, 31 studies, 2819 participants, RR 1.03 (Cl 95% 0.93 to 1.14). Looking at Abstinence from cocaine use, even though not statistically significant, the difference shown by the analysis in the three-weeks abstinence rate was in favour of antidepressants (eight studies, 942 participants, RR 1.22 (Cl 95% 0.99 to 1.51)). Considering only studies involving tricyclics, five studies, 367 participants, or only desipramine, four studies, 254 participants, the evidence was in favour of antidepressants. However, selecting only studies with operationally defined diagnostic criteria, statistical significance favouring antidepressants, as well as the trend for significance shown by the full sample, disappeared. Looking at safety

issues, the results did not show evidence of differences (number of patients withdrawn for medical reasons, thirteen studies, 1396 participants, RR 1.39 (Cl 95% 0.91 to 2.12)). Subgroup analysis considering length of the trial, associated opioid dependence or associated psychosocial interventions as confounding factors, failed in showing consistent and statistically significant differences in favour of antidepressants.

Antidepressants versus other drugs: Comparing antidepressants with dopamine agonists or with anticonvulsants, no evidence of differences was shown on dropouts and on other outcomes (abstinence from cocaine use, adverse events).

Authors' conclusions

At the current stage of evidence data do not support the efficacy of antidepressants in the treatment of cocaine abuse/dependence. Partially positive results obtained on secondary outcome measures, such as depression severity, do not seem to be associated with an effect on direct indicators of cocaine abuse/dependence. Antidepressants cannot be considered a mainstay of treatment for unselected cocaine abusers/dependents.

PLAIN LANGUAGE SUMMARY

Antidepressants for cocaine abuse and dependence

A pharmacological agent with proven efficacy does not exist for treatment of cocaine dependence. Cocaine is an alkaloid derived from the erythroxylon coca leaf that is 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 because its use can be associated with medical and psychosocial complications including the spread of infectious diseases (such as AIDS, hepatitis and tuberculosis), crime, violence and neonatal drug exposure. This review looked at the evidence on the efficacy and acceptability of antidepressants alone or in combination with a psychosocial intervention for the treatment of cocaine abuse and dependence.

Current evidence from randomised controlled trials does not support the use of antidepressants. Positive results obtained by antidepressants on mood-related outcomes are consistent with the primary effect of antidepressants. They do not seem to be associated with any effect on dropouts from treatment, cocaine use or side effects, which are direct indicators of cocaine abuse and dependence. A total of 37 randomised controlled clinical studies involving 3551 participants were included in the review. All the studies except one took place in the USA; 33 trials were conducted with outpatients in the community or in mental health centres. In 10 trials patients were also treated for opioid dependence with methadone or buprenorphine. The antidepressants included desipramine, fluoxetine and bupropion and the mean duration of the trials was 10.7 weeks. The included studies utilised 43 different rating instruments and differed in design, quality, characteristics of patients, tested medication, services and the treatments delivered.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Antidepressants compared to placebo according to any definition for cocaine abuse and dependence

Patient or population: patients with cocaine abuse and dependence
Settings:
Intervention: Antidepressants
Comparison: placebo according to any definition

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk placebo according to any definition	Corresponding risk Antidepressants				
Dropout - Dropouts: excluding studies with high risk of bias objective Follow-up: mean 10.7 weeks	**Study population**		**RR 1.01** (0.91 to 1.12)	2417 (27 studies)	⊕⊕⊕○ **moderate**[1]	
	461 per 1000	**475 per 1000** (429 to 521)				
	Medium risk population					
	434 per 1000	**447 per 1000** (404 to 490)				
Abstinence, for at least three consecutive weeks objective Follow-up: mean 10.7 weeks	**Study population**		**RR 1.22** (0.99 to 1.51)	942 (8 studies)	⊕⊕⊕⊕ **high**	
	215 per 1000	**262 per 1000** (213 to 325)				
	Medium risk population					
	182 per 1000	**222 per 1000** (180 to 275)				

Adverse events - Withdrawn due to adverse events Follow-up: mean 10.7 weeks	**Study population**		**RR 1.39** (0.91 to 2.12)	1396 (13 studies)	⊕⊕⊕○ **moderate**[2]
	45 per 1000	**63 per 1000** (41 to 95)			
	Medium risk population				
	27 per 1000	**38 per 1000** (25 to 57)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 16/27 studies with unclear allocation concealment
[2] 8 studies with unclear allocation concealment and one study with high risk of bias for randomisation and allocation concealment

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 2009).

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 (Brugal 2009; Darke 2005; Higgins 1994; Schwartz 2010). 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; EMCDDA 2009; SAMSHA 2007). 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% (EMCDDA 2009; SAMSHA 2007). 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 2009). 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% (SAMSHA 2007). 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 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 mesolimbic 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). While administration of cocaine acutely increases intercellular dopamine, serotonin, and norepinephrine levels by blocking their presynaptic reuptake (Gold 1997), chronic cocaine abuse leads to down-regulation of monoamine systems (Gardner 1999; Martinez 2009; Volkow 1997; Volkow 2010). Post-cocaine use depression and cocaine craving may be linked to this down-regulation.

Other persistent changes in areas of the brain involved in adaptive behaviour and memory processes, such as nucleus accumbens and amygdala (modification of gene expression; changes in the architecture and morphology of neurons) (Thomas 2008; Vezina 2004) or in areas involved in impulsivity, decision making, and control of behavior, such as the ventromedial prefrontal cortex (Bechara 2005), as well as changes in other neural systems such as the stress system (Goeders 2003; Piazza 1998), have been related to craving, self-administration behavior and loss of control (Bechara 2005; Goeders 2003; Volkow 2002; Volkow 2003). These same areas and circuits and similar changes have been involved in regulation of mood (Carlezon 2004; Drevets 2007; Pietrini 2000; Robbins 1992).

How the intervention might work

These pre-clinical and clinical findings are the theoretical foundations on which the use of antidepressants for the treatment of cocaine dependence is based on. Under this assumption, antidepressant pharmacotherapy, by augmenting monoamine levels, may alleviate cocaine abstinence symptomatology, as well as relieving dysphoria and associated craving by general antidepressant action (Kosten 1992; Margolin 1995). Alternatively, antidepressants might interfere with the other neurobiological alterations which are shared between cocaine addiction and mood disorders.

Why it is important to do this review

Although effective pharmacotherapy is available for heroin (Faggiano 2003; Mattick 2008; Mattick 2009) and alcohol dependence (Amato 2010; Rösner 2010a; Rösner 2010b) none exists currently for cocaine dependence despite three decades of clinical trials on the efficacy of pharmacological and psychosocial interventions to treat this syndrome.

Four Cochrane reviews have been published on the efficacy of antipsychotics (Amato 2007), anticonvulsants (Minozzi 2008), dopamine agonists (Amato 2011) and psychostimulants (Castells 2010) for cocaine dependence, but none of them found support for the efficacy of these treatments. Moreover, a Cochrane review assessing the efficacy and safety of disulfiram (Pani 2010) has shown low evidence supporting the clinical use of it for the treatment of cocaine dependence.

One Cochrane review has been published on the efficacy of psychosocial treatments for cocaine and psychostimulants depen-

dence (Knapp 2007) showing that existing treatments have shown modest outcomes at best, leading to the conclusion that there is still a need to develop and test different formats of existing treatment models and newer psychosocial interventions should be undertaken.

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.

The former Cochrane review on antidepressants for cocaine dependence was published in 2003 (Silva de Lima 2003) and never updated. Because this class of drugs is largely utilised in clinical practice, there is a need of an update.

OBJECTIVES

To investigate the efficacy and acceptability of antidepressants alone or in combination with any psychosocial intervention for the treatment of cocaine dependence and problematic cocaine use when compared with placebo, no treatment, other pharmacological or psychosocial interventions.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials which focus on the use of any antidepressant medication for cocaine dependence or problematic cocaine use.

Types of participants

Cocaine dependent patients as diagnosed by the Diagnostic and Statistical Manual of Mental Disorder (DSM-IV-R) or International Classification of Diseases (ICD-10). However, we accepted also trials which did not employ explicit diagnostic criteria. We examined the effect of including patients with uncertain diagnoses in the sensitivity analyses. Trials including patients 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 to clinical management of these people. People with comorbid mental health conditions were included and considered in a subgroup analysis.

Types of interventions

Experimental intervention:

Any antidepressant medication alone or in combination with any psychosocial intervention.

Control Intervention

- Placebo
- No intervention
- Other pharmacological interventions
- Any psychosocial intervention

When we found trials that compared different antidepressant medications, we made separate subgroup analysis.

Furthermore we considered different factors as confounders and took them into account in the analysis wherever 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.

Types of outcome measures

Primary outcomes

1. Dropouts from the treatment as number of participants who did not complete the treatment;
2. 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);
4. Amount of cocaine use (as measured by self-reported grams used or money spent);
5. Psychiatric symptoms/psychological distress diagnosed using standard criteria e.g. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-R) criteria or measured by validated

scales e.g. Hamilton depression rating scale (HDRS), Profile of Mood States Scale (POMSS), Positive and Negative Syndrome Scale (PANSS);

6. Quality of life measures;
7. Death.

Search methods for identification of studies

The search incorporated a number of methods to identify completed or ongoing studies.

Electronic searches

Relevant trials from the last search were obtained from the following sources:

1. The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library issue 7 2011) which also contains the Cochrane Drugs and Alcohol Group's Trials
2. PubMed (from 1966 - July 2011)
3. EMBASE (from 1988 - July 2011)
4. CINAHL (1982- July 2011)

Databases were searched using a strategy developed incorporating the filter for the identification of RCTs (Higgins 2011) combined with selected MeSH terms and free text terms relating to cocaine abuse and dependence.The search strategy for, PubMed, EMBASE, CINHAL and CENTRAL are shown in Appendix 1; Appendix 2; Appendix 3.

We also searched for ongoing clinical trials via Internet searches on the following sites:

- http://www.controlled-trials.com;
- http://clinicalstudyresults.org;
- http://centrewatch.com;
- Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali (https://oss-sper-clin.agenziafarmaco.it/);
- trialsjournal.com

The search strategy for ongoing trials is shown in Appendix 4

Searching other resources

We also searched:

- Personal communication: The authors of the identified studies were contacted for obtaining of information on potential additional published or unpublished RCTs;
- Attempts were made to obtain unpublished trials from pharmaceutical companies;
- The reference lists of all relevant papers to identify further studies;
- conference proceedings likely to contain trials relevant to the review;

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

Data collection and analysis

Selection of studies

Two authors (Pani, Trogu) inspected the search hits by reading titles and abstracts. Each potentially relevant study located in the search was obtained in full text and assessed for inclusion independently by two authors (Pani, Trogu). Doubts were resolved by discussion between all the authors.

Data extraction and management

Data were extracted independently by two authors (Trogu, Pani). A standardised checklist was used collecting information on methodology, participants (socio-demographic and clinical information relevant to the review aims), interventions (medications and non pharmacologic interventions), primary and secondary outcomes. Any disagreement was discussed and persisting disagreement was dealt with by a third reviewer (Amato), acting as a mediator.

Assessment of risk of bias in included studies

Two authors (Trogu, Pani) assessed study quality according to the criteria indicated in Cochrane Reviews Handbook (Higgins 2011).The risk of bias assessment for RCTs and CCTs in this review was performed using the 5 criteria recommended by the Cochrane Handbbok (Higgins 2011). The recommended approach for assessing risk of bias in studies included in Cochrane Review is a two-part tool, addressing five specific domains (namely sequence generation, allocation concealment, blinding, incomplete outcome data, and other issues). 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: low risk; high risk; unclear risk. To make these judgments we used the criteria indicated by the handbook adapted to the addiction field.

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

Blinding of participants, personnel and outcome assessor (avoidance of performance bias and detection bias) was considered separately for objective outcomes (e.g. retention in treatment, use of substance of abuse measured by urine analysis) and subjective outcomes (e.g. severity of depression, other psychiatric symptoms/ psychological distress, severity of dependence).

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. Retention was assessed at the end of the study period. See Appendix 5 for a detailed description of the assessment of risk of bias in the included studies.

Measures of treatment effect

Dichotomous outcomes (dropout, use of primary substance, results at follow up) have been analysed calculating the Relative Risk (RR) for each trial with the uncertainty in each result being expressed by their confidence intervals (CI).

Continuous outcomes (use of primary substance, craving, psychiatric symptoms/psychological distress) have been analysed calculating the Mean Difference (MD) with 95% CI. Mean differences and 95% CI had to be calculated comparing and pooling the mean score differences from the end of treatment to baseline for each group. In case of missing data about the standard deviation (SD) of the changes, this measure had to be imputed using the SD at the end of treatment for each group.

When studies all assess the same outcome but measure it using different scales, the standardized mean difference had to be applied as a summary statistic to standardize the results to a uniform scale (according to Cochrane Reviews Handbook suggested procedures (Higgins 2011)).

We have not used data presented as number of positive urine tests over the total number of tests in the experimental and control group as measure of substance use. This decision was made because using number of tests instead of number of subjects as unit of the analysis violates the hypothesis of independence among observations. In fact, the results of test done for each participants are not independent.

Unit of analysis issues

If all arms of a multi-arm trial had to be included in the meta-analysis and one arm had to be included in more than one comparisons, we divided the number of events and the number of participants in that arm by the number of comparisons made. Such method avoids the multiple use of participants in the pooled estimate of treatment effect while retaining information from each arm of the trial. The precision of the pooled estimate results slightly compromised.

Dealing with missing data

Information on missing data was collected from the studies and requested to the original investigators. Moreover, in the absence of supplemental data from the authors, whenever needed measures were available in primary studies, missing data were obtained according to Cochrane Reviews Handbook suggested procedures from available values (Higgins 2011).

Assessment of heterogeneity

The presence of heterogeneity between the trials was tested using the I-squared (I^2) statistic. A P-value of the test lower than 0.05 indicates a significant heterogeneity.

Assessment of reporting biases

Funnel plot (plot of the effect estimate from each study against the sample size or effect standard error) was used to assess the potential for bias related to the size of the trials.

Data synthesis

The outcomes from the individual trials, when possible, have been combined through meta-analysis (comparability of intervention and outcomes between trials) using a fixed effect model unless there was significant heterogeneity, in which case a random effect model had been used.

Subgroup analysis and investigation of heterogeneity

We made analysis of sub-groups according to length of trial, operationally defined diagnostic criteria, category and type of antidepressant and associated interventions.

Subgroup analyses were performed only when results from at least 2 studies were available.

Sensitivity analysis

To incorporate assessment in the review process we first plotted intervention effects estimates stratified for the presence of risk of bias in any of the domains of the Cochrane risk of bias tool. If differences in results were present among studies at different risk of bias, we then performed sensitivity analysis excluding the analysis with high risk of bias.

RESULTS

Description of studies

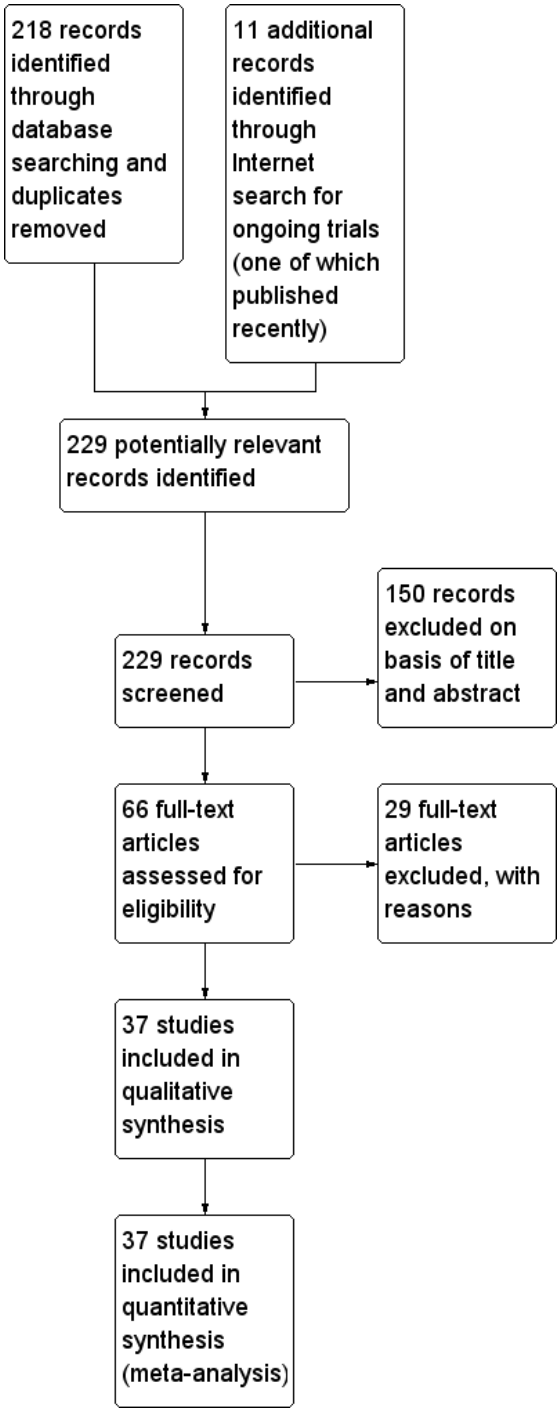
See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

For substantive descriptions of studies see Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies Tables.

Results of the search

We identified 229 reports, including 11 ongoing trials and 2 unpublished study presented at conferences. 150 were excluded on basis of title and abstract; 66 articles were retrieved for more detailed evaluation, 29 of which were excluded after reading the full text. The results of one of the ongoing trials was recently released (Winstanley 2011); the other 10 ongoing trials and the 2 unpublished studies had insufficient information to be included in the analysis. Therefore, 37 studies satisfied all the criteria to be included in the review. See Figure 1.

Figure 1. Flow chart of studies.



Included studies

37 studies with 3551 participants met the inclusion criteria for this review, for details see Characteristics of included studies.
It was possible to extract data from 37 studies.

Duration of trials:

The mean duration of the trials was 10.7 weeks (range 2 to 25 weeks).

Treatment regimes and setting:

The medications studied in the included studies were: Desipramine (17 trials), Fluoxetine (5 trials), Bupropion (3 trials), Nefazodone and Ritanserin (2 trials each), Buspirone, Gepirone, Paroxetine, Citalopram, Venlafaxine, Selegiline, Tryptophan, Sertraline and Imipramine (1 trial each). Dosages were those used for the treatment of depression. For more information see Appendix 6.

In ten trials patients were concomitantly treated for opioid dependence with methadone (Arndt 1992; Grabowsky 1995; Kolar 1992; Kosten 1992 a; Margolin 1995; O'Brien 1988; Poling 2006; Winstanley 2011) or buprenorphine (Kosten 2003; Oliveto 1999). In one study patients were concomitantly treated with bromocriptine (Giannini 1987 b).

22 studies assessed medication compliance trough plasma concentrations (Arndt 1992; Batki 1996; Campbell 2003; Carroll 1994; Ciraulo 2005 a; Cornish 2001; Covi 1993; Gawin 1989; Grabowsky 1995; Hall 1994; Kolar 1992; Kosten 1992 a; Kosten 2003; Margolin 1995; McDowell 2005; Moeller 2007; Nunes 1995; O'Brien 1988; Oliveto 1999; Shoptaw 2008; Weddington 1991; Winhusen 2005); 2 studies adding riboflavine to medication and placebo (Jones 2004; Schmitz 2001); 5 studies trough the return of unused medications (Elkashef 2006; Hall 1994; Johnson 1997; Shoptaw 2008; Winhusen 2005); 2 studies trough supervision of the ingestion of medication (Poling 2006; Winstanley 2011); for 9 studies the information was not available (Ciraulo 2005 b; Giannini 1986; Giannini 1987 a; Giannini 1987 b; Giannini 1993; Jenkins 1992; Lambert Passos 2005; McElroy 1989;Tennant 1985).

33 trials were conducted with outpatients, at the community level or in mental health centres. In four trials patients were hospitalised at the beginning of the study.

All the studies, except one (Lambert Passos 2005), were conducted in USA.

The psychosocial treatments concomitantly given with antidepressants were:

- Cognitive Behavioral Psychotherapy or Relapse Prevention Therapy
- Interpersonal Psychotherapy
- Counselling
- Contigiency Management
- Not Otherwise Specified Psychotherapy

For more information see Appendix 7.

Rating Instrumets utilized in the included studies:

The 37 included studies utilised 43 different rating instruments, to see a list of them, see Appendix 8

Participants

3551 cocaine addicts according to DSM criteria (DSM-III-R; DSM-IV-R) or otherwise defined problematic use of cocaine. 67% were males; mean age was 35 years.

- ***Comparisons*** :

1. Antidepressants versus placebo according to any definition: 37 studies, 3302 participants;
2. Antidepressants versus placebo for operationally defined cocaine dependence: 26 studies, 2591 participants;
3. Different classes of antidepressants:
    - tricyclics versus placebo: 18 studies, 1293 participants;
    - SSRIs versus placebo: 8 studies, 662 participants;
4. Specific antidepressants versus placebo:
    - desipramine versus placebo: 17 studies, 1180 participants;
    - fluoxetine versus placebo: 4 studies, 462 participants;
    - bupropion versus placebo: 3 studies, 325 participants;
    - ritanserin versus placebo: 2 studies, 145 participant;
5. Antidepressants versus different class of other medications:
    - Antidepressants versus dopamine agonists: 4 studies, 171 participants;
    - Antidepressants versus anticonvulsants: 3 studies, 162 participants;
6. Different class of antidepressants versus different class of other medications:
    - SSRIs versus anticonvulsants: 2 studies, 66 participants;
7. Specific antidepressants versus specific other medications:
    - Desipramine versus Amantadine: 3 studies, 131 participants;
8. Antidepressants versus placebo according to associated psychosocial interventions:
    - Associated Psychotherapy: 18 studies, 1865 participants;
    - Associated counselling: 9 studies 684 participants;
9. Antidepressants versus placebo according to opioid dependence status:
    - Associated opioid dependence: 10 studies, 1006 participants;
    - No opioid dependence: 23 studies, 1813 participants;
10. Antidepressants versus placebo according to length of trial:
    - Up to six weeks of treatment: 6 studies, 282 participants;
    - More than six weeks of treatment: 26 studies, 2881 participants;
11. Antidepressants versus placebo excluding medications with uncertain antidepressant activity: 30 studies, 2867 participants.

Excluded studies

29 studies did not meet the criteria for inclusion in this review. The grounds for exclusion were: study design not in the inclusion criteria: 19 studies (Carroll 1995; Cornelius 1998; Ehrman 1996; Feingold 2002; Galloway 1996; Gawin 1984 a; Gonzalez 2003; Haberny 1995; Kampman 1999; Kosten 1987; Kosten 1992 c; Kosten 2005; Leal 1994; Levin 2002; Levin 2008; McDowell 2000; Milligan 2004; Montoya 2002; Sofuoglu 2003; Szerman 2005; Ziedonis 1991; Zueco Pérez 2002); objectives and outcomes measures not in the inclusion criteria: 6 studies (Kampman 2003; Kosten 1992 b; Oliveto 1995; Reid 2005; Rowbotham 1984; Upadhyaya 2001); overview of other included studies: one study (Kampman 2005). See Characteristics of excluded studies.

Risk of bias in included studies

All studies were randomised controlled trial.

Allocation

The random sequence generation was judged adequate (low risk of bias) in 18 studies and inadequate (high risk of bias) in one study. In the other remaining studies details provided did not allow a specific evaluation on this criteria. Allocation concealment was judged adequate in 14 studies and inadequate in one study. In the other studies details provided did not allow a specific evaluation on the procedures adopted to prevent participants and investigators from foreseeing assignment.

Blinding

For both subjective and objective outcomes the knowledge of the allocated interventions during the study was judged adequately prevented in 29 studies. In two studies, where medications were not identical, the prevention of the knowledge of the allocated interventions was judged adequate for objective and unclear for subjective outcomes. One study was single blind and was judged as inadequate (high risk of bias). The remaining studies did not provided sufficient information to allow a specific evaluation on this criteria.

Incomplete outcome data

In 12 studies missing data on patients were considered using appropriate methods (low risk of bias); in 10 studies this issue was not appropriately addressed (high risk of bias); in all the other studies provided information did not allow a specific evaluation on incomplete outcome data addressing (unclear risk).

Other potential sources of bias

No other potential threats to validity were detected.
See Figure 2 and Figure 3 for a summary of these results.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

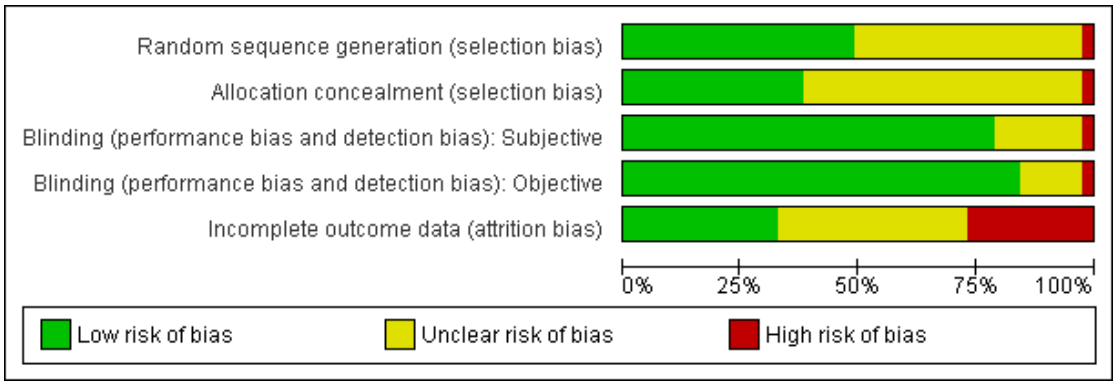
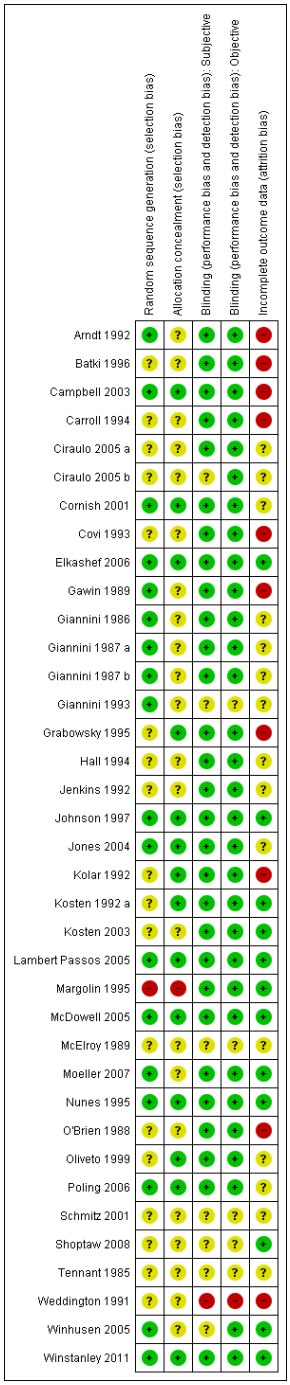


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Effects of interventions

See: **Summary of findings for the main comparison** Antidepressants compared to placebo according to any definition for cocaine abuse and dependence

See Summary of findings for the main comparison

The results were summarized, with comparison of quantitative data where at least two of the included studies use the same outcome measures. For some outcomes, it was impossible to pool data due to the different ways of reporting the results. Different rating methods were utilized and for some of them the authors did not indicate the data needed for proceeding with the meta-analysis. If we found a statistically significant heterogeneity, the results of the comparisons were reported first including all studies and thereafter excluding those with high risk of bias.

1. Andidepressants versus placebo according to any definition

1.1 Dropouts

1.1.1 Dropouts: all studies

31 studies (Arndt 1992; Batki 1996; Campbell 2003; Ciraulo 2005 a; Ciraulo 2005 b; Cornish 2001; Elkashef 2006; Gawin 1989; Giannini 1986; Giannini 1993; Grabowsky 1995; Hall 1994; Jenkins 1992; Johnson 1997; Jones 2004; Kolar 1992; Kosten 1992 a; Kosten 2003; Margolin 1995; McDowell 2005; McElroy 1989; Nunes 1995; O'Brien 1988; Oliveto 1999; Poling 2006; Schmitz 2001; Shoptaw 2008; Tennant 1985; Weddington 1991; Winhusen 2005; Winstanley 2011), 2819 participants, RR 1.03 (Cl 95% 0.93 to 1.14). The analysis did not found evidence of difference between antidepressants and placebo. To be noticed in this comparison a statistically significant, although of low degree, result for heterogeneity (Tau^2 = 0.02; Chi^2 = 48.55, df = 32 (P = 0.03); I^2 = 34%).

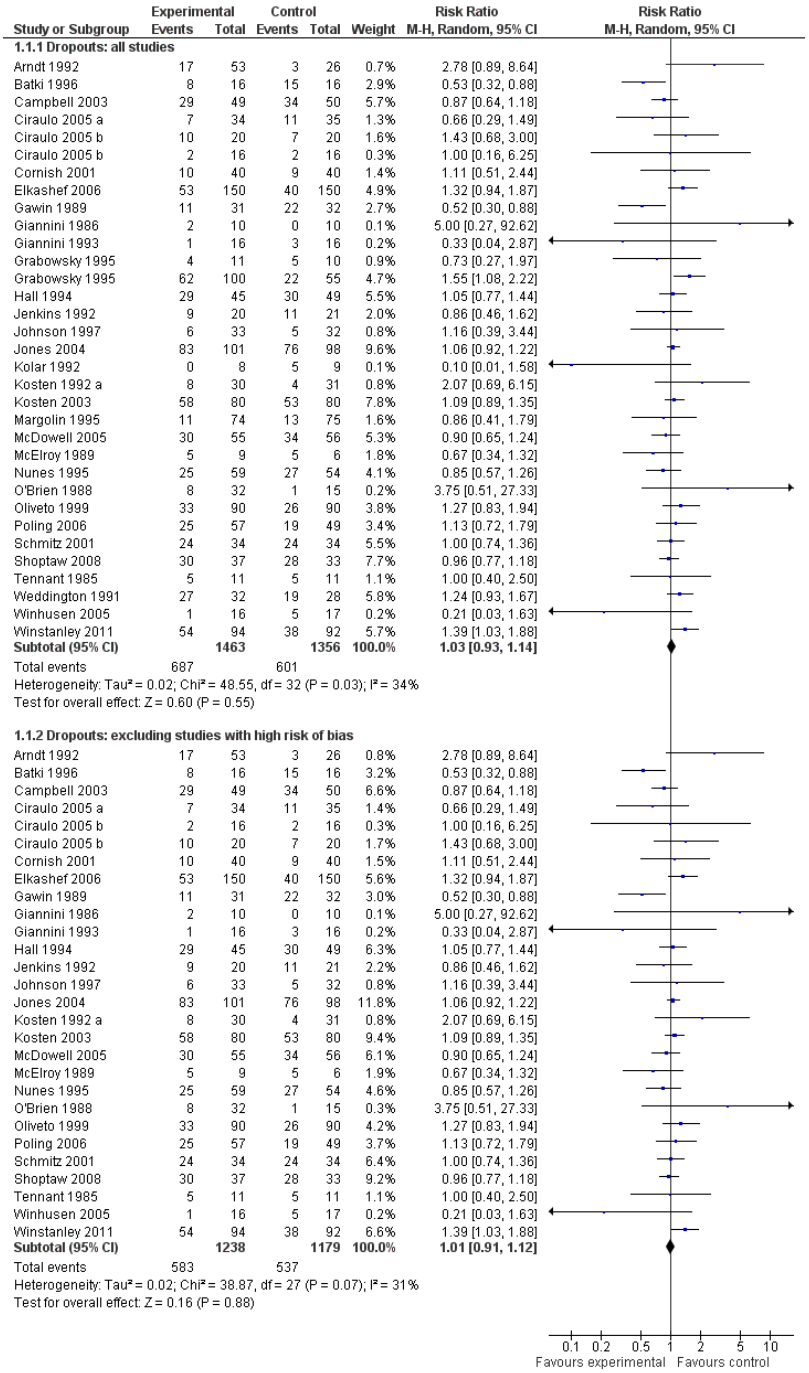
One more study reporting this outcome (Carroll 1994) was not included in meta-analysis for the unclearness of the sample size. The first arm of this study (desipramine plus clinical management versus placebo plus clinical management) showed a dropout rate of 63% for the desipramine group versus 61% for the placebo group, while the second arm (desipramine plus relapse prevention versus placebo plus relapse prevention) showed a dropout rate of 51% for the desipramine group versus 64% for the placebo group. Differences were not statistically significant.

1.1.2 Dropouts: excluding studies with high risk of bias

27 studies (Arndt 1992; Batki 1996; Campbell 2003; Ciraulo 2005 a; Ciraulo 2005 b; Cornish 2001; Elkashef 2006; Gawin 1989; Giannini 1986; Giannini 1993; Hall 1994; Jenkins 1992; Johnson 1997; Jones 2004; Kosten 1992 a; Kosten 2003; McDowell 2005; McElroy 1989; Nunes 1995; O'Brien 1988; Oliveto 1999; Poling 2006; Schmitz 2001; Shoptaw 2008; Tennant 1985; Winhusen 2005; Winstanley 2011), 2417 participants, RR 1.05 (Cl 95% 0.97 to 1.14). Again there was no evidence that antidepressants are associated with a higher or lower rate of participants leaving the treatment. In this analysis, Arndt 1992, Batki 1996, Campbell 2003; Gawin 1989 and O'Brien 1988 were included, although judged with high risk of bias for the incomplete outcome data addressing, since the incompleteness does not refer to data required to evaluate retention in treatment.

For all see Figure 4 or Analysis 1.1.

Figure 4. Forest plot of comparison: 1 Antidepressants vs placebo according to any definition, outcome: 1.1 Dropout.

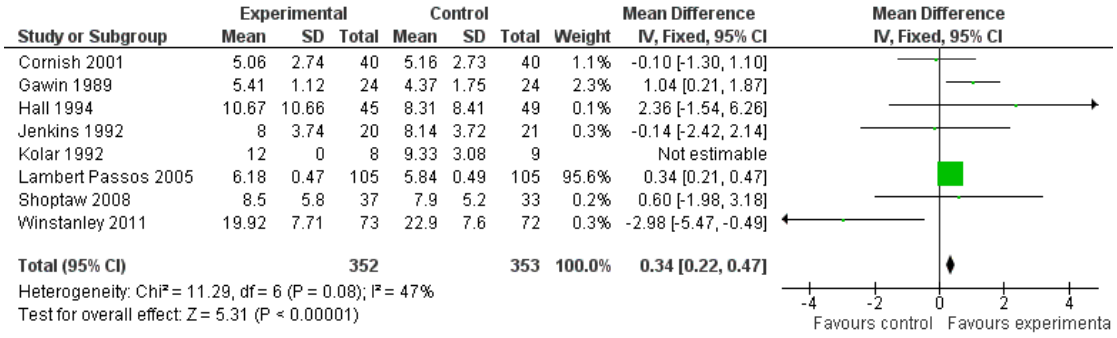


To be noticed that due to RevMan limitation to the choice of different effect model for subgroups, in Figure 4 and Analysis 1.1 a random effect model is applied to both subgroups (1.1.1 and 1.1.2).

1.2 Retention in treatment as mean number of weeks in treatment

Eight studies (Cornish 2001; Gawin 1989; Hall 1994; Jenkins 1992; Kolar 1992; Lambert Passos 2005; Shoptaw 2008; Winstanley 2011), 705 participants, MD 0.34 (Cl 95% 0.22 to 0.47). Antidepressants were found to be more efficacious than placebo. See Figure 5 or Analysis 1.2.

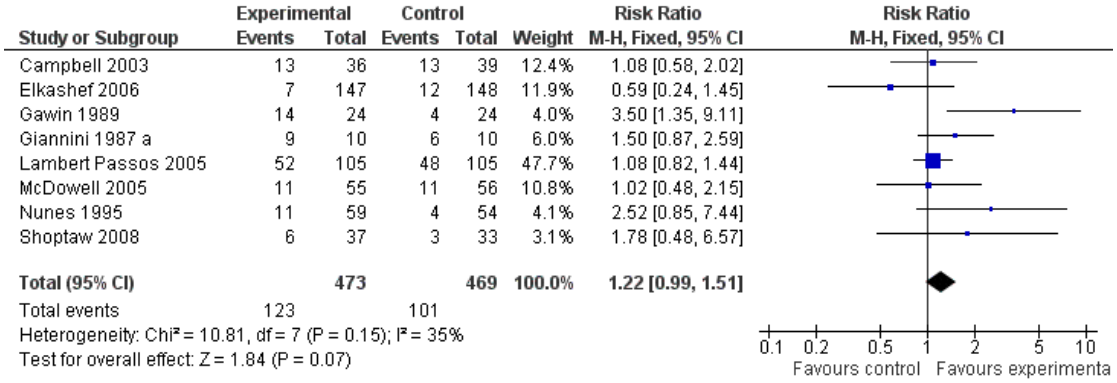
Figure 5. Forest plot of comparison: 1 Antidepressants vs placebo according to any definition, outcome: 1.2 Retention in treatment as mean number of weeks in treatment.



1.3 Abstinence for at least three consecutive weeks

Eight studies (Campbell 2003; Elkashef 2006; Gawin 1989; Giannini 1987 a; Lambert Passos 2005; McDowell 2005; Nunes 1995; Shoptaw 2008), 942 participants, RR 1.22 (Cl 95% 0.99 to 1.51). Even though not statistically significant, the difference shown by the analysis was in favour of antidepressants. See Figure 6 or Analysis 1.3.

Figure 6. Forest plot of comparison: 1 Antidepressants vs placebo according to any definition, outcome: 1.3 Abstinence, for at least three consecutive weeks.



Furthermore, Abstinence rate last week was considered in six studies (Covi 1993; Giannini 1987 a; Hall 1994; Kolar 1992; Margolin 1995; Weddington 1991), 333 participants, RR 1.06 (Cl 95% 0.81 to 1.38). No evidence of difference was found between antidepressants and placebo.

1.4 Abstinence as number of weeks of continuous abstinence

Seven studies (Carroll 1994; Elkashef 2006; Jones 2004; Kosten 2003; Lambert Passos 2005; Shoptaw 2008; Weddington 1991), 1062 participants, MD 0.00 (Cl 95% -0.21 to 0.22). No difference was found between antidepressants and placebo. See Analysis 1.4. For other studies considering continuous outcome measures of not cocaine use, it was not possible to undertake cumulative analyses due to the lack of at least two studies reporting useful data for the same outcome measures and providing means and standard deviations by group (or, according to Cochrane Reviews Handbook suggested procedures from available values (Higgins 2011), measures useful to obtain them). Among these studies:

- Poling 2006, with the use of hierarchical linear modelling MIXPREG (HLM Poisson analysis) indicated a significantly higher maximum consecutive weeks of cocaine abstinence in bupropion plus contingency management (CMB) treated subjects (6.74 weeks) than in the corresponding contingency management plus placebo (CMP) treated group (4.28 weeks; p < 0.001) and in the bupropion plus voucher condition (VCB) treated group (4.9 weeks) than in the placebo plus voucher control (VCP) condition (3.04 weeks; p < 0.001), respectively. An HLM Poisson analysis evaluating cocaine urinary results at the end of the trial allowed an observed probability of a cocaine positive sample as follows: CMB, 0.22; CMP, 0.57; VCB, 0.66; VCP, 0.74 (p < 0.001);
- Winhusen 2005, 33 participants, using a Generalized Estimating Equations (GEE) approach, estimated that the sertraline group demonstrated 68% decrease in urine BE during the active study, whereas placebo group showed increase of 32%;
- Hall 1994, 94 participants, considered days to first cocaine use, applying proportional hazards models, with organization, drug condition and organization-drug condition interaction as independent variables, without finding significant differences as a function of these variables;
- Oliveto 1999, 180 participants, applying Hierarchical Linear Models (HLM) found a statistically significant difference between desipramine and placebo in the weekly mean proportions of urine tests negative for cocaine, in favour of antidepressant, in males (z = -4.4; p = 0.001) and in females (z = -42.6; p = 0.009). However, self-report of cocaine use did not show significant differences by desipramine condition;
- Shoptaw 2008, 70 participants, looking at the proportion of cocaine-free urine samples provided at each study visit by treatment group assignment, with Generalized Estimating Equations (GEE analysis), failed in finding a difference between the treatment groups;
- Elkashef 2006, 300 participants, looking at the weekly percentage of cocaine non-use days based on self-report and urinary Benzoilecgonine results, with Generalized Estimating Equations (GEE analysis), failed in finding a difference between the treatment groups (GEE, p = 0.94);
- Kosten 2003, 160 participants, looking at the bi-weekly rates of cocaine-free urine with hierarchical linear modelling (HLM), showed that the desipramine plus contingency management (CM) group attained substantially more cocaine free urine than the other three groups. However, while a desipramine and CM statistically significant effect was observed, only the CM by time interaction was significant.
- Moeller 2007, 76 participants, using repeated measures analysis as implemented in hierarchical generalized linear modelling (HGLM), found a statistically significant effect of

treatment on cocaine positive urine screens (F = 9.33; df 1.665; p = 0.002) and a statistically significant treatment by time interaction (F 4.13; df 1.665; p = 0.04).

- Weddington 1991, 38 participants, using ANOVA did not find a statistically significant difference in the number of weeks of cocaine free urine;
- Ciraulo 2005 b, 51 participants, using Generalized Estimating Equations (GEE analysis), failed in finding a difference between the treatment groups in the benzoylecgonine concentration mean lg;
- Lambert Passos 2005, 210 participants, did not show a statistically significant difference in in the mean time (days) until first relapse (log-rank test; P = 0.39).

1.5 Use of cocaine during the trials

Four studies (Johnson 1997; Margolin 1995; McElroy 1989; Tennant 1985), 251 participants, RR 1.05 (Cl 95% 0.91 to 1.21). No evidence of difference was shown. See Analysis 1.5.
Looking at primary studies, Winstanley 2011, 145 participants, applying longitudinal logistic regression models of cocaine use, failed in finding between-group or group x time statistically significant differences in favour of antidepressant (fluoxetine).
Looking at continuous measures of cocaine use, a rather extended range of measures was used, referring to the number of days of use, the weekly rate of self-reported cocaine use, the quantity of cocaine used, the percentage of cocaine positive urinalyses per patient, the benzoilecgonine urinary concentration. All performed meta analyses, involving from 334 to 135 participants and including from four to two studies, allocated patients to the treatment on the base of operationally defined criteria for the diagnosis of cocaine dependence. None of these comparisons showed a statistically significant difference between antidepressants and placebo with the exception of the mean percentage of positive urine result per patient, three studies, 334 participants, MD 6.10 (Cl 95% 0.04 to 12.16), where the evidence was in favour of placebo, and of the benzoilecgonine urinary concentration, five studies, 180 participants, MD -0.93 (Cl 95% -1.75 to -0.12), where the evidence was in favour of antidepressants.

1.6 Craving for cocaine

1.6.1 Craving score, different scales of measure
Nine studies (Batki 1996; Ciraulo 2005 a; Ciraulo 2005 b; Cornish 2001; Elkashef 2006; Kolar 1992; Margolin 1995; Weddington 1991; Winhusen 2005), 636 participants, SMD 0.02 (Cl 95% -0.13 to 0.18). No evidence of difference was shown. Here, given that the studies used different psychometric scales, the standardized mean difference was applied as a summary statistic (Higgins 2011).
1.6.2 Craving score, Mezinskis Scale, endpoint
Three studies (Ciraulo 2005 b; Elkashef 2006; Winhusen 2005), 312 participants, SMD 0.11 (Cl 95% -0.11 to 0.33), no evidence of difference.
For all see Analysis 1.6.
Looking at primary studies:

- Nunes 1995, 113 participants, applying random regression analysis, yielded main effects of time and of treatment, suggesting that at follow up point (weeks 1 through 12) scores were lower on imipramine than on placebo (Z = -2.93; p < 0.01).
- Arndt 1992, 59 participants, undertaking repeated measures multiple analysis (ANCOVA) using baseline and 12th week craving scores (20 point scale range score), found a statistically significant effect of time, but not of groups.

It was not possible to add these studies to meta-analysis because of the lack of standard deviations and of data needed to obtain them (according to Cochrane Reviews Handbook suggested procedures (Higgins 2008).
Finally, looking at the number of days per week craving cocaine, McDowell 2005, 111 participants, did not find a statistically significant difference between antidepressants and placebo (T= 0.58; P = 0,36).

1.7 Addiction Severity Index (ASI) score

1.7.1 Medical
Seven studies (Carroll 1994; Ciraulo 2005 a; Ciraulo 2005 b Cornish 2001; Elkashef 2006; Margolin 1995; Winhusen 2005), 654 participants, MD 0.00 (Cl 95% -0.06 to 0.07). In this analysis a statistically significant result for heterogeneity was shown (Tau^2 = 0.00; Chi^2 = 12.63, df = 6 (P = 0.05); I^2 = 52%). Excluding the study most outlier (Ciraulo 2005 b), remaining six studies, 614 participants, MD 0.03 (Cl 95% -0.02 to 0.07), no evidence of difference between antidepressants and placebo was shown. On the other hand, Ciraulo 2005 b, 40 participants, MD -0.20 (Cl 95% -0.38 to -0.02), showed a statistically significant difference in favour of antidepressants. Excluding studies with high risk of bias, four studies (Ciraulo 2005 a; Cornish 2001; Elkashef 2006; Winhusen 2005), 504 participants, again a significant result for heterogeneity was shown (Tau^2 = 0.01; Chi^2 = 11.04, df = 4 (P = 0.03); I^2 = 64%). Excluding the most outlier (Ciraulo 2005 b) 379 participants, MD 0.02 (Cl 95% -0.03 to 0.08), again no evidence of difference was shown.
1.7.2 Employment
Six studies (Carroll 1994; Ciraulo 2005 b; Cornish 2001; Elkashef 2006; Margolin 1995; Winhusen 2005), 603 participants, MD 0.00 (Cl 95% -0.04 to 0.05), no evidence of difference was shown.
1.7.3 Alcohol
Seven studies (Carroll 1994; Ciraulo 2005 a; Ciraulo 2005 b; Cornish 2001; Elkashef 2006; Margolin 1995; Winhusen 2005), 645 participants, MD -0.00 (Cl 95% -0.02 to 0.02), no evidence of difference was shown.
1.7.4 Drugs

Seven studies (Carroll 1994; Ciraulo 2005 a; Ciraulo 2005 b; Cornish 2001; Elkashef 2006; Margolin 1995; Winhusen 2005), 674 participants, MD 0.00 (Cl 95% -0.01 to 0.01), no evidence of difference was shown.

1.7.5 Legal

Seven studies (Carroll 1994; Ciraulo 2005 a; Ciraulo 2005 b; Cornish 2001; Elkashef 2006; Margolin 1995; Winhusen 2005), 648 participants, MD 0.01 (Cl 95% -0.01 to 0.04), no evidence of difference was shown.

1.7.6 Family/social

Seven studies (Carroll 1994; Ciraulo 2005 a; Ciraulo 2005 b; Cornish 2001; Elkashef 2006; Margolin 1995; Winhusen 2005), 647 participants, MD -0.02 (Cl 95% -0.04 to 0.01), no evidence of difference was shown.

1.7.7 Psychiatric

Seven studies (Carroll 1994; Ciraulo 2005 a; Ciraulo 2005 b; Cornish 2001; Elkashef 2006; Margolin 1995; Winhusen 2005), 646 participants, MD 0.01 (Cl 95% -0.02 to 0.03), no evidence of difference was shown.

For all see Analysis 1.7.

Looking at primary studies, Arndt 1992, 59 participants, undertaking repeated measures multiple analysis (ANCOVA) using baseline and 12th week ASI composite scores, found a statistically significant effect of time (F=5.7; df 1,58; $p < 0.1$), but not an overall difference between groups ($F < 1$; $p > 0.1$) and only a statistically significant difference in one of the ASI dimensions (psychiatric score: F = 4.15; df=1,56; $p < 0.05$). It was not possible to add this study to meta-analysis because of the lack of standard deviations and of data needed to obtain them (according to Cochrane Reviews Handbook suggested procedures (Higgins 2008).

1.8 Mood dichotomous measures

1.8.1 Depression response, Clinicians Global Impression (CGI)

Two studies reported the number of subjects resulting "much improved" or "very much improved" at the CGI scale (Jenkins 1992; McDowell 2005), 152 participants. RR 1.09 (Cl 95% 0.49 to 2.42). However, a statistically significant result for heterogeneity was shown ($Tau^2 = 0.25$; $Chi^2 = 4.03$, df = 1 (P = 0.04); $I^2 = 75\%$). Using data from singular studies, Jenkins 1992, 41 participants, RR 0.70 (Cl 95% 0.36 to 1.34), did not show a statistically significant result, while McDowell 2005, 111 participants, RR 1.58 (Cl 95% 1.00 to 2.51) showed a statistically significant result in favour of desipramine.

1.8.2 >50% reduction in Hamilton Depression Rating Scale

Two studies (Lambert Passos 2005; McDowell 2005), 321 participants, RR 1.31 (Cl 95% 1.08 to 1.60), the result was statistically significant in favour of antidepressants. However a trend for substantial heterogeneity between studies was observed ($Chi^2 = 3.46$, df = 1 (P = 0.06); $I^2 = 71\%$).

To be noticed that due to RevMan limitation to the choice of different effect model for subgroups, in Analysis 1.8 a random effect model is applied to both subgroups (1.8.1 and 1,8.2).

1.9 Mood continuous measures

1.9.1 Hamilton Depression Rating Scale score at the end of the treatment

Six studies (Ciraulo 2005 a; Ciraulo 2005 b; Cornish 2001 Margolin 1995; McDowell 2005; Winhusen 2005), 420 participants, MD -1.41 (Cl 95% -2.44 to -0.37), There was evidence that antidepressants are more effective than placebo on this measure of mood depression.

1.9.2 CGI depression severity score at the end of the treatment

Three studies (Ciraulo 2005 b; Elkashef 2006; McDowell 2005), 390 participants, MD -0.08 (Cl 95% -0.35 to 0.18), no evidence of difference was shown .

1.9.3 Beck Depression Inventory at the end of the treatment

Three studies (Cornish 2001; Kolar 1992; Weddington 1991), 115 participants, MD -0.81 (Cl 95% -4.11 to 2.48). In this analysis a statistically significant result for heterogeneity was shown ($Tau^2 = 5.70$; $Chi^2 = 6.11$, df = 2 (P = 0.05); $I^2 = 67\%$). Excluding the most outlier (Kolar 1992) and pooling Cornish 2001 and Weddington 1991 ($Chi^2 = 0.58$, df = 1 (P = 0.45); $I^2 = 0\%$), 98 participants, MD 0.78 (Cl 95% -1.42 to 2.97), no evidence of difference was shown. On the other hand, in Kolar 1992, 17 participants, MD -4.30 (Cl 95% -7.91 to -0.69), a statistically significant difference in favour of desipramine was shown. Both Kolar 1992 and Weddington 1991 were judged at high risk of bias.

1.9.4 Brief Psychiatric Rating Scale (BPRS) at the end of the treatment

Three studies (Giannini 1987 a; Giannini 1987 b; Giannini 1993), 72 participants, MD -13.89 (Cl 95% -21.52 to -6.26). In this analysis a statistically significant result for heterogeneity was shown ($Tau^2 = 37.64$; $Chi^2 = 13.49$, df = 2 (P = 0.001); $I^2 = 85\%$). Excluding the most outlier (Giannini 1987 b) and pooling the results of Giannini 1987 a and Giannini 1993, 48 participants, MD -18.00 (Cl 95% -18.55 to -17.45), desipramine was found to be more effective than placebo in improving BPRS-measured psychiatric status. On the other hand, Giannini 1987 b, 25 participants, RR -5.00 (Cl -11.92 to 1.92), did not show a statistically significant difference between desipramine and placebo.

For all see Analysis 1.9.

Looking at primary studies:

- Shoptaw 2008, 70 participants, using a General Linear Mixed Model (GLMM), did not find statistically significant difference between bupropion and placebo in BDI scores throughout the trial (F = 1.26; p = 0.21).
- Johnson 1997, 65 participants, looking at CGI severity score changes from baseline, with ANCOVA, found an improvement in both groups, without showing a statistically significant difference between ritanserin and placebo;
- Cornish 2001, 60 participants, using a two-way mixed model ANOVA, found a statistically significant effect of time,

but not a time by group interaction in the depression sub-scale of the Profile of Mood States (POMS);

- Covi 1993, 45 participants, using baseline and endpoint POMS depression measures and ANCOVA repeated analysis, did nor reveal statistically significant differences between fluoxetine and placebo;
- Poling 2006, 106 participants, using the Hierarchical Linear Modeling (HLM), did not find statistically significant differences by group in the Center for Epidemiological Studies Depression Scale (CES-D) scores.

These studies were not added to the meta-analysis because of the heterogeneity of instruments used for defining outcomes or the unavailability of standard deviation or data needed to obtain it;

1.10 Adverse events

1.10.1 Withdrawn due to adverse events

Therteen studies (Arndt 1992; Batki 1996; Ciraulo 2005 b; Elkashef 2006; Johnson 1997; Kolar 1992; Kosten 1992 a; Lambert Passos 2005; Margolin 1995; McDowell 2005; Nunes 1995; Winhusen 2005; Winstanley 2011), 1396 participants, RR 1.39 (Cl 95% 0.91 to 2.12). no evidence of difference was shown. Seven more studies (Campbell 2003; Covi 1993; Gawin 1989; Moeller 2007; Schmitz 2001; Shoptaw 2008) showed no dropouts due to adverse events.

1.10.2 Participants presenting al least one side effect

Three studies (Cornish 2001; Johnson 1997; Lambert Passos 2005), 355 participants, RR 1.08 (Cl 95% 0,71 to 1.65). However, a statistically significant result for heterogeneity was shown (Tau^2 = 0.11; Chi^2 = 8.11, df = 2 (P = 0.02); I^2 = 75%). Excluding the most outlier (Cornish 2001) and pooling the results of Johnson 1997 and Lambert Passos 2005 , 275 participants, RR 1.38 (Cl 95% 1.08 to 1.77), the result was statistically significant in favour of placebo. On the other hand, in Cornish 2001, 80 participants, RR 0.67 (Cl 95% 0.42 to 1.05), even though not significant, the difference between ritanserin and placebo was in favour of the antidepressant.

For all see Analysis 1.10

Other adverse events

Ten studies (Ciraulo 2005 a; Ciraulo 2005 b; Cornish 2001; Elkashef 2006; Giannini 1986; Johnson 1997; Nunes 1995; Moeller 2007; Shoptaw 2008; Winhusen 2005), 866 participants, considered several single different adverse events. In only one comparison (Abdominal pain) the result was statistically significant in favour of placebo: three studies (Ciraulo 2005 b; Elkashef 2006; Johnson 1997), 405 participants, RR 2.09 (Cl 95% 1.01 to 4.33). All the other comparisons did not show evidence of differences between antidepressants and placebo, although in two of these comparisons (Dry mouth; Diarrhea) a trend for an higher presence of side effects in the antidepressants-allocated subjects was shown, while in another comparison (Pharyngitis) a trend for an higher presence of side effects in the placebo-allocated subjects was shown. Furthermore, one study (Lambert Passos 2005), 110 participants, reported dichotomous measures of adherence to treatment and to prescription and continuous measures such as attendance to appointments, without finding any statistically significant differences between antidepressants and placebo.

2. Andidepressants versus placebo for operationally defined cocaine dependence

In the following analyses, were considered only studies selecting participants on the base of DSM cocaine dependence criteria.

2.1 Dropouts

2.1.1 Dropouts: all studies

22 studies (Batki 1996; Campbell 2003; Ciraulo 2005 a; Ciraulo 2005 b; Cornish 2001; Elkashef 2006; Gawin 1989; Grabowsky 1995; Hall 1994; Jenkins 1992; Johnson 1997; Jones 2004; Kolar 1992; Kosten 1992 a; Kosten 2003; Margolin 1995; McDowell 2005; McElroy 1989; Schmitz 2001; Weddington 1991; Winhusen 2005; Winstanley 2011), 2150 participants, RR 1.02 (Cl 95% 0.91 to 1.14), no evidence of difference was shown. To be noticed in this comparison a statistically significant, although low in magnitude, result for heterogeneity (Tau^2 = 0.03; Chi^2 = 38.95, df = 23 (P = 0.02); I^2 = 41%). See Analysis 2.1.

2.1.2 Dropouts: excluding studies with high risk of bias

19 studies (Batki 1996; Campbell 2003; Ciraulo 2005 a; Ciraulo 2005 b; Cornish 2001; Elkashef 2006; Gawin 1989; Hall 1994; Jenkins 1992; Johnson 1997; Jones 2004; Kolar 1992; Kosten 1992 a; Kosten 2003; McDowell 2005; McElroy 1989; Schmitz 2001; Winhusen 2005; Winstanley 2011), 1765 participants, RR 0.98 (Cl 95% 0.86 to 1.11), no evidence of difference was shown. To be noticed, again, a statistically significant, although low in magnitude, result for heterogeneity (Tau^2 = 0.03; Chi^2 = 31.89, df = 19 (P = 0.03); I^2 = 40%). In this analysis, Batki 1996, Campbell 2003 and Gawin 1989, were included, although judged with high risk of bias for the incomplete outcome data addressing, since the incompleteness does not refer to data required to evaluate retention in treatment.

For all, see Analysis 2.1.

2.2 Retention in treatment

2.2.1 Time of retention in treatment (mean number of weeks): all studies

Seven studies (Cornish 2001; Gawin 1989; Hall 1994; Jenkins 1992; Kolar 1992; Lambert Passos 2005; Winstanley 2011), 635 participants, MD 0.24 (Cl 95% -0.46 to 0.94). In this analysis, a statistically significant result for heterogeneity was shown (Tau^2 = 0.33; Chi^2 = 11.26, df = 5 (P = 0.05); I^2 = 56%). Excluding the study most outlier (Winstanley 2011), remaining six studies, 490 participants, MD 0.35 (Cl 95% 0.22 to 0.48), evidence of an higher retention in treatment of antidepressants-allocated participants was shown. On the other hand, Winstanley 2011, 145

participants, MD -2.98 (Cl 95% -5.47 to -0.49), showed a statistically significant result in favour of placebo.

2.2.2 Time of retention in treatment (mean number of weeks): excluding studies with high risk of bias

Five studies (Cornish 2001; Hall 1994; Jenkins 1992; Lambert Passos 2005; Winstanley 2011), 570 participants, MD 0.33 (Cl 95% 0,20 to 0.46). Again, antidepressants were found to be associated with an higher retention in treatment than placebo. In this analysis, Jenkins 1992, although judged with high risk of bias for the incomplete outcome data addressing, was included since this incompleteness did not refer to data required to evaluate retention in treatment.

For all see Analysis 2.2.

2.3 Abstinence for at least three consecutive week

Five studies (Campbell 2003; Elkashef 2006; Gawin 1989; Lambert Passos 2005; McDowell 2005), 739 participants, RR 1.12 (Cl 95% 0.89 to 1.41), no evidence of difference was shown. See Analysis 2.3.

2.4 Abstinence as number of weeks of continuous abstinence

Six studies (Carroll 1994; Elkashef 2006; Jones 2004; Kosten 2003; Lambert Passos 2005; Weddington 1991), 992 participants, MD -0.03 (Cl -0.25 to 0.19), no evidence of difference was shown. See Analysis 2.4.

2.5 Use of cocaine during the trial

Three studies (Johnson 1997; Margolin 1995; McElroy 1989), 229 participants, RR 1.04 (Cl 95% 0.90 to 1.20), no evidence of difference was shown. See Analysis 2.5.

2.6 Adverse events as withdrawn due to adverse events

Eleven studies (Batki 1996; Ciraulo 2005 b; Elkashef 2006; Johnson 1997; Kolar 1992; Kosten 1992 a; Lambert Passos 2005; Margolin 1995; McDowell 2005; Winhusen 2005; Winstanley 2011), 1204 participants, RR 1.40 (Cl 95% 0.90 to 2.19), no evidence of difference was shown. See Analysis 2.6.

Other adverse events

Seven studies (Ciraulo 2005 a; Ciraulo 2005 b; Cornish 2001; Elkashef 2006; Johnson 1997; Moeller 2007; Winhusen 2005), 663 participants, considered several single different adverse events. All the comparisons did not show evidence of differences between antidepressants and placebo.

3. Different classes of antidepressants versus placebo

3.1 Dropouts

3.1.1 Tricyclics

15 studies (Arndt 1992; Campbell 2003; Gawin 1989; Giannini 1986; Hall 1994; Kolar 1992; Kosten 1992 a; Kosten 2003; McDowell 2005; McElroy 1989; Nunes 1995; O'Brien 1988; Oliveto 1999; Tennant 1985; Weddington 1991), 1141 participants, RR 1.00 (Cl 95% 0.85 to 1.18), no evidence of difference was shown. However, it should be noticed in this comparison a statistically significant, although low in magnitude, result for heterogeneity (Tau^2 = 0.03; Chi^2 = 23.72, df = 14 (P = 0.05); I^2 = 41%). Excluding studies with high risk of bias, remaining 13 studies (Arndt 1992; Campbell 2003; Gawin 1989; Giannini 1986; Hall 1994; Kosten 1992 a; Kosten 2003; McDowell 2005; McElroy 1989; Nunes 1995; O'Brien 1988; Oliveto 1999; Tennant 1985), 1064 participants, RR 0.98 (Cl 95% 0.83 to 1.16), no evidence of difference was shown. See Analysis 3.1

Including only studies with diagnosis of cocaine dependence according to DSM criteria, nine studies (Campbell 2003; Gawin 1989; Hall 1994; Kolar 1992; Kosten 1992 a; Kosten 2003; McDowell 2005; McElroy 1989; Weddington 1991), 680 participants, RR 0.95 (Cl 95% 0.79 to 1.15), again no evidence of difference was shown. However it has to be noticed a statistically significant heterogeneity (Tau^2 = 0.04; Chi^2 = 16.36, df = 8 (P = 0.04); I^2 = 51%). After the exclusion of the most outlier study (Kolar 1992), remaining eight studies, 663 participants, RR 0.97 (Cl 95% 0.81 to1.15), the result did not substantially changed.

3.1.2 SSRIs

Six studies (Batki 1996; Ciraulo 2005 b; Grabowsky 1995; Schmitz 2001; Winhusen 2005; Winstanley 2011), 527 participants, RR 0.99 (Cl 95% 0.70 to 1.41) . To be noticed a statistically significance for a relevant heterogeneity (Tau^2 = 0.11; Chi^2 = 17.39 , df = 6 (P = 0.008); I^2 = 65%). Excluding the study most outlier for the dropout rate in the control group (Batki 1996), remaining five studies, 495 participants, RR 1.25 (Cl 95% 1.04 to 1.50), evidence of an higher dropout rate for SSRIs than for placebo-treated group was found. Excluding studies with high risk of bias, and excluding the most outlier for dropout rate in the control group (Batki 1996) because of heterogeneity (Tau^2 = 0.14; Chi^2 = 12.74, df = 4 (P = 0.01); I^2 = 69%), remained four studies (Ciraulo 2005 b; Schmitz 2001; Winhusen 2005; Winstanley 2011), 319 participants, RR 1.16 (Cl 95% 0.93 to 1.45). No evidence of difference was shown.

See Analysis 3.1.

None of the studies reporting this outcome enrolled participants with uncertain or other than cocaine dependence diagnoses.

3.2 Retention in treatment as mean number of weeks in treatment: tricyclics

Three studies (Gawin 1989; Hall 1994; Kolar 1992), 159 participants, MD 1.10 (Cl 95% 0.28 to 1.91). Evidence of an higher retention in treatment of antidepressants-allocated participants was shown. See Analysis 3.2.

3.3 Abstinence for at least three consecutive weeks: tricyclics

Five studies (Campbell 2003; Gawin 1989; Giannini 1987 a; McDowell 2005; Nunes 1995), 367 participants, RR 1.55 (CI 95% 1.10 to 2.17). Evidence for an higher abstinence rate of antidepressants-allocated participants was shown. See Analysis 3.3. Selecting only studies with cocaine dependence according to DSM criteria, three studies (Campbell 2003; Gawin 1989; McDowell 2005), 234 participants, RR 1.41 (CI 95% 0.93 to 2.14), no evidence of difference was shown .

3.4 Abstinence as average number of weeks of continuous abstinence: tricyclics

Three studies (Carroll 1994; Kosten 2003; Weddington 1991), 308 participants, MD 0.71 (CI 95% -0.02 to 1.44). Even though not statistically significant, the difference shown by the analysis was in favour of antidepressants. See Analysis 3.4.

3.5 Use of cocaine during the trial: tricyclics

Two studies (McElroy 1989; Tennant 1985), 37 participants, RR 0.85 (CI 95% 0.34 to 2.11), no evidence of difference was shown. See Analysis 3.5.

3.6 Craving for cocaine: continuous measures

3.6.1 Craving score, different scales of measure: SSRIs

Three studies (Batki 1996; Ciraulo 2005 b; Winhusen 2005), 93 participants, SMD -0.22 (CI 95% -0.64 to 0.19), no evidence of difference was shown.

3.6.2 Craving score, different scales of measure: tricyclics

Two studies (Kolar 1992; Weddington 1991), 55 participants, SMD 0.01 (CI 95% -0.52 to 0.54), no evidence of difference was shown.

3.6.3 Craving score, Mezinskis Scale: SSRIs

Two studies (Ciraulo 2005 b; Winhusen 2005), 65 participants, SMD 0.04 (CI 95% -0.45 to 0.53), no evidence of difference was shown.

For all see Analysis 3.6.

3.7 ASI score (Drugs): SSRIs

Two studies (Ciraulo 2005 b; Winhusen 2005), 65 participants, MD 0.01 (CI 95% -0.03 to 0.06), no evidence of difference was shown. See Analysis 3.7.

3.8 Mood continuous measures

3.8.1 Beck Depression Inventory (BDI) at the end of the treatment: tricyclics

Two studies (Kolar 1992; Weddington 1991), 55 participants, MD -1.27 (CI 95% -7.05 to 4.51). In this analysis, a relevant and statistically significant result for heterogeneity was shown (Tau² = 14.49; Chi² = 5.97, df = 1 (P = 0.01); I² = 83%). Looking at singular studies, Kolar 1992, 17 participants, MD -4.30 (CI 95% -7.91 to -0.69), showed a result statistically significant in favour of antidepressant, while in Weddington 1991, 38 participants, MD 1.60 (CI 95% -1.46 to 4.66), the result was not statistically significant.

3.8.2 Brief Psychiatric Rating Scale (BPRS) at the end of the treatment: tricyclics

Two studies (Giannini 1987 a; Giannini 1987 b), 44 participants, MD -11.98 (CI 95% -24.68 to 0.73). Again, a relevant and statistically significant result for heterogeneity was shown (Tau² = 78.23; Chi² = 13.47, df = 1 (P = 0.0002); I² = 93%). Looking at singular studies, Giannini 1987 a, 20 participants, RR -18.00 (CI 95% -18.55 to -17.45), showed a statistically significant result in favour of desipramine, while Giannini 1987 b, 22 participants, RR -5.00 (CI 95% -11.92 to 1.92), did not show a statistically significant result.

For all see Analysis 3.8.

3.9 Adverse events

3.9.1 Withdrawn due to adverse events: tricyclics

Five studies (Arndt 1992; Kolar 1992; Kosten 1992 a; McDowell 2005; Nunes 1995), 381 participants, RR 1.24 (CI 95% 0.64 to 2.43), no evidence of difference was shown. Including only studies with cocaine dependence according to DSM criteria, three studies (Kolar 1992; Kosten 1992 a; McDowell 2005), 189 participants, RR 1.22 (CI 95% 0.57 to 2.63), again no evidence of difference between tricyclics and placebo was shown. In this analysis, Arndt 1992 was included, although judged with high risk of bias for the incomplete outcome data addressing, since the incompleteness does not refer to data required to evaluate withdrawn for medical reasons.

3.9.2 Withdrawn due to adverse events: SSRIs

Three studies (Batki 1996; Winhusen 2005; Winstanley 2011), 251 participants, RR 3.55 (CI 95% 1.11 to 11.34). SSRIs were found to withdrawn at an higher rate than placebo.

For all see Analysis 3.9.

Furthermore, two studies considering SSRIs (Moeller 2007; Winhusen 2005), 109 participants, compared groups on several different adverse events, without showing evidence of differences; moreover, three studies considering tricyclics (Giannini 1986; Kolar 1992; Nunes 1995), 133 participants, also considered some different adverse events, none of which reported in more than one study. The comparisons did not show evidence of difference between the two groups.

4. Specific antidepressants versus placebo

4.1 Dropouts

4.1.1 Dropouts: Desipramine

14 studies (Arndt 1992; Campbell 2003; Gawin 1989; Giannini 1986; Hall 1994; Kolar 1992; Kosten 1992 a; Kosten 2003; McDowell 2005; McElroy 1989; O'Brien 1988; Oliveto 1999; Tennant 1985; Weddington 1991), 1028 participants, RR 1.02 (Cl 95% 0.85 to 1.22). To be noticed a statistically significant result for heterogeneity (Tau² = 0.04; Chi² = 22.92, df = 13 (P = 0.04); I² = 43%). Excluding the most outlier study (Kolar 1992), remained 1011 participants, RR 1.06 (Cl 95% 0.95 to 1.20), the result did not show evidence of difference between desipramine and placebo on this outcome. On the other and, Kolar 1992, 17 participants, RR 0.10 (Cl 95% 0.01 to 1.58), showed a statistically significant result in favour of desipramine. Including only studies with cocaine dependence according to DSM criteria, nine studies (Campbell 2003; Gawin 1989; Hall 1994; Kolar 1992; Kosten 1992 a; Kosten 2003; McDowell 2005; McElroy 1989; Weddington 1991), 680 participants, RR 0.95 (Cl 95% 0.79 to 1.15). again a statistically significant presence of heterogeneity was shown (Tau² = 0.04; Chi² = 16.36, df = 8 (P = 0.04); I² = 51%). Excluding the most outlier study (Kolar 1992), leaving 663 participants, RR 0.98 (Cl 95% 0.87 to 1.10), no evidence of difference was shown. Excluding studies with high risk of bias, remaining 13 studies (Arndt 1992; Campbell 2003; Gawin 1989; Giannini 1986; Hall 1994; Kosten 1992 a; Kosten 2003; McDowell 2005; McElroy 1989; O'Brien 1988; Oliveto 1999; Tennant 1985), 951 participants, RR 1.05 (Cl 95% 0.92 to 1.19), again no evidence of difference was shown. In this analysis, Arndt 1992, Campbell 2003; Gawin 1989, and O'Brien 1988 were included, although judged with high risk of bias for the incomplete outcome data addressing, since the incompleteness does not refer to data required to evaluate retention in treatment.

4.1.2 Dropouts: fluoxetine

Four studies (Batki 1996; Grabowsky 1995; Schmitz 2001; Winstanley 2011), 462 participants, RR 1.04 (Cl 95% 0.72 to 1.49). The analysis showed a statistically significant result for a relevant degree of heterogeneity (Tau² = 0.11; Chi² = 15.08, df = 4 (P = 0.005); I² = 73%). Excluding the most outlier study (Batki 1996) and pooling the remaining studies, 430 participants, RR 1.30 (Cl 95% 1.08 to 1.57), evidence of an higher dropout rate of antidepressants-allocated participants was shown. On the other hand, Batki 1996, 32 participants, RR 0.53 (Cl 95% 0.32 to 0.88), showed a statistically significant lower dropout rate in favour of antidepressants. Batki 1996 was considered for this outcome since, although judged with high risk of bias for the incomplete outcome data addressing, this incompleteness does not refer to data required to evaluate retention in treatment. None of the studies reporting this outcome enrolled participants with uncertain or other than cocaine dependence diagnoses. Excluding studies with high risk of bias, three studies (Batki 1996; Schmitz 2001; Winstanley 2011), 286 participants, RR 0.94 (Cl 95% 0.58 to 1.52), it should be noticed a relevant and statistically significant result for heterogeneity (Tau² = 0.14; Chi² = 10.62, df = 2 (P = 0.005); I² = 81%). Excluding the most outlier study (Batki 1996), remaining two studies (Schmitz 2001; Winstanley 2011), 254 participants, RR 1.24 (Cl 95% 0.99 to 1.55), no evidence of difference was shown.

4.1.3 Dropouts: bupropion

Three studies (Margolin 1995; Poling 2006; Shoptaw 2008), 325 participants, RR 0.99 (Cl 95% 0.79 to 1.25), no evidence of difference was shown. Including only cocaine dependence according to DSM criteria (Poling 2006; Shoptaw 2008), 176 participants, RR 1.03 (Cl 95% 0.82 to 1.29), again no evidence of difference was shown.

4.1.4 Dropouts: ritanserin

Two studies (Cornish 2001; Johnson 1997), 145 participants, RR 1.13 (Cl 95% 0.60 to 2.14), no evidence of difference was shown. For all see Analysis 4.1.

4.2 Retention in treatment as mean number of weeks in treatment: desipramine

Three studies (Gawin 1989; Hall 1994; Kolar 1992), 159 participants, MD 1.10 (Cl 95% 0.28 to 1.91). Evidence of an higher retention in treatment in favour of desipramine was shown. See Analysis 4.2.

4.3 Abstinence for at least three consecutive weeks: desipramine

Four studies (Campbell 2003; Gawin 1989; Giannini 1987 a; McDowell 2005), 254 participants, RR 1.43 (Cl 95% 1.00 to 2.03), evidence of an higher abstinence rate in favour of desipramine was shown. See Analysis 4.3.

Including only studies with cocaine dependence according to DSM criteria, three studies (Campbell 2003; Gawin 1989; McDowell 2005), 234 participants, RR 1.41 (Cl 95% 0.93 to 2.14), no evidence of difference was shown.

4.4 Abstinence as average weeks of continuous abstinence: desipramine

Three studies (Carroll 1994; Kosten 2003; Weddington 1991), 308 participants, MD 0.71 (Cl 95% -0.02 to 1.44). Even though not statistically significant, the difference shown by the analysis was in favour of desipramine. See Analysis 4.4.

4.5 Use of cocaine during the trial: desipramine

Two studies (McElroy 1989; Tennant 1985), 37 participants, RR 0.85 (Cl 95% 0.34 to 2.11), no evidence of difference was shown. See Analysis 4.5.

4.6 Craving for cocaine: desipramine

Two studies (Kolar 1992; Weddington 1991), 55 participants, MD 0.18 (Cl 95% -3.67 to 4.03), no evidence of difference was shown. See Analysis 4.6

4.7 Mood continuous measures: desipramine

4.7.1 Beck Depression Inventory (BDI) at the end of the treatment
Two studies (Kolar 1992; Weddington 1991), 55 participants, MD -1.27 (Cl 95% -7.05 to 4.51). To be noticed a relevant and statistically significant result for heterogeneity (Tau^2 = 14.49; Chi^2 = 5.97, df = 1 (P = 0.01); I^2 = 83%). Looking at singular studies, Kolar 1992, 17 participants, MD -4.30 (Cl 95% -7.91 to -0.69), showed a statistically significant result in favour of desipramine, while in Weddington 1991, 38 participants, MD 1.60 (Cl 95% -1.46 to 4.66), the result was not statistically significant.
4.7.2 Brief Psychiatric Rating Scale (BPRS) at the end of the treatment
Two studies (Giannini 1987 a; Giannini 1987 b), 44 participants, MD -11.98 (Cl 95% -24.68 to 0.73). Again a relevant and statistically significant result for heterogeneity was shown (Tau^2 = 78.23; Chi^2 = 13.47, df = 1 (P = 0.0002); I^2 = 93%). Looking at singular studies, Giannini 1987 a, 20 participants, RR -18.00 (Cl 95% -18.55 to -17.45), showed a statistically significant result in favour of desipramine, while Giannini 1987 b, 22 participants, RR -5.00 (Cl 95% -11.92 to -1.92), did not show a statistically significant result.
For both see Analysis 4.7.

4.8 Adverse events

4.8.1 Withdrawn due to adverse events: desipramine
Four studies (Arndt 1992; Kolar 1992; Kosten 1992 a; McDowell 2005), 268 participants, RR 1.42 (Cl 95% 0.68 to 2.96), no evidence of difference was shown.
Including only studies with cocaine dependence according to DSM criteria, three studies (Kolar 1992; Kosten 1992 a; McDowell 2005), 189 participants, RR 1.22 (Cl 95% 0.57 to 2.63), no evidence of difference was shown. In this analysis, Arndt 1992 was included, although judged with high risk of bias for the incomplete outcome data addressing, since the incompleteness does not refer to data required to evaluate withdrawn for medical reasons.
4.8.2 Withdrawn due to adverse events: fluoxetine
Two studies (Batki 1996; Winstanley 2011), 218 participants, RR 3.60 (Cl 95% 1.03 to 12.62). Evidence of an higher dropout due to adverse events in fluoxetine-treated participants was shown.
4.8.3 Participants presenting al least one side effect; ritanserin
Two studies (Cornish 2001; Johnson 1997), 145 participants, RR 0.90 (Cl 95% 0.51 to 1.57). In this analysis a relevant and statistically significant result for heterogeneity was shown (Tau^2 = 0.13; Chi^2 = 4.30, df = 1 (P = 0.04); I^2 = 77%). Looking at singular studies, Johnson 1997 , 65 participants, RR 1.15 (Cl 95% 0.85 to 1.54), the result was not statistically significant. On the other hand, in Cornish 2001, 80 participants, RR 0.67 (Cl 95% 0.42 to 1.05), the result was not statistically significant.
For all see Analysis 4.8.

5. Antidepressants versus different class of other medications

Among classes of medication to be compared with antidepressants it was possible to consider dopamine agonists (amantadine and promipexole) and anticonvulsants (carbamazepine, riluzole and tiagabine).

5.1 Dropouts

5.1.1 Dropouts: antidepressants versus dopamine agonists
Four studies (Ciraulo 2005 b; Kolar 1992; Kosten 1992 a; Weddington 1991), 171 participants, RR 1.06 (Cl 95% 0.80 to 1.41), no evidence of difference was shown.
5.1.2 Dropouts: antidepressants versus anticonvulsants
Three studies (Campbell 2003; Ciraulo 2005 b; Winhusen 2005), 162 participants, RR 0.86 (Cl 95% 0.63 to 1.17), no evidence of difference was shown.
For all see Analysis 5.1.

5.2 Craving for cocaine: antidepressants versus dopamine agonists

In these comparisons, mean craving scores obtained by different scales of measures were pooled together and summarized as standardized mean difference.
Three studies (Ciraulo 2005 b; Kolar 1992; Weddington 1991), 86 participants, SMD -0.16 (Cl 95% -0.59 to 0.26), no evidence of difference was shown. See Analysis 5.2.

5.3 Withdrawn due to adverse events: antidepressants versus dopamine agonists

Two studies (Ciraulo 2005 b; Kosten 1992 a), 103 participants, RR 2.48 (Cl 95% 0.38 to 16.19), no evidence of difference was shown. See Analysis 5.3.

6. Different class of antidepressants versus different class of other medications

6.1 Dropouts: SSRIs versus anticonvulsants

Two studies (Ciraulo 2005 b; Winhusen 2005), 66 participants, RR 0.80 (Cl 95% 0.19 to 3.29), no evidence of difference was shown. See Analysis 6.1.

6.2 Use of cocaine continuous measures: SSRIs versus anticonvulsants

6.2.1 Rate of self-reported cocaine use (days/wk) at the end of the treatment

Two studies (Ciraulo 2005 b; Winhusen 2005), 64 participants, MD -0.12 (Cl 95% -1.19 to 0.96), no evidence of difference was shown.

6.2.2 Benzoilecgonine (BE) concentration (endpoint ln of BE values or mean value)

Two studies (Ciraulo 2005 b; Winhusen 2005), 66 participants, MD -0.27 (Cl 95% -1.48 to 0.95), no evidence of difference was shown.

For all see Analysis 6.2.

6.3 Craving for cocaine: SSRIs versus anticonvulsants

Two studies (Ciraulo 2005 b; Winhusen 2005), 66 participants, MD -0.02 (Cl 95% -0.79 to 0.83), no evidence of difference was shown. See Analysis 6.3.

6.4 Addiction Severity Index (ASI) score, Drugs: SSRIs versus anticonvulsants

Two studies (Ciraulo 2005 b; Winhusen 2005), 66 participants, MD -0.00 (Cl 95% -0.05 to 0.04), no evidence of difference was shown. See Analysis 6.4.

7. Desipramine versus Amantadine

Among medications compared with antidepressant, only Amantadine was used in more than one trial (Kolar 1992; Kosten 1992 a; Weddington 1991), in all these trials the evaluated antidepressant was desipramine.

7.1 Dropouts

Three studies (Kolar 1992; Kosten 1992 a; Weddington 1991), 131 participants, RR 0.92 (Cl 95% 0.69 to 1.23), no evidence of difference was shown. See Analysis 7.1.

7.2 Abstinence as abstinence rate in the last week

Two studies (Kolar 1992; Weddington 1991), 43 participants, RR 2.30 (Cl 95% 0.62 to 8.55), no evidence of difference was shown. Both studies were among those with high risk of bias. See Analysis 7.2.

7.3 Craving for cocaine

In this comparison, mean craving scores obtained by different scales of measures were pooled together and summarized as standardized mean difference.

Two studies (Kolar 1992; Weddington 1991), 46 participants, SMD -0.16 (Cl 95% -0.74 to 0.43), no evidence of difference was shown. See Analysis 7.3.

7.4 Mood (BDI)

Two studies (Kolar 1992; Weddington 1991), 46 participants, MD -0.17 (Cl 95% -1.93 to 1.59), no evidence of difference was shown. Both studies were at high risk of bias. See Analysis 7.4.

8. Antidepressant plus psychosocial interventions versus placebo

8.1 Dropouts

8.1.1 Antidepressants plus psychotherapy

17 studies (Ciraulo 2005 b; Elkashef 2006; Gawin 1989; Grabowsky 1995; Hall 1994; Johnson 1997; Jones 2004; Kosten 1992 a; Kosten 2003; McDowell 2005; Oliveto 1999; Poling 2006; Schmitz 2001; Shoptaw 2008; Weddington 1991; Winhusen 2005; Winstanley 2011), 1845 participants, RR 1.10 (Cl 95% 1.01 to 1.20). Evidence of an higher dropout rate of antidepressants-allocated participants was shown.

8.1.2 Antidepressants plus counselling

9 studies (Arndt 1992; Batki 1996; Campbell 2003; Cornish 2001; Giannini 1986; Kolar 1992; Margolin 1995; Nunes 1995; Winstanley 2011), 684 participants, RR 0.99 (Cl 95% 0.70 to 1.40), no evidence of difference was shown. However, a statistically significant result for heterogeneity was shown (Tau^2 = 0.14; Chi^2 = 21.61, df = 8 (P = 0.006); I^2 = 63%). Excluding the most outlier study (Winstanley 2011), remaining eight studies, 589 participants, RR 0.89 (Cl 95% 0.72 to 1.09), the result was still not statistically significant. On the other hand Winstanley 2011, 95 participants, RR 1.70 (Cl 95% 1.14 to 2.53), showed a statistically significant result in favour of placebo. Excluding studies with high risk of bias, remaining three studies (Cornish 2001; Giannini 1986; Nunes 1995), 213 participants, RR 0.97 (Cl 95% 0.68 to 1.38), no evidence of difference was shown.

See Analysis 8.1

8.2 Retention in treatment as mean number of weeks in treatment

8.2.1 Antidepressants plus psychotherapy

Four studies (Gawin 1989; Hall 1994; Shoptaw 2008; Winstanley 2011), 237 participants, RR 0.92 (Cl 95% 0.16 to 1.68), Evidence of an higher retention in treatment of antidepressants-allocated participants was shown.

8.2.2 Antidepressants plus counselling

Three studies (Cornish 2001; Kolar 1992; Winstanley 2011), 174 participants, RR -1.92 (Cl 95% -6.09 to 2.24), The analysis showed a statistically significant result for heterogeneity (Tau^2 =

7.46; Chi² = 5.17, df = 1 (P = 0.02); I² = 81%). Only two studies contributed to this analysis since Kolar 1992 standard deviation for the antidepressant group was zero. Looking at singular studies, Cornish 2001, 80 participants, MD -0.10 (Cl 95% -1.30 to 1.10), did not show a statistically significant result, while Winstanley 2011, 77 participants, MD -4.40 (Cl 95% -7.91 to -0.89), showed a statistically significant result in favour of placebo.
See Analysis 8.2

8.3 Abstinence as people abstinent for at least three consecutive weeks

8.3.1 Antidepressants plus psychotherapy
Five studies (Elkashef 2006; Gawin 1989; Giannini 1987 a; McDowell 2005; Shoptaw 2008), 544 participants, RR 1.30 (Cl 95% 0.89 to 1.88), no evidence of difference was shown.
8.3.2 Antidepressants plus counselling
two studies (Campbell 2003; Nunes 1995), 188 participants, RR 1.44 (Cl 95% 0.84 to 2.48), no evidence of difference was shown.
See Analysis 8.3.

8.4 Adverse events as withdrawn due to adverse events

8.4.1 Antidepressants plus psychotherapy
Seven studies (Ciraulo 2005 b; Elkashef 2006; Johnson 1997; Kosten 1992 a; McDowell 2005; Winhusen 2005; Winstanley 2011), 701 participants, RR 1.81 (Cl 95% 0.91 to 3.58). Even though not statistically significant, the difference shown by the analysis was in favour of placebo.
8.4.2 Antidepressants plus counselling
Six studies (Arndt 1992; Batki 1996; Kolar 1992; Margolin 1995; Nunes 1995; Winstanley 2011), 485 participants, RR 1.60 (Cl 95% 0.74 to 3.47), no evidence of difference was shown.
See Analysis 8.4

9. Antidepressants versus placebo: Participants also opioid dependent

9.1 Dropouts

Ten studies (Arndt 1992; Grabowsky 1995; Kolar 1992; Kosten 1992 a; Kosten 2003; Margolin 1995; O'Brien 1988; Oliveto 1999; Poling 2006; Winstanley 2011), 1006 participants, RR 1.22 (Cl 95% 1.05 to 1.41), Evidence of a higher dropout rate of antidepressants-allocated participants was shown. See Analysis 9.1.

9.2 Adverse events as withdrawn due to adverse events

Five studies (Arndt 1992; Kolar 1992; Kosten 1992 a; Margolin 1995; Winstanley 2011), 492 participants, RR 2.47 (Cl 95% 1.03 to 5.90), the evidence was in favour of placebo. See Analysis 9.2.

10. Antidepressants versus placebo according to the length of trials

10.1 Dropouts

10.1.1 Dropouts: up to six weeks of treatment
Six studies Cornish 2001; Gawin 1989; Giannini 1986; Giannini 1993; Johnson 1997; Tennant 1985;), 282 participants, RR 0.80 (Cl 95% 0.56 to 1.15), no evidence of difference was shown.
10.1.2 Dropouts: more than six weeks of treatment
25 studies (Arndt 1992; Batki 1996; Campbell 2003; Ciraulo 2005 a; Ciraulo 2005 b; Elkashef 2006; Grabowsky 1995; Hall 1994; Jenkins 1992; Jones 2004; Kolar 1992; Kosten 1992 a; Kosten 2003; Margolin 1995; McDowell 2005; McElroy 1989; Nunes 1995; O'Brien 1988; Oliveto 1999; Poling 2006; Schmitz 2001; Shoptaw 2008; Weddington 1991; Winhusen 2005; Winstanley 2011), 2671 participants, RR 1.09 (Cl 95% 0.99 to 1.20). Although not statistically significant, the difference shown by the analysis was in favour of placebo. To be noticed a statistically significant result for heterogeneity, although not relevant (Tau² = 0.02; Chi² = 42.76, df = 26 (P = 0.02); I² = 39%).
See Analysis 10.1.
To be noticed that because of RevMan limitation to the choice of different effect model for subgroups, Analysis 10.1 shows results with a random effect model for both subgroups (10.1.1 and 10,1.2).

10.2 Retention in treatment: more than six weeks of treatment

Six studies (Hall 1994; Jenkins 1992; Kolar 1992; Lambert Passos 2005; Shoptaw 2008; Winstanley 2011), 577 participants, MD 0.33 (Cl 95%0.20 to 0.46). The evidence is in favour of antidepressants. See Analysis 10.2.

10.3 Abstinence for at least three consecutive weeks: more than six weeks of treatment

Six studies (Campbell 2003; Elkashef 2006; Lambert Passos 2005; McDowell 2005; Nunes 1995; Shoptaw 2008), 874 participants, RR 1.10 (Cl 95% 0.87 to 1.39), no evidence of difference was shown. See Analysis 10.3

10.4 Withdrawn due to adverse events: more than six weeks of treatment

Eleven studies (Arndt 1992; Batki 1996; Ciraulo 2005 b; Elkashef 2006; Kolar 1992; Kosten 1992 a; Lambert Passos 2005; Margolin 1995; McDowell 2005; Nunes 1995; Winstanley 2011), 1298 participants, RR 1.34 (Cl 95% 0.87 to 2.07), no evidence of difference was shown. See Analysis 10.4

11. Antidepressants vs placebo excluding medication with questionable or uncertain antidepressant activity

To take account of the uncertainty in the antidepressant activity for some of the included medications, in this subgroup analysis we included only medications approved for major depressive or dysthymic disorder by the US, Canadian, or European Union drug regulatory agencies, therefore excluding trials involving buspirone (Giannini 1993, gepirone (Jenkins 1992) and tryptophan (Jones 2004).

11.1 Dropouts

28 studies (Arndt 1992; Batki 1996; Campbell 2003; Ciraulo 2005 a; Ciraulo 2005 b; Cornish 2001; Elkashef 2006; Gawin 1989; Giannini 1986; Grabowsky 1995; Hall 1994; Johnson 1997; Kolar 1992*; Kosten 1992 a; Kosten 2003; Margolin 1995*; McDowell 2005; McElroy 1989; Nunes 1995; O'Brien 1988; Oliveto 1999; Poling 2006; Schmitz 2001; Shoptaw 2008; Tennant 1985; Weddington 1991; Winhusen 2005*; Winstanley 2011), 2547 participants, RR 1.03 (Cl 95% 0.92 to 1.16), no evidence of difference was shown. To be noticed in this comparison a statistically significant, although of low degree, result for heterogeneity (Tau^2 = 0.03; Chi^2 = 47.24, df = 29 (P = 0.02); I^2 = 39%). See Analysis 11.1

27 studies (Arndt 1992; Batki 1996; Campbell 2003; Ciraulo 2005 a; Ciraulo 2005 b; Cornish 2001; Elkashef 2006; Gawin 1989; Giannini 1986; Giannini 1993; Hall 1994; Jenkins 1992; Johnson 1997; Jones 2004; Kosten 1992 a; Kosten 2003; McDowell 2005; McElroy 1989; Nunes 1995; O'Brien 1988; Oliveto 1999; Poling 2006; Schmitz 2001; Shoptaw 2008; Tennant 1985; Winhusen 2005; Winstanley 2011), 2417 participants, RR 1.05 (Cl 95% 0.97 to 1.14). Again there was no evidence that antidepressants are associated with a higher or lower rate of participants leaving the treatment. In this analysis, Arndt 1992, Batki 1996, Campbell 2003; Gawin 1989 and O'Brien 1988 were included, although judged with high risk of bias for the incomplete outcome data addressing, since the incompleteness does not refer to data required to evaluate retention in treatment.

11.2 Retention in treatment as mean number of week in treatment

Seven studies (Cornish 2001; Gawin 1989; Hall 1994; Kolar 1992; Lambert Passos 2005; Shoptaw 2008; Winstanley 2011), 664 participants, MD 0.29 (Cl 95% -0.41 to 1.00). To be noticed a statistically significant result for heterogeneity (Tau^2 = 0.33; Chi^2 = 11.12, df = 5 (P = 0.05); I^2 = 55%). Excluding the study most outlier (Winstanley 2011), remaining six studies, 519 participants, MD 0.35 (Cl 95% 0.23 to 0.48), evidence of an higher retention in treatment favouring antidepressants was shown. On the other hand, Winstanley 2011, 145 participants, MD -2.98 (Cl 95% -5.47 to -0.49), showed a statistically significant difference result in favour of placebo. Excluding studies with high risk of bias, remaining five studies (Cornish 2001; Hall 1994; Lambert Passos 2005; Shoptaw 2008; Winstanley 2011), 599 participants, MD 0.33 (Cl 95% 0.20 to 0.46), the evidence was in favour of antidepressants. See Analysis 11.2.

11.3 Abstinence as number of weeks of continuous abstinence

Six studies (Carroll 1994; Elkashef 2006; Kosten 2003; Lambert Passos 2005; Shoptaw 2008; Weddington 1991), 883 participants, MD 0.08 (Cl 95% -0.17 to 0.32), no evidence of difference was shown. See Analysis 11.3.

11. Funnel plots

We visually inspected funnel plots related to the primary outcomes: dropouts and abstinence. While funnel plot of dropouts looked roughly symmetrical, the one on abstinence may be suggestive for some degree of publication bias. See Figure 7 and Figure 8.

Figure 7. Funnel plot of comparison: 1 Antidepressants vs placebo according to any definition, outcome: 1.1 Dropout.

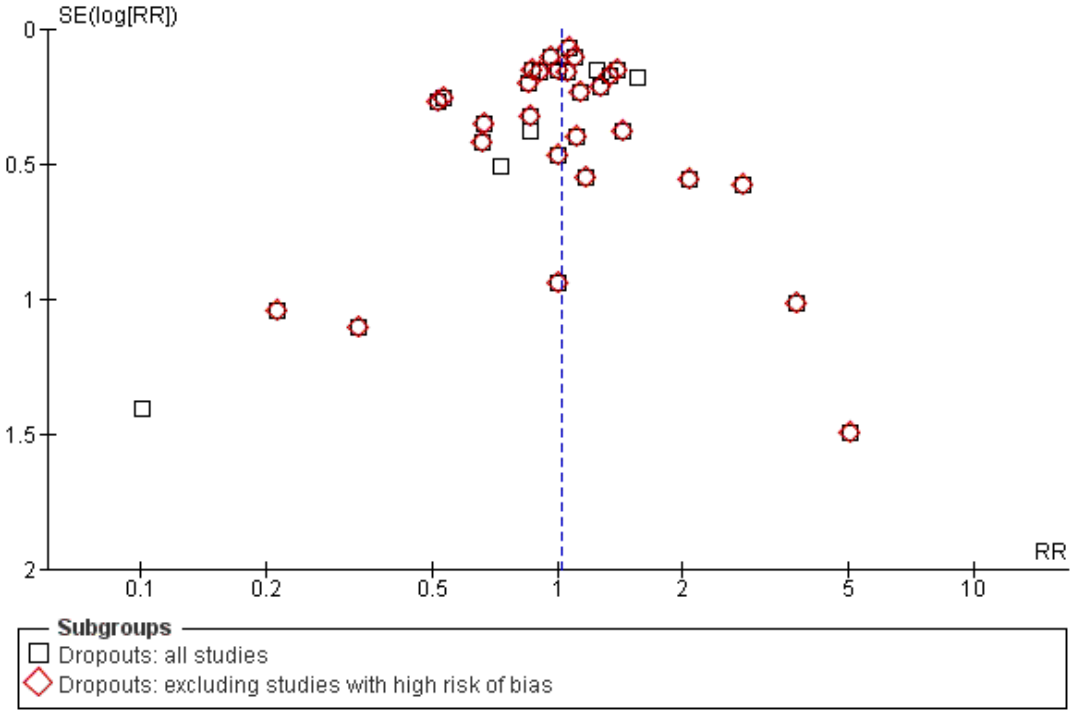
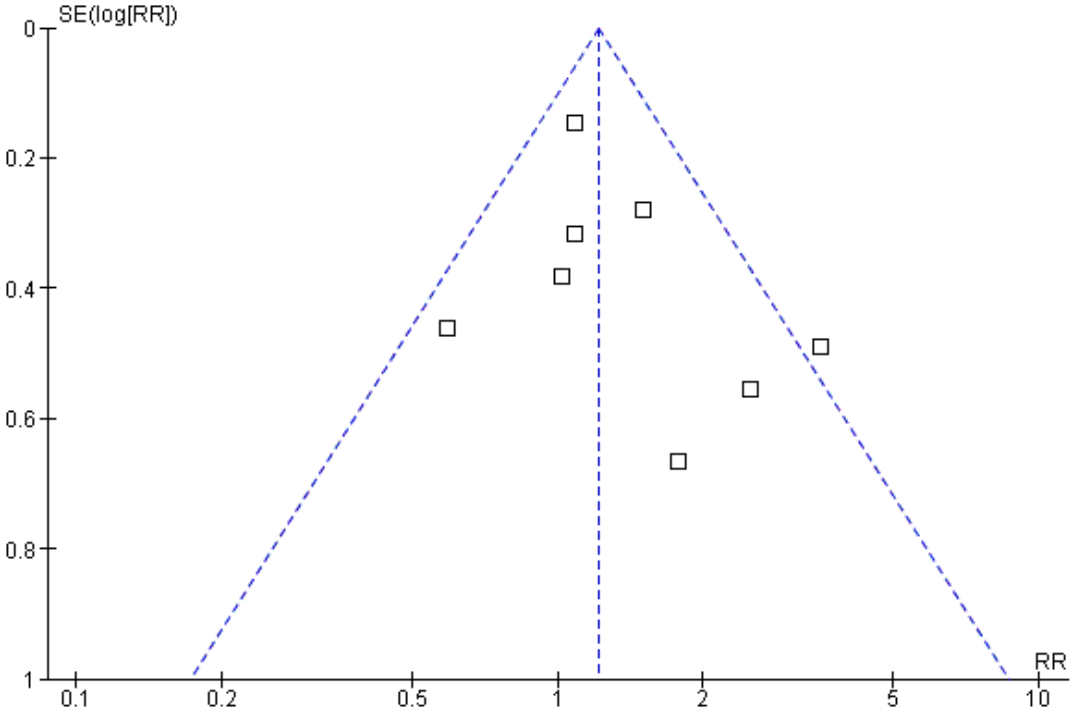


Figure 8. Funnel plot of comparison: 1 Antidepressants vs placebo according to any definition, outcome: 1.3 Abstinence, for at least three consecutive weeks.



DISCUSSION

Summary of main results

Cocaine addiction is a major public health problem that is characterized by recidivism and a host of medical and psychosocial complications (EMCDDA 2009). Despite decades of efforts done to find effective treatments, the considerable advances in the neurobiology of this disorder have not been followed by the discover of pharmacological treatment of proved efficacy.

Given the property of antidepressants to increase monoamine levels, their use has been proposed in cocaine addiction to revert the down-regulation of monoaminergic system characterizing chronic cocaine abuse. Other commonalities between pathophysiology of cocaine use disorders and mood disorders may indicate the potential efficacy of antidepressants. Several antidepressants with different profile have been studied, such as tricyclics, MAOs, SSRI, NARI and other new compounds. In this review we have included 37 studies, selected according to pre-established criteria.

Although all selected studies are RCTs comparing antidepressants versus placebo or other medications, they differ for design, quality, characteristics of patients, tested medication, services and treatments delivered:

- the length of the studies varied, with one study lasting 25 weeks, two 16 weeks, one lasting 13 weeks, twenty 12 weeks, one 10 weeks, six 8 weeks, three 6 weeks, two 4 and one 2 weeks.
- 27 were based on formal diagnostic DSM criteria for cocaine dependence, while 10 enrolled patients with other or uncertain diagnoses (cocaine use, combination of free-base cocaine and phencyclidine abuse, not otherwise specified cocaine addiction, cocaine abuse or dependence, not otherwise specified cocaine dependence);
- the antidepressant evaluated in the 37 studies, all placebo controlled, was: desipramine in 17 trials; fluoxetine in five trials; bupropion in three trials; nefazodone and ritanserin in two trials each; buspirone, gepirone, paroxetine, citalopram, venlafaxine, selegiline, tryptophan, sertraline, and imipramine in one trial each;
- 7 of the above studies compared also antidepressants with other medications: amantadine in three trials; carbamazepine, lithium carbonate, pentoxifylline, riluzole, pramipexole,

donepezil or tiagabine in one trial each.

- 10 studies involved subjects co-treated with methadone (nine trials) or buprenorphine (two trials). In one study patients were concomitantly treated with bromocriptine;
- 22 studies assessed medication compliance trough plasma concentrations; 2 studies adding riboflavine to medication and placebo; 5 studies trough the return of unused medications; 2 studies trough supervision of the ingestion of medication. For 9 studies the information was not available.
- 4 studies did not report on the presence of concomitant associated psychosocial treatment. The remaining 33 associated:
    - Cognitive Behavioral Psychotherapy or Relapse Prevention Therapy in 14 trials;
    - Interpersonal Psychotherapy in 3 trials;
    - Counselling in 12 trials;
    - Contigency Management in 3 trials;
    - Not Otherwise Specified Psychotherapy in 2 trials;
- in four studies participants were hospitalised at the beginning of the study; all the other were outpatient studies;
- all the studies, except one, were conducted in USA.

Looking at the effects of interventions, it has to be considered that studies differ also for outcome variables and their definition, conditioning the possibility to pool together data and carry out meta-analyses.

Antidepressants versus placebo

Considering comparisons between antidepressants and placebo, the following results were obtained:

Dropouts: it was possible to pool data from 31 studies, 2819 participants. The result of meta-analysis did not show evidence of difference between antidepressant and placebo. Excluding studies with not operationally defined cocaine dependence as well as those with high risk of bias, the result did not change. Excluding studies involving medications with questionable or uncertain antidepressant activity, again the result did not change. Looking at specific classes of antidepressants (SSRI), a statistically significant difference was seen in favour of placebo. This difference was not observable anymore after the exclusion of studies with high risk of bias.

Looking at the average number of weeks of treatment, eight studies and 705 participants, MD 0.34 (Cl 95% 0.22 to 0.47), the evidence was in favour of antidepressants. This result was confirmed including only studies which used operationally definitions of cocaine dependence and excluding studies with high risk of bias, as well as excluding studies involving medications with questionable or uncertain antidepressant activity. Considering only tricyclics (desipramine), three studies,159 participants, again the result was statistically significant in favour of antidepressants.

Abstinence from cocaine use: the result of meta-analysis did not show a statistically significant difference between antidepressant and placebo, although a trend for statistical significance favouring antidepressant was shown in the three-weeks abstinence rate (eight studies, 942 participants, RR 1.22 (Cl 95% 0.99 to 1.51). Moreover, considering only studies involving tricyclics, five studies, 367 participants, or only desipramine, four studies, 254 participants, this result was statistically significant in favour of antidepressants. However, selecting only studies with operationally defined criteria for cocaine dependence, this significance, as well as the trend for significance shown by the full sample, disappeared.

Looking at continuous measures of abstinence, meta-analyses considering the average number of weeks of continuous abstinence, seven studies, 1062 participants, did not show evidence of difference between antidepressants and placebo. The result did not substantially change after the exclusion of studies not operationally defining cocaine dependence as criteria for the allocation of participants or excluding studies involving medications with questionable or uncertain antidepressant activity. Considering only studies involving tricyclics (desipramine), three studies, 308 participants, the difference shown by the analysis, even though not statistically significant, was in favour of desipramine.

Use of cocaine: As regards to the use of cocaine during the trial, evaluated as number of participants using cocaine (ascertained by both self reports or urinalyses), four studies, 251 participants, no evidence of difference was shown. The result, did not substantially change after the exclusion of studies not operationally defining cocaine dependence, as well as considering only studies on tricyclics (desipramine).

Measures of craving: looking at meta-analysis carried out on craving scores, nine studies, 636 participants, the result did not show evidence of difference between antidepressants and placebo. These results were also confirmed looking at specific classes of antidepressants (tricyclics or SSRIs).

Addiction Severity Index (ASI): looking at ASI composite scores, the results of meta-analyses, carried out including seven studies and more than 600 participants, did not show evidence of differences. The exclusion of studies with high risk of bias did not change the results.

Depression severity: As regards to mood changes (Severity of depression measured as the mean by group HDRS total score at the end of the study), it was possible to pool results from six studies, 420 participants. There was evidence that antidepressants are more effective than placebo on this measure of mood depression. Looking at CGI depression severity, three studies, 390 participants, the result did not show evidence of difference.

Adverse events:Looking at safety issues, overall, studies investigating the subject, thirteen studies, 1396 participants, failed in showing evidence of differences in the number of patients withdrawn for medical reasons. The result did not change including only studies with operationally defined cocaine dependence or excluding studies involving medications with questionable or uncertain antidepressant activity. Considering different classes of antidepressants (SSRIs) or specific antidepressants (fluoxetine) the result was statistically significant in favour of placebo.

No evidence of difference was seen in the number of patients reporting other adverse events in 37 out of 38 comparisons for different adverse events (ten studies, 866 participants). In the remaining comparison, the result was statistically significant in favour of placebo. Sensitivity analyses performed excluding studies with diagnoses other than cocaine dependence or with uncertain diagnoses did not substantially change the results.

Other subgroup analyses

Given the heterogeneity of measures defining confounders/moderators and the lack of data needed for proceeding with meta-analyses, only some potentially confounding factors were considered in subgroup analysis (scheduled length of the trial, associated opioid dependence, associated psychosocial interventions). Looking at primary outcomes (dropout rate, cocaine use or withdrawing for medical problems):

- a statistically significant higher dropout rate, favouring placebo, was observed in trials associating psychotherapy;
- a statistically significant higher dropout rate and withdrawn due to adverse events, favouring placebo, was observed in trials involving associated opioid dependence;

Data available did not allow us to take into account factors such as dose of medication, severity of depression, severity of dependence, environmental conditions. See Summary of findings for the main comparison for an overall synthesis of the most relevant outcomes.

Antidepressants versus other drugs

Considering comparisons between antidepressants and other medications, globally no evidence was seen.

Overall completeness and applicability of evidence

Besides the limits in external validity due to the general requirement of RCTs in terms of strict inclusion criteria, highly homogenous study groups, limitations in dose adjustment, etc., the types of participants (adults abusers/dependents on cocaine or on cocaine and opioids) are quite representative of the general population of cocaine addicts. Moreover, the interventions (antidepressant dosages, medication for concurrent opioid addiction), the settings (prevailing outpatient treatment) and the outcomes investigated (retention in treatment, cocaine use, adverse events) are important to populations, practitioners and decision makers, and relevant for the context of current practice. However, an important limitation to the generalization of the evidence is the location of the study. Despite the systematic bibliographic search, only one out of 37 included studies was conducted out of the USA. In regard to this it should be considered that different social contests can influence differently the severity of dependence and the availability to enter an experimental design and 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

For the evaluation of quality of the evidence, supplementary information was collected from the authors of the studies. Altough the strength of the review, due to the inclusion of 37 studies and 3551 participants, from a methodological perspective the overall quality of the included studies was low: although about 78% were double blind studies, only 47% were judged with low risk of bias for the sequence generation, 36% for the allocation concealment and 30% for outcome data addressing. Moreover 25% of studies did not specify on how compliance with medication intake was monitored. However, excluding studies with high risk of bias from the analysis comparing antidepressants versus placebo for the evaluation of relevant outcomes such as retention in treatment and cocaine use, the number of studies and of participants remained high without substantially changing the results. Therefore, the overall quality of the evidence for the efficacy of antidepressants versus placebo evaluated using primary outcomes may be judged as moderate. However, moving to subgroup analysis, such is the case of single classes of antidepressants (SSRIs) and of the majority of single types of medications, the finding of the review are limited by the small number of studies included in the meta-analysis of most study outcomes. Therefore the precision of the calculated effects is low. See Summary of findings for the main comparison. Finally, the great heterogeneity of the scales used in the primary studies and the way in which results were reported made often not possible to undertake a cumulative analysis.

Potential biases in the review process

Reporting bias can jeopardize the validity of any meta-analysis. We have tried to limit the influence of reporting bias by screening several data sets and requesting unpublished results to the contact authors. Proceeding that way has resulted in a substantial increase in the available data. We have also carried out funnel plots related to the primary outcomes: dropouts and abstinence. The one on abstinence may be suggestive for some degree of publication bias. See Figure 7 and Figure 8.

Agreements and disagreements with other studies or reviews

The interest in the pharmacological treatment of cocaine dependence has increased in the last 25 years. Results from first studies have suggested antidepressants could be helpful in the process of withdraw from cocaine use (Gawin 1984 a; Tennant 1985 Giannini 1986). Since then, randomised controlled trials have addressed the issue of clinical efficacy for a range of antidepressants, particularly desipramine, but more recently other medications such as fluoxetine, bupropion, nefazodone and other. A meta-analysis of desipramine for the treatment of cocaine addiction (Levin 1991), including seven randomised studies with a total

of 200 patients, found that desipramine is no better than placebo in retaining patients in treatment. However, it was also suggested that while patients were in treatment, desipramine is helpful in promoting abstinence (data from six trials). A preceding version of this Cochrane review (Silva de Lima 2003), including 18 RCTs and involving 1177 subjects suggest lack of evidence regarding the efficacy of antidepressants comparing to placebo. The conclusion of the review was that at the current stage of evidence, there was no data supporting the efficacy of antidepressants for cocaine dependence and antidepressants were not judged promising as a mainstay of treatment for unselected cocaine abusers. More recently, another systematic reviews evaluating pooled data with meta-analyses has been published (Torrens 2005). Although carried out on the base of pre-established criteria for searching literature, selecting studies and assessing their risk of bias, this review was not specifically designed for evaluating the efficacy and safety of antidepressant treatment in cocaine use disorders, it did not apply Cochrane criteria for systematic reviews, and did not consider dropout as a primary outcome. This review, looking at the efficacy of antidepressants in patients without comorbid depression (14 trials), failed in showing a statistically significant difference between SSRIs and placebo in terms of reduction of cocaine consumption (two studies, 120 participants (OR 0.50 (CI 95% 0.22 to 1.13)), while showing a statistically significant difference in favour of antidepressants, when comparing the other included antidepressants (desipramine, imipramine, bupropione and gepirone) with placebo (seven studies, 338 participants (OR 1.85 (CI 95% 1.06 to 3.22)). Moreover, looking at patients with comorbid depression (five studies) failed in showing statistically significant difference between antidepressants and placebo both in terms of antidepressant activity (two studies, 137 participants) or of cocaine use (three studies, 151 participants). Overall, this review does not provide consistent data for the use of antidepressant medication in cocaine addiction.

Our decision to include dropout in the review, which is consistent with inclusion criteria adopted in the previous version of this review (Silva de Lima 2003) is based on the established evidence that leaving the treatment and relapsing in addictive behaviour is a very common event in a drug addict's life (Daley 1993; McLellan 2000), while staying in treatment protects against consequences of drug addiction and is associated with positive outcomes (Ball 1991; Davoli 2007). Consequentely the ability of treatment programs to retain patients in treatment may be considered a primary goal in the addiction field. The difficulties of persons with addictive disorders to remain in treatment and to comply with it represents also a relevant methodological problem to manage in clinical trials (Nunes 1997; Nich 2002). On the whole, the results we obtained on this outcome, consistent with that on the number of patients withdrawn for medical reasons, does not show substantial difference between antidepressants and placebo. However, looking at specific classes of antidepressants (SSRI), at trials involving associated treatment for opioid dependence, as well as at trials involving associated psychotherapy, a statistically significant difference in favour of placebo was seen. While in the case of associated treatment for opioid dependence, an higher dropout rate in the antidepressant-treated patients might require the investigation of possible pharmacological interference (Kapur 2011), we do not have plausible explanations for the increasing of dropouts in patients treated with SSRIs or exposed to psychotherapy.

The issue of the preferential or selective efficacy of antidepressants not only on depression but also on cocaine use in cocaine addicts with depression has been considered by some studies (Ziedonis 1991; Ziedonis 1991a; Torrens 2005; Carroll 1994; Margolin 1995; Weddington 1991). Looking at our review, partially positive results obtained by antidepressants on mood-related outcomes, which are consistent with the primary effect of antidepressants, do not seem to associate whit an effect on primary outcomes (dropout, cocaine use, side effects). Looking at primary studies, some trials performed ex post exploratory analyses on this outcomes (Carroll 1994; Margolin 1995; Weddington 1991), reporting no consistent results; other trials stratified for depressive status (Jones 2004; Nunes 1995) or considered depression an inclusion criteria (Ciraulo 2005 a; McDowell 2005; Schmitz 2001). Unfortunately, the limited usable data coming from these studies prevented us from considering mood depression as a confounding/modifying factor in subgroup analysis. Some ongoing trials considering this issue (Afshar 2006; Nunes 2005; Oliveto 2006; Raby 2005; Schmitz 2005b) will help to be more conclusive on this point in the future.

AUTHORS' CONCLUSIONS

Implications for practice

Although the efficacy of antidepressants has been suggested in individual studies, at the current stage of evidence data do not support their efficacy in the treatment of cocaine abuse/dependence. Positive results obtained on secondary outcome measures, such as depression severity, do not seem to be associated with an effect on direct indicators of cocaine abuse/dependence such as dropout and use of primary substance of abuse. Since data available did not allow us to investigate in subgroup analysis the presence of mood depression, we cannot be conclusive on their efficacy on cocaine abuse/dependence in patients with comorbid depression.

In spite of the presence of still ongoing studies, antidepressants cannot be considered a mainstay of treatment for unselected cocaine abusers. Based on the lack of data, we have not reasons to preclude or recommend the use of antidepressants for the treatment of cocaine dependence in patients with comorbid depression, although the same use in cocaine dependents treated with opioid agonists for opioid dependence should be weight against the risk of dropout.

Even the association of antidepressants with a more potent psychosocial intervention, which, in the lack of evidence, was suggested by the preview Cochrane review (Silva de Lima 2003), is not supported by our results.

Implications for research

Some considerations may be done in the light of the results of this review.

First, there is no evidence that desipramine, the most investigated tricyclic antidepressant (17 trials) would be effective for the treatment of cocaine abuse/dependence. Continuing research on this compound should not be encouraged.

Second, it seems that the generic belonging to the antidepressants pharmacological classes is not a good reason for testing medications in clinical trials for the treatment of cocaine abuse/dependence.

Tird, the issue of the efficacy of antidepressants for patients with cocaine dependence and comorbid depressive disorder deserve further investigation.

Finally, considering the discouraging results obtained with antidepressants, in front of the multitude of potential beneficiaries from an effective treatment and the constrains of financial resources, a severe evaluation on the relevance of new research proposal, in terms of scientific plausibility supporting its supposed efficacy and of preclinical and clinical available evidence, should guide future research.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Arndt 1992

Methods	Randomised placebo controlled double blind trial
Participants	79 subjects on methadone maintenance treatment; mean age 40.5 years; male 100%; 90% African-American; 53% high school diploma; 35% married; 3 years of cocaine use on the average; 83% using cocaine I.V. 51% meeting DSM-III criteria for antisocial personality disorder Inclusion criteria: being 20-50 years old; being in methadone maintenance treatment for at least one month; meeting the criteria for a DSM-III cocaine abuse disorder lasting at least three months; showing cocaine positive urines samples in the last month; Exclusion criteria: having any medical condition contraindicants desipramine treatment;
Interventions	(1) desipramine plus methadone, 53 participants; (2) placebo plus methadone, 26 participants Drug dose: desipramine 250-300 mg/day; methadone 45 mg/day on the average Participants were required to meet with counsellor at least twice at month. Social work service, employment counselling, psychiatric and medical care were part of the standard clinical services Setting: outpatient. Duration 12 weeks. Country of origin: USA.
Outcomes	Dropout; side effects; craving for cocaine (self administered cocaine craving scale); ASI results (McLellan 1985); BDI results (Beck 1972); DIS results (Robins 1981); cocaine use (13-items QCI; urine toxicology screenings).
Notes	Characteristic of the participants are related to the 59 subjects who completed the trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomisation in a 2:1 ratio active medication versus placebo". No further details given
Allocation concealment (selection bias)	Unclear risk	The method of concealment is not described.
Blinding (performance bias and detection bias) Subjective	Low risk	Double blind stated; solutions adopted to protect blindness.
Blinding (performance bias and detection bias) Objective	Low risk	Double blind stated; solutions adopted to protect blindness.

Arndt 1992 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	Only data from patients completing the study treatment were used in the statistical analysis

Batki 1996

Methods	Randomised placebo controlled double blind trial
Participants	Participants: 32 subjects; mean age 34.3 years; male 66%; African-American 53%; 13 years of education on the average; 47% employed; 32% with lifetime major depressive disorder according to DSM-III-R criteria; 21% with antisocial personality disorder according to DSM-III-R criteria, 21% with current alcohol abuse/dependence; 31 subjects smoked the crack form of cocaine; 1 used intravenous cocaine Inclusion criteria: meeting DSM-III-R criteria for current cocaine dependence (SCID Interview, Spitzer 1990); being in treatment at STOP (Stimulant Treatment Out-Patient Program, San Francisco) for at least 2 weeks, yet continuing to use cocaine (cocaine positive urine drug test during the previous week or at least two positive urines within last month, or a self-report of cocaine use at least 2 days in the past week or 10 days in the past month) Exclusion criteria: bipolar disorder or psychosis.
Interventions	(1) fluoxetine, 16 participants; (2) placebo, 16 participants Drug dose: fluoxetine up to 40 mg/day. STOP program consisted of group counselling session 3-5 days/week and weekly individual counselling. Subjects were reimbursed $ 10.00 for the intake and each of the weekly assessments Setting: outpatient Duration: 12 weeks. Country of origin: USA
Outcomes	Primary outcomes: weekly quantitative measures of cocaine and BE urine concentration; retention; self-report of cocaine use (cocaine use measured as: weekly frequency, amount, route of cocaine use, using the QCI (Batki 1993)). Secondary outcomes: cocaine craving (quality of high and amount of control over craving); depression and anxiety measured by the HDRS (Hamilton 1960) and the HARS (Hamilton 1959).
Notes	All outcomes, but no retention in treatment, were evaluated at the week 6 because of the high drop out rates on placebo group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided.

Batki 1996 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	The method of concealment is not described.
Blinding (performance bias and detection bias) Subjective	Low risk	Double blind stated; medications were identical in appearance and taste
Blinding (performance bias and detection bias) Objective	Low risk	Double blind stated; medications were identical in appearance and taste
Incomplete outcome data (attrition bias) All outcomes	High risk	All outcomes, but not retention in treatment, were evaluated at the week 6 because of the high drop out rates on placebo group; No intent-to-threat analysis: only data from patients completing 2 weeks of treatment (29 subjects) were addressed for urine and plasma scores, and only data from 28 subjects were included in the score of self-report of cocaine use

Campbell 2003

Methods	Randomised placebo controlled double blind trial
Participants	Participants: 146 subjects; mean age 33.5 years; male 74.5%; African-American 84%; 38% with 11 or more years of education; married 10%; on probation/parole 54%; 28% with current major depression; 38% with Antisocial personality Disorder. Inclusion criteria: cocaine dependence (DSM-III-R); no further specification were given Exclusion criteria: psychosis; organic brain syndromes; suicidal or homicidal ideation; unstable medical disorders
Interventions	(1) desipramine, 49 participants; (2) carbamazepine, 47 participants; (3) placebo, 50 participants Drug dose: desipramine up to 200 mg/day; carbamazepine up to 800 mg/day One hour of individual or family counselling per week was offered. Setting: Outpatient. Duration: 8 weeks. Country of origin: USA.
Outcomes	Retention in treatment; urine toxicology; subjective and behavioral factors related to cocaine craving as measured by Hal-DIRS (Halikas 1991)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Campbell 2003 (*Continued*)

Random sequence generation (selection bias)	Low risk	The subjects were randomised according to a computer-generated list
Allocation concealment (selection bias)	Low risk	The randomisation list was held by the investigational pharmacy, where the medication or placebo was packaged and dispensed. When the subject completed screening and met inclusion and not exclusion criteria, the investigational pharmacy was notified that a subject was ready, and the pharmacy prepared the study drug or placebo according to the randomisation list, and delivered the appropriate study drug for the subject. None of the investigators or study staff who interacted with, or assessed the subjects, had contact with the pharmacy
Blinding (performance bias and detection bias) Subjective	Low risk	Double blind stated; procedures adopted to protect blindness
Blinding (performance bias and detection bias) Objective	Low risk	Double blind stated; procedures adopted to protect blindness
Incomplete outcome data (attrition bias) All outcomes	High risk	Intent to treat analysis was undertaken. Reasons for drop out was not reported by medication group. Many of the analyses included only subjects who remained in the clinical trial for a minimum of two weeks

Carroll 1994

Methods	Randomised placebo controlled double blind trial
Participants	110 participants; mean age 29 years; male 72%; college education 34%; 47% unemployed; using 4.5 grams of cocaine grams per week on the average; 4.2 years of regular cocaine use on the average; 61% predominantly using freebase cocaine; 48% meeting DSM-III-R lifetime criteria for antisocial personality, 64% for any other personality disorder, 49% for alcohol dependence, 20% for affective disorder, and 12% for anxiety disorder. Inclusion criteria: meeting current DSM-III-R current criteria for cocaine dependence, using SCID interview (Spitzer 1985); reporting the use at least 12 grams of cocaine during the past 3 months. Exclusion criteria: having a current physical dependence for opiates, barbiturates, alcohol, or other principal drug of dependence; meeting current DSM-III-R criteria for an Axis I disorder other than depressive or anxiety disorders; meeting lifetime criteria for

	schizophrenia or mania; expressing significant suicidal or homicidal ideation; having a current medical condition that would contraindicate ambulatory tricyclic antidepressant therapy; having been treated for substance abuse during the previous 2 months; being currently involved in psychotherapy or pharmacotherapy for any other psychiatric disorder; having condition or probation or parole requiring reports of drug use to officers of the court
Interventions	(1) desipramine plus clinical management, 25 participants; (2) placebo plus clinical management, 27 participants; (3) desipramine plus relapse prevention, 29 participants; (4) placebo plus relapse prevention, 29 participants Drug dose: desipramine up to 300 mg/day. Clinical management (with supportive psychotherapy) was delivered in weekly individual sessions, manual guided according to Fawcett 1987. Relapse prevention (cognitive-behavioral treatment) was delivered in weekly individual sessions, manual guided according to Carrol 1991. Setting: Outpatient. Duration: 12 weeks. Country of origin: USA.
Outcomes	Primary outcomes: reduction in frequency of cocaine use; duration of longest period of consecutive abstinence while in treatment (subjects' self-reports verified through urine toxicology screens obtained at every visit) Secondary outcomes: general functioning and multidimensional outcome measured with ASI (McLellan 1980); depressive symptoms measured with BDI (Beck 1972) and HDRS (Hamilton 1960).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Unclear risk	The method of concealment is not described.
Blinding (performance bias and detection bias) Subjective	Low risk	Double blind stated; procedures adopted to protect blindness
Blinding (performance bias and detection bias) Objective	Low risk	Double blind stated; procedures adopted to protect blindness
Incomplete outcome data (attrition bias) All outcomes	High risk	Intention-to-treat and end-point analyses were undertaken, but presented only those carried out on subjects who received some exposure to treatment (one week)

		No details on withdrawn by group for medical reasons was given

Ciraulo 2005 a

Methods	Randomised placebo controlled double blind trial
Participants	69 subjects; mean age 40.4 years; male 71%; African-American 69.6%; ASI results: days cocaine use past 30 days, 15.8 on the average; years of cocaine use, 12 on the average; ASI employment status, 0.67 on the average; ASI psychiatric status, 0.41 on the average; ASI alcohol use, 0.22 on the average; 68.1% with Major depressive Disorder Inclusion criteria: age between 21 and 55 years; scoring 12 or higher on the HDRS scale (Hamilton 1967); meeting DSM-IV criteria for cocaine dependence according to SCID interview (First 1996); providing at least one urine positive for benzoylecgonine; subjects with an Axis I diagnosis of major depression, anxiety disorder or dysthymia were included; individual with mixed substance abuse or dependence had to identify cocaine as their drug or choice; a diagnosis of nicotine or marijuana dependence was not exclusionary Exclusion criteria: being acutely suicidal, psychotic; being pregnant; being medically ill or taking medications that were known to interact with nefazodone; having a physiological dependence on opioid or ethanol; being enrolled in an opioid substitution program within 45 days of study; using methadone, LAAM or naltrexone within 14 days of enrolment
Interventions	(1) nefazodone, 34 participants; (2) placebo, 35 participants Drug dose: nefazodone up to 400 mg/day. Treatment included weekly 1-hour counselling session (at New York site) and individual manualized relapse prevention therapy (at Boston site). Setting: Outpatient. Duration: 8 weeks. Country of origin: USA.
Outcomes	Retention in treatment; drug use (urine analysis, mean weekly BE value); craving (CCS scores, Halikas 1991, Mezinskis 2001); Depression severity (HDRS scores, Hamilton 1967, Williams 1988); Anxiety severity (HARS scores, Hamilton 1967; Bruss 1994); Variations in dimensions of the ASI (McLellan 1985); changes in risk assessment scores (Navaline 1994); changes in CGI; adverse events.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Unclear risk	The method of concealment is not described.

Ciraulo 2005 a (*Continued*)

Blinding (performance bias and detection bias) Subjective	Low risk	Double blind stated. Medications and placebo were supplied by the manufacturer in identically appearing tablets
Blinding (performance bias and detection bias) Objective	Low risk	Double blind stated. Medications and placebo were supplied by the manufacturer in identically appearing tablets
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat and end-point analyses were applied. Reasons for drop out were not reported by medication group. No details on withdrawn by group for medical reasons was given

Ciraulo 2005 b

Methods	Randomised placebo controlled double blind trial
Participants	**First trial*:** 64 subjects; mean age 40 years; males 72%; African-American 77%; 13 years of education on the average; married 14%; ASI results: 13 days of cocaine use in the past 30 days on the average; 12 years of cocaine use on the average; alcohol score, 0.25 on the average Inclusion criteria: being between 18 and 59 years; meeting DSM-IV criteria for cocaine dependence, diagnosed with the use of SCID interview (First 1996); using at least $50 worth of cocaine over the 30-day period preceding the study admission; providing two urine positive for cocaine during any consecutive 2-week segment of a 4-week screening period; female of child-bearing capacity were required to use one method of birth control Exclusion criteria: being dependent on any substance other than cocaine, alcohol and nicotine; evidence of severe psychiatric or medical disorder; using drugs that would interact adversely with any of the study medications; being pregnant or lactating; taking medication with a potential to interact with study drugs; having a history of renal stone formation **Second Trial*:** 60 subjects; mean age 43 years; male 72%; African-American 92%;12.3 years of education on the average; married 48%; ASI results: 18 days of cocaine use in the past 30 days on the average; 15 years of cocaine use on the average; alcohol score 0.27 on the average Inclusion criteria: being between 18 and 60 years; meeting DSM-IV criteria for cocaine dependence, diagnosed with the use of SCID interview (First 1996); using cocaine on at least six occasions or days within 28 days prior to screening; having three of six urine toxicologic specimens positive for BE in a consecutive 2-week period during the 30-day screening period; female of child-bearing capacity were required to use one method of birth control Exclusion criteria: being dependent on any substance other than cocaine and nicotine; having a physiological dependence on alcohol requiring medical detoxification; having neurological or psychiatric disorders requiring treatment or that would make medication compliance difficult; having serious medical illnesses that could compromise safety participation or study conduct; being pregnant or lactating; taking medication with a

Ciraulo 2005 b (*Continued*)

	potential to interact with study drugs; having a history of adult asthma or being actively using beta-adrenergic agonist medications evidence of severe psychiatric or medical disorder; use of drugs that would interact adversely with any of the study medications
Interventions	First Trial: (1) paroxetine, 16 participants; (2) pentoxifylline, 16 participants; (3) riluzole, 16 participants; (4) placebo, 16 participants Drug dose: paroxetine 20 mg/day; pentoxifylline, 1200 mg/day; riluzole, 100 mg/day Second Trial: (1) venlafaxine, 20 participants; (2) pramipexole, 20 participants; (3) placebo, 20 participants Drug dose: venlafaxine up to 150 mg/day; pramipexole up to 1.5 mg/day For both trials treatment included standardized manual guided cognitive-behavioral therapy Setting: Outpatient. Duration: 8 weeks. Country of origin: USA.
Outcomes	Retention in treatment; drug use (urine analysis, mean weekly BE value; drug use self report); craving (CCS scores); Depression severity (HDRS, Hamilton 1967); Anxiety severity (HARS scores, Hamilton 1967); Variations in dimensions of the ASI (McLellan 1980); changes in risk assessment scores; changes in CGI; adverse events
Notes	*The study reports results of two different trials.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Unclear risk	The method of concealment is not described.
Blinding (performance bias and detection bias) Subjective	Unclear risk	Medications were not identical. Participants, therapist and research staff were blind to the medication identity. Unblinded pharmacists monitored safety and compliance
Blinding (performance bias and detection bias) Objective	Low risk	Medications were not identical. Participants, therapist and research staff were blind to the medication identity. Unblinded pharmacists monitored safety and compliance
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat and end-point analyses were applied. Dropout reasons are not reported by group. No details on withdrawn by group for medical reasons was given

Cornish 2001

Methods	Randomized placebo controlled double blind study
Participants	80 participants; mean age 37.7; male 100%; African-American 97.5%; 12.3 years of education on the average; 11.6 days of cocaine use in the past 30 days on the average; Beck Depression Inventory score, 11.5 on the average; HDRS score, 9.5 on the average; ASI alcohol score, 0.28 on the average; ASI psychiatric score, 0.21 on the average; ASI Drug score, 0.24 on the average Inclusion criteria: being 21-65 years old; meeting DSM-III-R criteria for cocaine dependence (DSM-III-R). Individuals with a concurrent diagnosis of alcohol dependence were eligible if detoxified and alcohol-free for a period of seven days; overcoming a single blind observation phase lasting 1-3 weeks Exclusion criteria: having a current psychiatric illness requiring psychiatric treatment; having a history of psychosis unrelated to cocaine abuse; being physically dependent on alcohol, opiates, sedative hypnotics or benzodiazepines; having clinically significant cardiovascular, hematological, hepatic, renal, pulmonary, neurological or endocrinological abnormalities; using antihypertensives, phenothiazines, antidepressant, MAO inhibitors or other medication known to interfere adversely with study medication; having a known hypersensivity to the study medication
Interventions	(1) ritanserin, 40 participants; (2) placebo, 40 participants Drug dose: ritanserin 10 mg/day Participants received daily treatment in a day-hospital rehabilitation program that provided counselling, medical care, social work services and education. Setting: Outpatient. Duration 4 weeks (plus 4 weeks follow-up period). Country of origin: USA
Outcomes	Primary outcomes: retention in treatment; use of cocaine, evaluated using results of urine testing; craving, evaluated with a Visual Analogue Scale; adverse events; Secondaty outcomes: Mean scores of BDI (Beck 1988); ASI results (McLellan 1985); HDRS results (Williams 1988); POMS results (McNair 1971)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A block randomisation procedure was followed.
Allocation concealment (selection bias)	Low risk	Medication was packaged individually for each subject and was labelled to identify the protocol, subject and visit number. Active medication and placebo tablets were identical in size and appearance.Tablets were maintained and dispensed by the pharmacy

Cornish 2001 (*Continued*)

Blinding (performance bias and detection bias) Subjective	Low risk	Double blind stated. Active medication and placebo tablets were identical in size and appearance
Blinding (performance bias and detection bias) Objective	Low risk	Double blind stated. Active medication and placebo tablets were identical in size and appearance
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat analyses was applied. Missing urinalyses were analysed as either lacking or being positive. Dropout reasons and withdrawn for medical reasons are not reported by group

Covi 1993

Methods	Randomised placebo controlled double blind trial
Participants	Participants: 59 subject; mean age 30.0 years; male 80%; African-American 44.4%; 18 days using cocaine in the past 30 on the average; 66.6% meeting DSM-III-R criteria for tobacco dependence, 22% for alcohol dependence, 18% for anxiety disorders, 7% for antisocial personality disorder; route of cocaine administration: 33.3% intranasal, 22.2% intravenous, 42.2% smoking, 2.2% oral ingestion; 60% had never been treated for drug abuse Inclusion criteria: meeting the criteria for a DSM-III-R cocaine dependence, with a minimum use of 1 gram of cocaine per week during the 12 weeks preceding intake Exclusion criteria: other current substance dependencies, except nicotine; illiteracy; current medical illness; pregnancy; psychiatric conditions severe enough to require immediate psychiatric care; legal problems implying imminent imprisonment
Interventions	(1) fluoxetine 20 mg, 10 participants; (2) fluoxetine 40 mg, 11 participants; (3) fluoxetine 60 mg, 10 participants; (4) active placebo (diphenhydramine), 14 participants Drug dose: fluoxetine from 20 to 60 mg/day; active placebo (diphenhydramine), 12.5 mg/day Participants received two weekly 50-minute individual manualized interpersonal psychotherapy sessions (Rounsaville 1985). Setting: Outpatient. Duration: 12 weeks. Country of origin: USA.
Outcomes	Retention in treatment; side effects; cocaine use (urine toxicology); craving (craving scale) ; POMS scores (McNair 1964).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Covi 1993 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "Subjects were randomly assigned to groups by the pharmacist". No further details provided
Allocation concealment (selection bias)	Unclear risk	The method of concealment is not described.
Blinding (performance bias and detection bias) Subjective	Low risk	Quote: "All subjects and participating personnel except for the principal investigator and the pharmacist, neither of whom made any research rating of the subjects, were blind to the medication assignments". "The capsules of each group were indistinguishable from each other"
Blinding (performance bias and detection bias) Objective	Low risk	Quote: "All subjects and participating personnel except for the principal investigator and the pharmacist, neither of whom made any research rating of the subjects, were blind to the medication assignments". "The capsules of each group were indistinguishable from each other"
Incomplete outcome data (attrition bias) All outcomes	High risk	Analyses were conducted only on the 45 subjects who had complied with the study protocol for at least 1 week

Elkashef 2006

Methods	Randomised placebo controlled double blind multicenter trial
Participants	300 participants; mean age 40.8 years; male 78%; African-American 62.7%; 13.2 years of education on the average; 17.6 days cocaine use in past 30 days on the average; 13.6 years of cocaine use on the average; ASI alcohol score, 0.24 on the average; ASI psychiatric score, 0.14 on the average; HDRS score, 10 on the average; Route of cocaine administration: 11% intranasal, 85.7% smoked, 4% other Inclusion criteria: aged at least 18 years; meeting DSM-IV criteria for cocaine dependence; seeking treatment; providing at least 3 positive urine BE specimens during the baseline assessment period; using an acceptable form of birth control (if female); able to provide voluntary informed consent and comply with study procedures Exclusion criteria: pregnancy or lactation; any serious medical illness; psychiatric disorder requiring treatment; court-mandated treatment; previous adverse reaction to selegiline; other MAO-inhibitor or phenylethylamine use; use of any contraindicated medications
Interventions	(1) selegiline transdermal system patches, 150 participants; (2) placebo, 150 participants Drug dose: 20 cm^2 patch containing 1.0 mg/cm^2 of selegiline per day. participants received standardized, manual-guided individual behavioral psychotherapy once per week

	Setting: Outpatient. Duration 8 weeks. Country of origin: USA.
Outcomes	Primary outcomes: weekly mean proportion of days of cocaine non-use as determined by self use report (SUR) confirmed by urine assay for BE; Secondary outcomes: the proportion of subjects successful at reducing their overall cocaine use days to 75% or less and to 50% or less of the baseline rate; the longest number of consecutive cocaine non-use days; weekly proportion of non-use days according to SUR without regard to BE levels; weekly mean urine BE level; reduction in the severity of cocaine dependence and craving, based on results from the Brief Substance Craving Scale (Halikas 1991, Mezinskis 1998), CGI (Tracy 2000), ASI scores (McLellan 1985); safety of the Selegiline Transdermal System assessed by adverse events, laboratory data, physical exams, and vital signs; HDRS scores (Hamilton 1967) were also considered.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Adaptive randomisation was handled via a central data coordinating center.The treatment group was balanced with respect to gender, diagnosis of attention deficit disorder, historical self-report of cocaine use, severity of depression. Each subjects was randomised with a "biased coin" procedure which uses randomisation probabilities to improve the balance on group assignment. The process was performed by a computer-based program created by the data-center
Allocation concealment (selection bias)	Low risk	Randomization codes were maintained at the data-coordinating center. Randomization was accomplished by assigning subjects to pre coded medication supplies. The list was submitted to the pharmacy-coordinating center, which prepared medication supplies for each subject based on the treatment assignment on the list
Blinding (performance bias and detection bias) Subjective	Low risk	Double blind stated. Selegiline and matched placebo patches were used
Blinding (performance bias and detection bias) Objective	Low risk	Double blind stated. Selegiline and matched placebo patches were used

Elkashef 2006 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analyses was applied. A generalizing estimating equations (GEE) model was used to control for differences in cocaine non-use days between medication conditions

Gawin 1989

Methods	Randomised placebo controlled double blind trial
Participants	100 participants; mean age 29 years; male 76%; 12.9 years of education on the average; administration route: 50% intranasal, 31.9% freebase, 18.1% intravenous; probably or definite psychiatric disorder, as defined by Research Diagnostic Criteria (Endicott 1976) , occurred in 13% of the sample. Inclusion criteria: Meeting DSM-III-R criteria for cocaine dependence; reporting more than 14 grams of total cocaine use during the 12 weeks prior to seeking treatment; inability to sustain abstinence from cocaine for more than one week during the 12 weeks prior to seeking treatment Exclusion criteria: meeting DSM-III-R criteria for current or lifetime dependence on any other abused substance; having external contingencies that could influence the accuracy of self-reports; having medical abnormalities that contraindicate desipramine or lithium treatment
Interventions	(1) desipramine, 31 participants; (2) lithium carbonate 37 participants; (3) placebo, 32 participants Drug dose: desipramine 2.5 mg/kg per day; lithium carbonate 600 mg/day; placebo was active for the only first administration (atropine 0.1 mg) All subjects were provided weekly individual psychotherapy meetings lasting 60 minutes (Rounsaville 1985). Setting: Outpatient. Duration: 6 weeks. Country of origin: USA.
Outcomes	Primary outcomes: frequency and duration of abstinence; cocaine use measured by random urinalyses; severity of craving for cocaine measured by Cocaine Use Inventory and Cocaine craving Scale (Gawin 1984 b); retention in treatment; side effects.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A random number table was used.
Allocation concealment (selection bias)	Unclear risk	The method of concealment is not described.

Gawin 1989 (*Continued*)

Blinding (performance bias and detection bias) Subjective	Low risk	Double blind stated. Arrangements were made for maintain the double blind conditions
Blinding (performance bias and detection bias) Objective	Low risk	Double blind stated. Arrangements were made for maintain the double blind conditions
Incomplete outcome data (attrition bias) All outcomes	High risk	Subjects were included in the analyses only if they continued receiving treatment for seven days after beginning medication. Because of the high attrition rate, endpoint analyses were employed in some repeated-measures

Giannini 1986

Methods	Randomised placebo controlled double blind trial
Participants	Participants: 20 chronic cocaine abusers; age: range 20-34 years; male 100%; Caucasian 100%; use of substance: abusers used only cocaine at least 3 times weekly and had a history of abuse of at least one year. No subject had a history of major affective disorder Inclusion criteria: no details given Exclusion criteria: no details given
Interventions	(1) desipramine, 10 participants; (2) active placebo (diphenhydramine), 10 participants Drug dose: desipramine 150 mg/day; diphenhydramine 25 mg/day Counseling at five-day intervals. Setting: Outpatient. Duration: 40 days. Country of origin: USA.
Outcomes	Depression measured with HDRS scale (Hamilton 1960); retention in treatment (dropout); side effect; weekly laboratory testing establishing a drug-free state
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	random selection program (Texas Instrument Programmable 58).
Allocation concealment (selection bias)	Unclear risk	The method of concealment is not described.

Giannini 1986 (*Continued*)

Blinding (performance bias and detection bias) Subjective	Low risk	Double blind stated. Arrangements made to maintain blindness
Blinding (performance bias and detection bias) Objective	Low risk	Double blind stated. Arrangements made to maintain blindness
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information is not available. Dropout reasons and withdrawn for medical reasons are partially reported by group

Giannini 1987 a

Methods	Randomised placebo controlled double blind trial
Participants	Participants: 20, space-base (combination of free-base cocaine and phencyclidine) abusers; age: range 21-28 years; male 100%; Caucasians 100%; use of substance: abusers smoked space-base on a twice week or more frequency Inclusion criteria: no details given Exclusion criteria: no details given
Interventions	(1) desipramine, 10 participants; (2) placebo, 10 participants Drug dose: desipramine 200 mg/day; diphenhydramine 25 mg/day. All patients were on weekly psychotherapy. Setting: Outpatient. Duration: 45 days. Country of origin: USA.
Outcomes	Abstinence; retention in treatment; BPRS score.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	random selection program (Texas Instrument Programmable 58).
Allocation concealment (selection bias)	Unclear risk	The method of concealment is not described.
Blinding (performance bias and detection bias) Subjective	Low risk	Double blind stated. Arrangements made to maintain blindness

Giannini 1987 a (*Continued*)

Blinding (performance bias and detection bias) Objective	Low risk	Double blind stated. Arrangements made to maintain blindness
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information is not available. Dropout numbers and reasons are not reported by group. Participants withdrawn for medical reasons are not reported

Giannini 1987 b

Methods	Randomised placebo controlled double blind trial
Participants	Participants: 24 cocaine addicts 27-38 years old; male 100%; all withe; having attended college for at least two years; all employed; no use of other drugs besides cocaine Inclusion criteria: no details given Exclusion criteria: no details given
Interventions	(1) desipramine plus bromocriptine, 12 participants; (2) placebo plus bromocriptine, 12 participants Drug dose: desipramine 200 mg/day; bromocriptine 0.625 qid mg/day. All patients were on weekly psychotherapy. Setting: Outpatient. Duration: 12 weeks. Country of origin: USA.
Outcomes	Abstinence; retention in treatment; BPRS score.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	random selection program (Texas Instrument Programmable 68).
Allocation concealment (selection bias)	Unclear risk	The method of concealment is not described.
Blinding (performance bias and detection bias) Subjective	Low risk	Double blind stated. Arrangements made to maintain blindness
Blinding (performance bias and detection bias) Objective	Low risk	Double blind stated. Arrangements made to maintain blindness

Giannini 1987 b (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information is not available. Dropout numbers and reasons are not reported. Participants withdrawn for medical reasons are not reported

Giannini 1993

Methods	Randomised placebo controlled trial
Participants	Participants: 32 chronic cocaine abusers 22-26 years old; all employed; using cocaine at least one year and three times at week; reporting occasional use of other psychoactive substances; none having history of anxiety disorder, panic of phobias or meeting DSM III criteria for these disorders
Interventions	(1) buspirone, 16 participants; (2) placebo, 16 participants Drug dose: buspirone 30 mg/day. All patients received twice weekly counselling. Setting: Outpatient. Duration: four weeks. Country of origin: USA.
Outcomes	retention in treatment; BPRS score.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	random selection program (Texas Instrument Programmable 68).
Allocation concealment (selection bias)	Unclear risk	The method of concealment is not described.
Blinding (performance bias and detection bias) Subjective	Unclear risk	Information is not available.
Blinding (performance bias and detection bias) Objective	Unclear risk	Information is not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information is not available. Participants withdrawn for medical reasons are not reported

Grabowsky 1995

Methods	Randomised placebo controlled double blind trial
Participants	**First Trial*:** 155 participants; mean age 32 years; male 72%; African-American 64%; 12.4 years of education on the average; married 23%; unemployed 52%; BDI score, 16 on the average; HDRS score, 10 on the average; POMS score, 72 on the average; mean ASI composite scores: alcohol 0.17, drug 0.23, psychiatric 0.21; cocaine use in the past 30 days ,14 days on the average Inclusion criteria: meeting the criteria for a DSM-III-R cocaine dependence disorder;generally in good physical and psychiatric health; having completed a 2-week stabilization period Exclusion criteria: medical disorder precluding the use of fluoxetine; axis I diagnosis of major depression or schizophrenia; a positive tuberculosis test result; probation or parole for charges other than drug use; spouse or significant other in the study; inability to read English; inability/unwillingness to meet study participation requirements **Second Trial*:** 21 participants; mean age 39.3 years; male 76.2%; African-American 38%; 13.5 years of education on the average; married 33%; unemployed 39%; BDI score, 6.5 on the average; HDRS score, 11.8 on the average; POMS score, 58 on the average; mean ASI composite scores: alcohol 0.14, drug 0.27, psychiatric 0.09 Inclusion criteria: meeting the criteria for a DSM-III-R cocaine dependence disorder; being in methadone maintenance treatment; having 50% or more of urine screens benzoylecgonine positive during the last 2 months of the methadone treatment Exclusion criteria: medical disorder precluding the use of fluoxetine; axis I diagnosis of major depression or schizophrenia; a positive tuberculosis test result; probation or parole for charges other than drug use; spouse or significant other in the study; inability to read English; inability/unwillingness to meet study participation requirements
Interventions	**First Trial:** (1) fluoxetine 20 mg plus two visits/week 25 participants; (2) fluoxetine 20 mg plus five visits/week 25 participants; (3) fluoxetine 40 mg plus two visits/week 25 participants; (4) fluoxetine 40 mg plus five visits/week 25 participants; (5) placebo plus two visits/week, 29 participants; (6) placebo plus five visits/week, 26 participants Drug dose: fluoxetine 20 mg/day; fluoxetine 40 mg/day. One hour of standardized behavioral-psychological therapy was provided each week Setting: Outpatient. Duration 12 weeks. Country of origin: USA **Second Trial:** (1) fluoxetine plus methadone, 11 participants; (2) placebo plus methadone, 10 participants Drug dose: fluoxetine 20 mg/day; methadone 50-80 mg/day (mean dose 70.9 mg) Methadone and fluoxetine were administered at scheduled daily visits under the observation of a research nurse at the clinic dispensing window. Take-home doses of both drugs were provided on weekends Setting: Outpatient. Duration 8 weeks. Outpatient. Country of origin: USA
Outcomes	Retention in treatment; urinalysis results for drug use; craving (Desire to Use Drugs Inventory, 9-point scale); side effects

Grabowsky 1995 (*Continued*)

Notes	* This study includes two different trials. Patients were paid at a rate of $ 7/hour for time devoted to the research elements of treatment and received $ 15.00 per week for participation compliance

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization stated. No further details given.
Allocation concealment (selection bias)	Low risk	A third party generated the allocation sequence and assigned participants. The randomisation code was not available to study staff
Blinding (performance bias and detection bias) Subjective	Low risk	Capsules of fluoxetine and placebo, identical in appearance, were in blister packages with printed medication code. Clinical staff and faculty were blind with respect to fluoxetine dose/code
Blinding (performance bias and detection bias) Objective	Low risk	Capsules of fluoxetine and placebo, identical in appearance, were in blister packages with printed medication code. Clinical staff and faculty were blind with respect to fluoxetine dose/code
Incomplete outcome data (attrition bias) All outcomes	High risk	Only subjects having completed a 2-week stabilization period were included in analyses Statistical methods to account for dropouts and missing data were applied (i.e., list wise deletion, last observation carried forward, etc.)

Hall 1994

Methods	Randomised placebo controlled double blind trial
Participants	94 participants; mean age 38 years; male100%; African-Americans 85%; 12.8 years of education on the average; married or with partner 10%; unemployed 78%; homeless 34%; cocaine use, 8.6 years on the average Inclusion criteria: diagnosis of cocaine dependence according to DSM-III-R criteria (Robins 1989); crack or other freebase as primary mode of administration; outpatient aftercare as treatment of choice; intention to remain in the treatment area for the duration of the study; ability to name two contact for follow-up purpose. Patients who abused other drug in addiction to cocaine were included

Hall 1994 (*Continued*)

	Exclusion criteria: sedative-hypnotic or alcohol dependence as primary diagnosis; severe alcohol dependence; schizophrenia or bipolar disorder; any other serious medical condition where desipramine might pose an undue risk
Interventions	(1) desipramine 200 mg plus Continuity*, 23 participants; placebo plus Continuity*, 28 participants; (3) desipramine 200 mg plus Standard Care**, 22 participants; (4) placebo plus Standard Care**, 21 participants. Drug dose: desipramine 200 mg/day. Participants were expected to attend three hours of group therapy per week; the group content was eclectic with an abstinence oriented philosophy, but including some cognitive behavioral techniques; Cocaine Anonymous attendance was encouraged, but not required; individual therapy sessions were scheduled once per week initially and reduced to once per month as treatment proceeded. Setting: inpatient at beginning (~2 weeks), then outpatient. Duration: 12 weeks. Country of study: USA
Outcomes	Self report of cocaine use; positive urine sample for cocaine metabolites; measures of social support (Cohen 1985); commitment to abstinence (Hall 1991); withdrawal symptoms (Hall 1991); craving measured by the Self-Efficacy About Cocaine Scale (adapted from Candiotte 1981); compliance (number of individual and group session attended); ASI results (McLellan 1980); non entrance in outpatient program (not leaving the hospital) ; retention in treatment
Notes	*Continuity - subjects had the same counsellor during inpatient and outpatient treatment and joined therapy groups at the outpatient immediately after entrance into the study **Standard Treatment - subjects had a different counsellor during inpatient and outpatient treatment: inpatient and outpatient treatment were separate. Subjects were reimbursed $20 at weeks 3 and 8 and $35 at week 12

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given.
Allocation concealment (selection bias)	Unclear risk	The method of concealment is not described.
Blinding (performance bias and detection bias) Subjective	Low risk	Double blind stated. Arrangements were made for maintain the double blind conditions
Blinding (performance bias and detection bias) Objective	Low risk	Double blind stated. Arrangements were made for maintain the double blind conditions

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat-analysys was applied and procedures were followed to take into account missing data. Dropouts reasons and withdrawn for medical reasons were not reported by medication group

Jenkins 1992

Methods	Randomised placebo controlled double blind multicenter trial
Participants	41 participants; mean age 30.8 years; male 95%; African-American 66%; 13.5 years of education on the average; employed 56%; married 22%; average cocaine use, 7 grams/ week Inclusion criteria: being at least 18th years old, meeting DSM-III-R criteria for cocaine dependence on the SCID (Spitzer 1988); having been engaged in at list one per week pre-study cocaine binge Exclusion criteria: childbearing potential; suffering from organic brain syndrome, schizophrenia, psychotic disorder, or hallucination; requiring additional psychopharmacologic agents other than chloral hydrate for sleep; having been injecting heroin or cocaine within 6 months of the study; meeting DSM-III-R criteria for dependence on another substance of abuse except nicotine or caffeine; having defined medical condition or illnesses; having a significant risk of suicide; having participated in another clinical trial within 1 month of the study It was considered desirable for patients to be employed and live in a moderately stable social situation, and not have Antisocial Personality Disorder
Interventions	(1) gepirone, 20 participants; placebo, 21 participants. Drug dose: gepirone 5-30 mg/day (mean dose 16.25 mg/day) Setting: inpatients in the first week of the trial, then outpatient duration: 12 weeks. Country of study: USA
Outcomes	Primary outcomes: retention in treatment; Secondary outcomes: facilitation of abstinence (i.e., measure of clean or negative urine screens for cocaine); scores of the following rating scales and questionnaires: HDRS (Hamilton 1960); Global Assessment Scale (Endicott 1976); HARS (Hamilton 1959); QCI and CCS (Gawin 1984 a); ASI (McLellan 1980), CGI (Guy 1976).
Notes	Data are related to a six week interim analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given.

Jenkins 1992 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	The method of concealment is not described.
Blinding (performance bias and detection bias) Subjective	Low risk	Double blind stated.
Blinding (performance bias and detection bias) Objective	Low risk	Double blind stated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No specification on how missing data were addressed. Dropouts reasons and withdrawn for medical reasons were not reported by medication group

Johnson 1997

Methods	Randomized placebo controlled double blind trial
Participants	65 participants; mean age 35 years; male 84%; African-American 49%; mean cocaine use, 0.60 grams/week; ASI alcohol composite score, 0.22 on the average; ASI drug composite score, 0.23 on the average; ASI psychiatric composite score, 0.28 on the average Inclusion criteria: being 21-65 years old; weighting between 40-110 kg; fulfilling at least 5 out of 9 DSM-III-R criteria for cocaine dependence, using the SCID interview (Spitzer 1992); being sufficiently literate in English; expressing desire to stop or reduce cocaine consumption; and willing to participate in a psycho educational treatment program Exclusion criteria: having a DSM-III-R diagnosis of any other psychiatric disorder other than nicotine dependence; being currently incarcerated, awaiting incarceration, compelled to participate in a drug treatment program to avoid incarceration, or mandated by an employer to join a drug treatment program as a condition of future or continuing employment; having evidence of opiate use with or without physical signs of withdrawal; having evidence of alcohol or benzodiazepine dependence; being pregnant, lactating or using birth control method other than oral contraceptive, barrier or levonorgestrel implant; expressing suicidal ideation; being medically unfit as evidenced by significant abnormalities on physical examination, hematological evaluation, biochemical screen or electrocardiographic analysis; being epileptic; having been enrolled in a clinical trial or treatment program within 30 days of screening
Interventions	(1) ritanserin, 33 participants; (2) placebo, 32 participants Drug dose: ritanserin 10 mg/day Subjects attended intensive outpatient psycho educational program for five hours per day, three times/week. The program included cognitive-behavioral group therapy, social work services and educational classes Duration: 4 weeks Setting outpatients. Country of origin: USA

Johnson 1997 (*Continued*)

Outcomes	Attendance at the intensive outpatient psycho educational program; medication compliance; self-reported cocaine consumption; benzoylecgonine levels; self-reported cocaine craving; CGI scale (Guy 1976) measures.
Notes	The study is part of a 10-week trial including 2-week single blind, 4-week double blind and 4-week with no medication follow up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated codes were applied.
Allocation concealment (selection bias)	Low risk	the randomisation code was not available during the study to researchers, clinicians and biostatistics
Blinding (performance bias and detection bias) Subjective	Low risk	Placebo was identical to ritanserin in appearance and formulation and packaged in identical containers. All study medication was labelled with the protocol number, patient number and visit number
Blinding (performance bias and detection bias) Objective	Low risk	Placebo was identical to ritanserin in appearance and formulation and packaged in identical containers. All study medication was labelled with the protocol number, patient number and visit number
Incomplete outcome data (attrition bias) All outcomes	Low risk	An intent-to-treat approach was used in the analysis and interpretation of all efficacy data. An end-point analysis was also performed

Jones 2004

Methods	Randomised placebo controlled double blind trial
Participants	199 participants; mean age 36.2 years; male 52%; withe 39%; 11.8 years of education on the average; married 14%; unemployed 69%; 21% scoring less than 15 at the BDI; on the average 24 cocaine using days in the past 30 days; on the average 8 alcohol using days in the past 30 days Inclusion criteria: age between 18 and 55 years; DSM -IV diagnosis of current cocaine dependence based on the SCID; having a preadmission cocaine-positive urine sample; having reported cocaine use on al least four out of the previous seven days at the time of application; having a negative pregnancy test Exclusion criteria: providing a breath sample positive for alcohol or a urine sample pos-

	itive for opioids (including methadone) or sedative/hypnotics on the day of admission; reporting regular (i.e., at least four out of the previous seven days) use for the corresponding drug; diagnosis of a medical or severe psychiatric illness requiring chronic medication
Interventions	(1) tryptophan plus Contigent Vouchers, 45 participants; (2) placebo plus Contigent Vouchers, 58 participants; (3) tryptophan plus Non Contigent Vouchers, 56 participants; (4) placebo plus Non Contigent Vouchers, 40 participants Drug dose: tryptophan 8 grams/day; since tryptophan can cause drowsiness, 5 mg of diphenhydramine hydrochloride was added to each placebo dose to provide a psychoactive control condition In Contigent Vauchers condition, patients earned voucher payments contingent on urine toxicology evidence of sustained cocaine abstinence. The schedule was set upon previous studies (Higgins 1994). Non-contigent voucher payments were blindly yoked to received payments on a voucher schedule previously generated by a participant in the contingent condition (see Jones 2004). Participants were expected to meet with a counsellor on a weekly basis and attend weekly group therapy; the treatment plan was based on a cognitive/behavioral manualized counselling program Setting: inpatient/outpatient Duration: inpatient 4-9 days, then outpatients12 weeks Country of origin: USA
Outcomes	Treatment retention; urine testing for cocaine (with BE quantification), opiates, methadone and benzodiazepines; self-reports on the use of various drugs; safety assessment with the Weekly Symptom Checklist
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Modifyed dynamic balanced randomisation (Signorini 1993) performed by a computer program assigned patients to the treatment groups according to a specified stratification
Allocation concealment (selection bias)	Low risk	A non-blind staff member generated the allocation sequence and assigned participants according to stratification
Blinding (performance bias and detection bias) Subjective	Low risk	Double blind stated; arrangements were made to protect blindness

Jones 2004 (*Continued*)

Blinding (performance bias and detection bias) Objective	Low risk	Double blind stated; arrangements were made to protect blindness
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intent-to-treat analysis and statistical techniques allowing for missing data were undertaken. No details on dropout reasons and withdrawn by group for medical reasons was given

Kolar 1992

Methods	Randomised placebo controlled double blind trial
Participants	22 participants; mean age 34.8 years; male 85%; African-American 68%; married 41%; 10.5 years of education on the average; methadone dose, 61.1 mg/day on the average; route of cocaine administration, 96% intravenous; 10.1 years of cocaine use on the average; axis-I lifetime psychiatric comorbidity 68% Inclusion criteria: meeting DSM-III-R criteria for current cocaine dependence (Spitzer 1987) and being stabilized on a daily methadone dose of 40 mg or greater for a minimum of 6 weeks; having used cocaine at least two times per week for the previous two months as verified by a minimum of two urine toxicologies positive for cocaine and by both client and staff report Exclusion criteria: current use or dependence on any other substance other than marijuana, nicotine or caffeine or taking prescribed medication; being currently medically ill, psychotic, and/or pregnant
Interventions	(1) desipramine plus methadone, 8 participants; (2) amantadine plus methadone, 5 participants; (3) placebo plus methadone, 9 participants Drug dose: desipramine up to 200 mg/day; amantadine 200 mg/day for 8 weeks, then placebo for four weeks All subjects were required to attend weekly group counselling sessions Setting: outpatients. Duration: 12 weeks. Country of origin USA
Outcomes	Use of cocaine evaluated by urine testing for cocaine and self-reports; craving for cocaine; retention in treatment; BDI score (Beck 1962); side effects.
Notes	Characteristic of the participants are related to subjects who completed almost 14 days of treatment

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given.

Kolar 1992 (*Continued*)

Allocation concealment (selection bias)	Low risk	Assignment to medication was made by the study pharmacist who had no client contact
Blinding (performance bias and detection bias) Subjective	Low risk	Subjects treatment, staff and researchers were blind to treatment conditions. Placebo capsules were identical in appearance to active medication
Blinding (performance bias and detection bias) Objective	Low risk	Subjects, treatment staff and researchers were blind to treatment conditions. Placebo capsules were identical in appearance to active medication
Incomplete outcome data (attrition bias) All outcomes	High risk	Endpoint analysis was used to adjust for attrition. Completing at least 14 days of treatment was considered an inclusion criteria

Kosten 1992 a

Methods	Randomised placebo controlled double blind trial
Participants	94 participants; mean age 32 years; male 48%; white 67.5%; married 72%; 8 years of use of cocaine on the average; 9 years of use of heroin on the average; receiving methadone maintenance for a mean of 7 months before entering the study; cocaine intravenous use, 57%; 15.5 days of cocaine use in the previous 30-day on the average; antisocial personality disorder, 27%; depression, 21% Inclusion criteria: meeting DSM-III-R criteria for cocaine dependence and opioid dependence; being in methadone-maintenance treatment for at least six weeks; having at least three of six urine toxicology screenings positive for benzoylecgonine during the 3 months before the onset of the study Exclusion criteria: current alcoholism; being in treatment with zidovudine for acquire immunodeficiency syndrome; medical contraindications including asthma, renal dysfunction, high blood pressure, diabetes; refusal to use adequate birth control
Interventions	(1) desipramine plus methadone, 30 participants; (2) amantadine plus methadone 33 participants; (3) placebo plus methadone 31 participants Drug dose: desipramine 150 mg/day; amantadine 150 mg/day; methadone 57.1 mg/day on the average participants were treated with weekly group relapse prevention therapy Setting: outpatient. Duration 12 weeks. Country of origin: USA.
Outcomes	Cocaine use assessed by toxicological urinalyses; craving for cocaine and other drugs, such as opioids, assessed by an analogue scale; side effects
Notes	
Risk of bias	

Kosten 1992 a (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given.
Allocation concealment (selection bias)	Low risk	The principal investigator, the pharmacist, and the laboratory director were not blind and held the code. The code was broken after study completion for each subject
Blinding (performance bias and detection bias) Subjective	Low risk	Double blind stated; medication and matching placebo were used
Blinding (performance bias and detection bias) Objective	Low risk	Double blind stated; medication and matching placebo were used
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intent-to-treat and end-point analyses were undertaken to take into account missing data

Kosten 2003

Methods	Randomised placebo controlled double blind trial
Participants	160 participants; mean age 37.5 years; male 65.5%; African-American 36.2; high school graduated 68%; 14.5 days of cocaine use in the previous 30 days on the average; 28 days of heroin use in the previous 30 days on the average; CES-D score, 120 on the average; current major depression, 55.7% Inclusion criteria: being dependent on opioid and cocaine according to DSM-IV criteria as determined from the SCID (First 1995); having positive urine toxicologic screens for opiate and cocaine Exclusion criteria: medical reason for not taking desipramine or buprenorphine (i.e pregnancy, cardiac conduction problems, acute hepatitis), current suicidality or psychosis, inability to read or understand the symptom check lists, currents alcohol or sedative dependence, use of non-diuretic antihypertensives or other medication that interact with the study medication Women of childbearing age were included provided they: had a negative urine pregnancy test; agreed to use adequate contraception; understood the risks of fetal toxicity due to medications while in the study; had monthly pregnancy tests
Interventions	(1) desipramine plus buprenorphine plus contingency management, 40 participants; (2) placebo plus buprenorphine plus contingency management, 40 participants; (3) desipramine plus buprenorphine plus non contingency management, 40 participants; (4) placebo plus buprenorphine plus non contingency management, 40 participants Drug dose: desipramine 150 mg/day; buprenorphine median dose 16 mg/day Contigiency management involved the worth of monetary vouchers for urine free from

Kosten 2003 (*Continued*)

	both cocaine and opiates Non contingency management involved the worth of monetary vouchers according to a schedule that was not contingent upon illicit opiate and cocaine abstinence Subjects participated in weekly group coping skill/relapse prevention therapy and weekly individual therapy sessions Setting: outpatients. Duration: 12 weeks. Country of origin USA
Outcomes	Retention in treatment; illicit opiate and cocaine use (urine toxicology screening and self-report); depressive symptoms measured using the Center for Epidemiologic Studies Depression Inventory (Radloff 1977).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Unclear risk	The method of concealment is not described.
Blinding (performance bias and detection bias) Subjective	Low risk	Double blind stated; arrangements made to protect blindness.
Blinding (performance bias and detection bias) Objective	Low risk	Double blind stated; arrangements made to protect blindness.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intent-to-treat and end-point analysis were undertaken. HLMs were also applied for urinalyses, taking into account missing data. Reasons for drop out are not given by medication group

Lambert Passos 2005

Methods	Randomised placebo controlled double blind trial.
Participants	210 participants; mean age 30.8 years; male 92.4%; white 55%; single 49.5%; employed 78.5%; less than 11 years of education 65%; Depressed 7%; HDRS baseline was 12 on the average; years of cocaine use were 11.1 on the average; daily use of cocaine 38.2%; other drug of abuse: alcohol 39.5%, marijuana 22.4% Inclusion criteria: being 18-65 years old; fulfilling cocaine dependence DSM-IV or ICD -10 criteria, regardless of dependence on other drugs

	Exclusion criteria: fulfilling diagnostic criteria for schizophrenia, schizophreniform, schizoaffective, brief reactive psychosis, organomental, mental retardation disorders; being under external contingencies which could influence the reliability of self-report; having health condition that precluded nefazodone use (women of child-bearing age and not on birth control methods, abnormal kidney and liver functions test results, hypersensitivity to other phenpiperazinic antidepressants; using terfenadine or astemizole; exhibiting suicidal ideation; having epilepsy; having been using monoaminoxidase inhibitors in the 15 days before first interview or other psychotropic medication; being crack or injectable cocaine users
Interventions	(1) nefazodone, 105 participants; (2) placebo, 105 participants, Drug dose; nefazodone up to 300 mg. All patients were offered individual psychotherapy, occupational and family therapy; participants were required to meet with counsellor at least twice at month; social work service, employment counselling and psychiatric and medical care were part of the standard clinical services Setting: outpatient. Duration 10 weeks. Country of origin: Brazil
Outcomes	Primary outcomes: abstinence; craving (Analogic Craving Scale); adherence to treatment and retention; depressive symptoms (HDRS scale, Hamilton 1960). Secondary outcomes; compliance with dosing schedule; adherence to non pharmacological interventions; adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The drug manufacturer supplied the nefazodone and placebo in containers numbered in a random fashion
Allocation concealment (selection bias)	Low risk	The drug manufacturer supplied the nefazodone and placebo in containers numbered in a random fashion. A sequential number was assigned to each patient upon enrolment in the trial
Blinding (performance bias and detection bias) Subjective	Low risk	Quote: "Both professionals and subjects were blind to the medication dispensed"
Blinding (performance bias and detection bias) Objective	Low risk	Quote: "Both professionals and subjects were blind to the medication dispensed"

Lambert Passos 2005 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis and end-points analyses were applied

Margolin 1995

Methods	Randomised placebo controlled double blind multicenter trial
Participants	149 participants; mean age 37.2 years; male 62%; African-american 12%; employed 7%; married 19%; 13 years of heroin use on the average; 7.7 years of cocaine use on the average; 74% were rated as severely cocaine dependent based on number of symptoms of dependence required to meet DSM-III-R criteria for cocaine dependence; 50% meeting criteria for antisocial personality disorder Inclusion criteria: being at least 18 years old; having been using cocaine at least three times per week in the month prior to enrolment; having received a diagnosis of cocaine dependence using the SCID (Spitzer 1987), according to DSM-III-R criteria; being on a stable dose of methadone for at least 3 weeks; having tested positive for cocaine on a minimum of two urine toxicology screens during last month (prior to enrolment) Exclusion criteria: dependence on any substance other than cocaine, methadone, nicotine or caffeine; history or evidence of seizures or seizure disorder; current diagnosis of major depressive episode, liver or renal dysfunction; taking a psychotropic medication (other than methadone). Pregnant women or women who did not agree to use of an acceptable method of contraception during the study; HIV positive patients, with a T-celle count less than 300/mm^3, with asymptomatic HIV disease, or receiving drug treatment for HIV disease
Interventions	(1) bupropion plus methadone, 74 participants; (2) placebo plus methadone 75 participants Drug dose: bupropion 300 mg/day subjects received standard methadone maintenance treatment, that include counselling (with differences within the three sites of the trial) Setting: outpatients Duration: 12 weeks. Country of origin: USA
Outcomes	Retention in treatment; cocaine use assessed by toxicological urine results and self-reports; craving assessed by a visual analogue scale; depression severity assessed by HDRS (Hamilton 1960); CGI changes; level of psychosocial functioning assessed by the ASI (McLellan 1991); side effects.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Sequential randomizations stratified for the presence of Antisocial Personality Disorder

Margolin 1995 (*Continued*)

Allocation concealment (selection bias)	High risk	Sequential randomizations. No other available information.
Blinding (performance bias and detection bias) Subjective	Low risk	Placebo matched bupropion medication. Participants and study personnel at each site were blind to subject assignment
Blinding (performance bias and detection bias) Objective	Low risk	Placebo matched bupropion medication. Participants and study personnel at each site were blind to subject assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis was undertaken; missing data were considered applying the generalized estimating equation method. Reasons for drop out are not given by medication group

McDowell 2005

Methods	Randomised, double blind, placebo controlled trial
Participants	111 participants; mean age 36 year; male 75%; African-American 30.5%; 13.7 years of education on the average; married 19%; employed 87%; intravenous or freebase cocaine use 44%; days per week using cocaine, 2 on the average; alcohol use 74%; current major depression 70%; HDRS score 16 on the average Inclusion criteria: meeting DSM-III-R criteria for both cocaine dependence and current major depression or dysthymia, with at least one of the following features: depression was chronologically primary (antedating the onset of substance abuse on a lifetime basis) ; the depression was chronologically secondary but persisted or emerged during a past episode of at least 6 months abstinence; the depression was of at least 3 months duration in the current episode; completing one week of single-blind placebo and not having a "placebo response", defined as having a CGI depression improvement score of 2 or 1 and no drug use or craving Diagnoses were carried out using the SCID (Spitzer 1992) modified to relate the course of depressive symptoms and substance abuse history (Nunes 1996). Exclusion criteria: history of bipolar disorder or psychotic illness other than brief psychotic symptoms attributable to cocaine intoxication; risk for suicidal behavior; medical instability; medical problems that contraindicated tricyclic antidepressant (as seizure or cardiac conduct disease); diagnosis of current dependence on other substances, except nicotine, alcohol, cannabis. In the case of concurrent alcohol or cannabis dependence, it was required that cocaine be the predominant clinical problem
Interventions	(1) desipramine, 55 participants; (2) placebo, 56 participants Drug dose: desipramine up to 300 mg/day. All patients receive weekly manual-guided individual relapse prevention therapy (Carroll 1994). Setting: outpatients. Duration: 12 weeks. Country of origin USA

McDowell 2005 (*Continued*)

Outcomes	Primary outcome: treatment response, intended as the proportion of patients who experienced: CGI score (Guy 1976) of 2 or 1; at least 50% reduction of HDRS total score (Williams 1988); at least a 75% reduction in cocaine use; at least three consecutive cocaine abstinent weeks. Both self-reports and toxicological urinary analyses were considered
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization in block of four, stratified for cocaine pattern of use
Allocation concealment (selection bias)	Low risk	The staff of the pharmacy carried out the randomisation, prepared medication and maintained the blind codes
Blinding (performance bias and detection bias) Subjective	Low risk	Desipramine and placebo were packaged in identical appearing capsules; Patients and all clinic staff were blind to medication assignment
Blinding (performance bias and detection bias) Objective	Low risk	Desipramine and placebo were packaged in identical appearing capsules; Patients and all clinic staff were blind to medication assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome analyses used the intent-to-treat sample of all patients randomised and the last observation carried forward data. Mixed Effects Models (Laird 1982; Brown 1999) were also applied to measures of cocaine use.

McElroy 1989

Methods	Randomised placebo controlled double blind trial
Participants	15 participants; mean age 29.5 years; male 73%; 4.9 years of cocaine use on the average; baseline HRDS score, 7.2 on the average; baseline BDI, 6.7 on the average; all patients used cocaine intranasally, 5 also smoked the drug and 4 also used it intravenously; all patients met criteria for current or past abuse of other drugs Inclusion criteria: having a diagnosis of cocaine dependence according to DSM-III-R criteria; being between 18-65 years old; consenting for urine screens or blood tests Patients were included if they met DSM-III-R criteria for other psychoactive substance use disorders, as long as cocaine was their preferred and most preeminent drug of abuse.

McElroy 1989 (*Continued*)

	Patients were also included if they had a past or current diagnosis of ADHD Exclusioni criteria: significant medical or neurological problems; no history of major mood, anxiety, eating, or psychotic disorders; participation in past therapeutic trials of thymoleptic medications
Interventions	(1) desipramine, 9 participants; (2) placebo, 6 participants Drug dose: desipramine 200 mg/day. Setting: inpatient at beginning; medication was begun approximately 1 week prior to discharge, after completion of the 4 to 8 week period of abstinence and inpatient treatment. Patient were randomly assigned to receive desipramine or placebo during the first 12 weeks of the study. After completing the first 12 weeks, patients were then crossed-over to the other condition for the remaining 12 weeks. Duration: 12 weeks. Country of origin USA.
Outcomes	Relapse in cocaine use, ascertained by both clinical interviews and urine toxicology screens; retention in treatment; cocaine craving; side effects; depression severity assessed with the use of BDI, (Beck 1961) and HDRS (Hamilton 1960).
Notes	Extracted data regards only the first phase of crossover (12 weeks)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given.
Allocation concealment (selection bias)	Unclear risk	The method of concealment is not described.
Blinding (performance bias and detection bias) Subjective	Unclear risk	Identical appearing capsules of desipramine or placebo; no other details were given
Blinding (performance bias and detection bias) Objective	Unclear risk	Identical appearing capsules of desipramine or placebo; no other details were given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not sufficient to permit judge.

Moeller 2007

Methods	Randomized placebo controlled double blind trial
Participants	76 participants; mean age 39 years; male 86.8%; African-American 67%; 11.8 years of cocaine use on the average; 10.7 days of alcohol use during the last 30 days on the average;

Moeller 2007 (*Continued*)

	Inclusion criteria: cocaine dependence (DSM-IV). Exclusion criteria: any DSM-IV Axis I disorder other than substance abuse or dependence; meeting criteria for current dependence on any substance other than cocaine; meeting criteria for current substance abuse other than alcohol or marijuana
Interventions	(1) citalopram, 36 participants; (2) placebo, 40 participants Drug dose: citalopram 20 mg/day. All subjects received manualized cognitive-behavioral therapy and Contingency Management (a point voucher system reinforced cocaine abstinence during treatment) Setting: outpatient. Duration: 12 weeks. Country of origin USA
Outcomes	Cocaine use assessed by urine analysis; retention in treatment; side effects; mood changes using the HDRS (Hamilton 1960), and HARS (Hamilton 1959).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Urn randomisation with baseline impulsivity score included as a factor
Allocation concealment (selection bias)	Unclear risk	The method of concealment is not described.
Blinding (performance bias and detection bias) Subjective	Low risk	A pharmacist prepared all medications and encapsulated them to appear identical with placebo
Blinding (performance bias and detection bias) Objective	Low risk	A pharmacist prepared all medications and encapsulated them to appear identical with placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	The conventions of Kampman, et al. (Kampman 2004) were used for dealing with missing cocaine urine outcomes: 1) Intermittent missing data were treated as cocaine positive urine, and 2) data missing by drop-out (i.e., no further observations occurred) were treated as missing and subject to list-wise deletion. Reasons for drop out are not given by medication group

Nunes 1995

Methods	Randomised placebo controlled double blind trial
Participants	113 participants; mean age 32 years; male 73%; African-American 34%; finished high school 59.5%; unmarried 75.5%; unemployed 46%; cocaine freebase/crack users 50.5%; 2 grams of cocaine use per week on the average; depressive disorder 61%; HDRS score, 8.4 on the average Inclusion criteria: meeting cocaine abuse or dependence (DSM-III-R) with the use of SCID (Spitzer 1992); age between 18 and 65 years; cocaine being the most frequent drug of abuse at the time of admission; reporting cocaine use or craving during a 1-week of single-blind placebo phase Exclusion criteria: medical or psychiatric condition which might increase the risk of taking imipramine or combining cocaine with imipramine, including coronary vascular disease or conduction system disease, untreated high blood pressure, severe liver disease, a seizure disorder, or history of mania or psychosis unrelated to drug taking; having histories in the past years of dangerous behavior (serious suicide attempts or violence) while on cocaine; living with a substance abuse spouse who not agreed to seek treatment
Interventions	(1) Imipramine, 59 participants; (2) placebo, 54 participants Drug dose: imipramine 150-300 mg/day Participants were involved in individual weekly counselling sessions including support, relapse prevention strategies and advice to attend self-help groups Setting: outpatient Duration: 12 weeks. Country of origin USA
Outcomes	Primary outcome: treatment response, intended as the presence of at least three consecutive, urine-confirmed, cocaine abstinent weeks; the presence of at least three consecutive, urine-confirmed, cocaine abstinent weeks at each subject's end-point was also considered Secondary outcomes: proportion of urine-confirmed cocaine-free weeks during the trial; number of urine-confirmed cocaine-free weeks out of the last three observed before the patient left the study; self-report cocaine use (Quantitative Cocaine Weekly Inventory, Gawin 1986); cocaine craving measured with a visual analogue scale (Gawin 1986); cocaine-induced euphoria, measured with a visual analogue scale; Mood improvement measured with the HDRS (Hamilton 1960); adverse events.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization was carried out with randomly permuted blocks of 4 and stratified for route of cocaine use and baseline depression
Allocation concealment (selection bias)	Low risk	A staff member, independent of the clinicians evaluating the patient, executed the randomisation.

Nunes 1995 (*Continued*)

Blinding (performance bias and detection bias) Subjective	Low risk	Double blind stated. Identical pills containing imipramine or placebo were used; arrangements for protecting blindness were made
Blinding (performance bias and detection bias) Objective	Low risk	Double blind stated. Identical pills containing imipramine or placebo were used; arrangements for protecting blindness were made
Incomplete outcome data (attrition bias) All outcomes	Low risk	An Intent-to-treat approach was applied. A random regression analysis was also applied to take into account missing data. Reasons for drop out are not given by medication group

O'Brien 1988

Methods	Randomised placebo controlled double blind trial.
Participants	47 participants; age 29 to 50 years; male 100%; 16.5 days of cocaine use in the last 30 days on the average; baseline BDI score, 15 on the average Inclusion criteria: being in methadone maintenance; meeting cocaine abuse disorder (DSM-III-R) and had been abusing cocaine for 3 or more months; urine test evidence of persistent cocaine use Exclusion criteria: sedative/alcohol dependence, schizophrenia, bipolar illness, glaucoma, or other medical illnesses in which desipramine might pose a hazard
Interventions	(1) desipramine plus methadone, 24 participants; (2) placebo plus methadone, 14 participants Drug dose: desipramine 250-300 mg/day; methadone not specified Setting: outpatient Duration: 12 weeks. Country of origin: USA
Outcomes	ASI scores (McLellan 1980); BDI scores (Rounsaville 1977); positive urine samples for cocaine metabolites; retention in treatment; cocaine craving
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomly assignation to active medication or placebo in a 2:1 ratio
Allocation concealment (selection bias)	Unclear risk	The method of concealment is not described.

O'Brien 1988 (*Continued*)

Blinding (performance bias and detection bias) Subjective	Low risk	Double blind stated; arrangements made to maintain blindness
Blinding (performance bias and detection bias) Objective	Low risk	Double blind stated; arrangements made to maintain blindness
Incomplete outcome data (attrition bias) All outcomes	High risk	Only subjects completing the trial were included in the analyses. Withdrawns for medical reasons are not reported by group

Oliveto 1999

Methods	Randomised placebo controlled double blind trial
Participants	180 participants, mean age 34; male 69%; African-American 21%; 12 years of education on the average; 12 days of cocaine use in the previous 30 days on the average; 29 days of heroin use in the previous 30 days on the average; 4.5 days of alcohol use in the previous 30 days on the average; BDI score 10.6 on the average; major depression 17% Inclusion criteria: having opioid dependence with documented prior treatment in a methadone maintenance program or having precipitated withdrawal on administration of naloxone hydrochloride; reporting regular cocaine use; having test positive for cocaine within a month before study entry Exclusion criteria: history of a psychosis; current alcohol or sedative dependence; current suicidal tendency; current use of prescribed psychoactive medications; pregnancy or breastfeeding; notable medical conditions; illiteracy; prior buprenorphine treatment
Interventions	(1) desipramine plus buprenorphine, 45 participants; (2) placebo plus buprenorphine, 45 participants; (3) desipramine plus methadone, 45 participants; (4) placebo plus methadone, 45 participants Drug dose: desipramine 150 mg/day; buprenorphine 12 mg/day; methadone 65 mg/day Participants were involved in a manualized weekly group relapse prevention therapy and monthly individual session therapy Setting: outpatients. Duration: 13 weeks. Country of origin: USA
Outcomes	Retention in treatment; illicit drug use measured by urine toxicology screening and self-report; opiate withdrawal; mood symptoms (BDI scores, Beck 1961); adverse effects.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Oliveto 1999 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	A "Simply randomisation procedure" was reported.
Allocation concealment (selection bias)	Low risk	Quote: "The principal investigator kept the medication assignment code in a sealed envelope for access in case of medical emergency"
Blinding (performance bias and detection bias) Subjective	Low risk	Staff and subjects were blind to both opioid medication and desipramine dosages; a double blind, double dummy procedure was applied
Blinding (performance bias and detection bias) Objective	Low risk	staff and subjects were blind to both opioid medication and desipramine dosages;a double blind, double dummy procedure was applied
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	HLMs were applied, taking into account missing data. Withdrawns for medical reasons are not reported by group

Poling 2006

Methods	Randomised placebo controlled double blind trial
Participants	108 participants; mean age 34.5 years; male 69%; withe 75%; SCID diagnosed cocaine dependence 89%; SCID diagnosed alcohol dependence 31%; SCID diagnosed major depressive disorder in the past month 28%; 16 days using cocaine in the past 30 days on the average (according to ASI); 25 days using heroin in the past 30 days on the average (according to ASI) Inclusion criteria: meeting DSM-IV criteria for opioid dependence using the SCID interview (First 1995); reporting the use of opiates and cocaine in the week before study entry; having had laboratory confirmation of opiate and cocaine use during the month before study entry Exclusion criteria: current diagnosis of alcohol or other drug physical dependence other than tobacco, opiates and cocaine; history of schizophrenia or psychosis; any past seizure episode or history of anorexia nervosa or bulimia; current use of psychoactive medications; liver enzyme levels greater than three times the normal; pregnancy or breastfeeding
Interventions	(1) bupropion plus methadone plus contingency management, 27 participants; (2) placebo plus methadone plus contingency management, 25 participants; (3) bupropion plus methadone plus voucher control condition, 30 participants; (4) placebo plus methadone plus voucher control condition, 24 participants Drug dose: bupropion 300 mg/day; methadone 60-120 mg/day. Contigency management involved the earn of monetary vouchers for urine free from both cocaine and opiates and for abstinence-related activities. Participants assigned to

Poling 2006 (*Continued*)

	the voucher control condition earned monetary vouchers for urine submitted regardless of results Participants received once-weekly manualized individual cognitive behavioral therapy (Carroll 1996). Setting: outpatient. Duration 25 weeks. Country of origin: USA.
Outcomes	Primary outcomes: results of cocaine and opiate urine toxicologic screening Other outcomes: retention in treatment; depression severity assessed with the Center for Epidemiological Studies Depression Scale (Radloff 1977).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A urn randomisation technique was used (Wei 1988). Participants were stratified for demographic variables.
Allocation concealment (selection bias)	Low risk	Only the research pharmacist was aware of the medication condition
Blinding (performance bias and detection bias) Subjective	Low risk	Bupropion and placebo were encapsulated at the pharmacy to appear identical. Only the research pharmacist was aware of the medication condition
Blinding (performance bias and detection bias) Objective	Low risk	Bupropion and placebo were encapsulated at the pharmacy to appear identical. Only the research pharmacist was aware of the medication condition
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	HLMs were applied, taking into account missing data (Bryk 1987). Reasons for drop out are not given by medication group. Withdrawns for medical reasons are not reported by group

Schmitz 2001

Methods	Randomised placebo controlled double blind trial
Participants	68 participants; mean age 37.3 years; male 57.3%; Caucasian 52,9%; employed 56%; 10.7 years of lifetime use of cocaine on the average; 16 years of lifetime use of alcohol on the average; 11 years of lifetime use of marijuana on the average; 15.1 days of cocaine use during the last 30 days on the average; 9.6 days of alcohol use during the last 30 days on the average; baseline BDI score 30.1 on the average; baseline HRSD score 28.9

Schmitz 2001 (*Continued*)

	on the average; meeting DSM-IV criteria for Antisocial Personality Disorder 36.4%, for Borderline Personality Disorder 25.8% Inclusion criteria: being 18-50 years old; speaking English; being diagnosed dually with current major depressive disorder and cocaine dependence according to DSM-IV criteria; having a BDI score >10 at intake; being free of serious legal and medical problems; being competent to give informed consent Exclusion criteria: currently dependence on alcohol or any other psychoactive substance (except nicotine or cannabis); meeting criteria for current primary Axis I disorders other than depression
Interventions	(1) fluoxetine, 34 participants; (2) placebo, 34 participants Drug dose: fluoxetine 40 mg/day. Participants received a manualized cognitive-behavioral therapy for substance use (relapse prevention) and depression (self-control therapy) Setting: outpatients. Duration: 12 weeks. Country of origin: USA
Outcomes	Retention on treatment; depression severity assessed by the BDI (Beck 1961) and the HDRS (Hamilton 1960); cocaine use evaluated by toxicology urine tests; medication compliance; adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided; randomisation stratified by clinical variables
Allocation concealment (selection bias)	Unclear risk	The method of concealment is not described.
Blinding (performance bias and detection bias) Subjective	Unclear risk	Double blind stated; no other information were provided.
Blinding (performance bias and detection bias) Objective	Unclear risk	Double blind stated; no other information were provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information provided insufficient to permit judgment; data for depression and cocaine use were analysed using REML mixed model analysis. Reasons for drop out are not given by medication group

Shoptaw 2008

Methods	Randomised placebo controlled double blind trial
Participants	70 participants; mean age 36.9 years; male 86%; African-American 54%; 11 days of cocaine use in the last 30 days on the average; route of cocaine administration: smoking 86%, nasal 10%; ASI alcohol score 0.7 on the average; ASI drug score 1.2 on the average; ASI psychiatric score 0.1 on the average; BDI score 13.7 on the average Inclusion criteria: male or non-pregnant, non-nursing female; aged 18-65 years; meeting DSM-IV criteria for cocaine abuse or dependence assessed with SCID interview; being able to understand and complete rating scales; if female, willing to commit to using an effective form of birth control; agreeable to the conditions of the study and able to provide voluntary informed consent Exclusion criteria: any current psychiatric disorder requiring pharmacologic treatment; current dependence, as defined in DSM-IV on alcohol, opiates, benzodiazepines, or other sedative-hypnotics; any active medical condition that would interfere with safe study participation; history of seizures; unstable behavior during screening
Interventions	(1) bupropion, 37 participants; (2) placebo, 33 participants Drug dose: bupropion 300 mg/day. All participants received thrice-weekly cognitive-behavioral psychosocial treatment based upon a 48-session relapse prevention model. Participants attended three 90-minute group counselling session each week Setting: Outpatient. Duration 16 weeks. Country of origin: USA.
Outcomes	Primary outcome: cocaine use as assessed by urine drug screens; Other outcomes: retention in treatment; medication adherence; depressive symptoms (BDI scores, Beck 1967); cocaine craving (as measured by a visual analogue scale); adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given.
Allocation concealment (selection bias)	Unclear risk	The method of concealment is not described.
Blinding (performance bias and detection bias) Subjective	Unclear risk	Double blind stated. Active medication and matching placebo prepared at research pharmacy. No further details were given
Blinding (performance bias and detection bias) Objective	Unclear risk	Double blind stated. Active medication and matching placebo prepared at research pharmacy. No further details were given

Shoptaw 2008 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All analyses used an intention-to-treat approach: The problem of missing data was addressed

Tennant 1985

Methods	Randomised placebo controlled double blind trial
Participants	Participants: 22, cocaine dependents; age, sex and race: unknown. Exclusion criteria: other drug/alcohol dependence.
Interventions	(1) desipramine, 11 participants; (2) placebo, 11 participants. Setting: unknown Duration: 12 days for desipramine patients, 15 for placebo. Country of origin: USA
Outcomes	Positive urine samples for cocaine metabolites; retention in treatment
Notes	Data was extracted from the abstract and from other review (Levin 1991). Authors contacted for further information.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information available.
Allocation concealment (selection bias)	Unclear risk	No information available.
Blinding (performance bias and detection bias) Subjective	Unclear risk	No information available.
Blinding (performance bias and detection bias) Objective	Unclear risk	No information available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information available.

Weddington 1991

Methods	Randomised placebo controlled double blind trial
Participants	83 participants; mean age 29 years; male 76%; African-American 31%; married 48%; intake cocaine use 3 grams/week on the average; route of cocaine administration: freebase 39%, I.V. 30%; lifetime psychiatric diagnosis: Major depression/dysthymia 46%

Weddington 1991 (*Continued*)

	Inclusion criteria: meeting DSM-III-R criteria for psychoactive substance use disorder, active cocaine dependence; at least one or more "grams of cocaine" (street terminology) per week for 12 weeks Eclusion criteria: current abuse or dependence on any substance other than nicotine; current medical illness or pregnancy
Interventions	(1) desipramine, 32 participants; (2) amantadine, 23 participants; (3) placebo 28 participants Drug dose: desipramine 200 mg/day; amantadine 400 mg/day for 4 weeks followed by placebo for 8 weeks All subjects also received twice-weekly interpersonal psychotherapy (according to Rounsaville 1985). Setting: outpatients. Duration: 12 weeks. Country of origin: USA
Outcomes	Positive urine sample for cocaine metabolites; craving for cocaine; (10 cm analogue scale) ; retention in treatment; side effects; BDI scores, short form (Beck 1961, Plumb 1977).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Unclear risk	The method of concealment is not described.
Blinding (performance bias and detection bias) Subjective	High risk	single-blind.
Blinding (performance bias and detection bias) Objective	High risk	single-blind.
Incomplete outcome data (attrition bias) All outcomes	High risk	Only subjects staying in treatment for 14 days, attending at least four out of six sessions and showing compliance with the medication regimen (by self-report, urinalyses and blood levels of desipramine) were included in the analyses. Last week of observations carried forward was used for analysing response. Reasons for drop out are not given by medication group. Withdrawns for medical reasons are not reported

Weddington 1991 (*Continued*)

		by group

Winhusen 2005

Methods	Randomised placebo controlled blind trial
Participants	67 participants; mean age 39.6 years; male 73%; African-American 91%; 12.7 years of education on the average; married 17%; unemployed 8%; 18.8 days of cocaine use in the past 30 days on the average; ASI drug composite score, 0.26 on the average; ASI Alcohol composite score, 0.19 on the average Inclusion criteria: being between 18 and 59 years; meeting DSM-IV criteria for cocaine dependence, diagnosed with the use of SCID interview (First 1996); providing two urines positive for cocaine during any consecutive 2-week segment of a 4-week screening period; female of child-bearing capacity were required to use one method of birth control Exclusion criteria: being dependent on any substance other than cocaine, alcohol and nicotine; evidence of severe psychiatric or medical disorder; using drugs that would interact adversely with any of the study medications; being pregnant or lactating; taking medication with a potential to interact with study drugs; having a history of renal stone formation; having a story of rashes or other sensitivity reactions to sertraline
Interventions	(1) sertraline, 16 participants; (2) donepezil, 17 participants; (3) tiagabine, 17 participants; (4) placebo, 17 participants Drug dose: sertraline 100 mg/day; donepezil 10 mg/day; tiagabine 20 mg/day Treatment included weekly one-hour individual standardized manual guided cognitive-behavioral therapy Setting: Outpatients. Duration 8 weeks. Country of origin: USA
Outcomes	Quantitative urine BE levels; self-report of substance use and craving (Mezinskis 1998); CGI scale scores (Tracy 2000); ASI score (McLellan 1992); Risk Assessment Battery for the evaluation of contracting HIV risk (Navaline 1994); Depression severity (HDRS, Hamilton 1967); Anxiety severity (HARS scores, Hamilton 1967).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A randomised block design was used to assign subjects to treatment groups.
Allocation concealment (selection bias)	Unclear risk	The method of concealment is not described. The investigational pharmacist was unblinded. All manipulations of medication, including the weekly pill count, was done by the research pharmacist

Winhusen 2005 (*Continued*)

Blinding (performance bias and detection bias) Subjective	Unclear risk	This is was a modified, placebo-controlled study with an unmatched placebo. The study Principal Investigator and the rest of the clinical research staff were not aware of what medication patients were taking.
Blinding (performance bias and detection bias) Objective	Low risk	This is was a modified, placebo-controlled study with an unmatched placebo. The study Principal Investigator and the rest of the clinical research staff were not aware of what medication patients were taking.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Strategies for handling missing data, such as baseline- endpoint analysis and Generalized Estimating Equation analysis, were undertaken. Reasons for drop out are not given by medication group

Winstanley 2011

Methods	Randomised placebo controlled double blind trial
Participants	186 participants, mean age 39; male 54.5%; African-American 48.3%; 11.5 years of education on the average; unemployed 75.9%; BDI score 13.5 on the average inclusion criteria: DSM-IV diagnosis of current opioid and cocaine dependence (based upon evaluation with the SCID (First 2002)); eligibility to receive methadone maintenance therapy; age between 18 and 60 years; no significant chronic medical illness; no serious psychiatric illness (e.g., schizophrenia) Exclusion criteria: urine sample positive for methadone on the day of admission; symptomatic HIV infection; laboratory test results found to be unacceptable for participation in the study as determined by medical staff not involved in the study as investigators; a positive pregnancy test for females
Interventions	(1) Fluoxetine plus methadone plus vouchers, 46 participants; (2) placebo plus methadone plus vouchers, 45 participants; (3) fluoxetine plus methadone plus standard care, 48 participants; (4) placebo plus methadone plus standard care, 47 participants Drug dose: fluoxetine 60 mg/day; methadone maximum 100 mg/day Contigiency management involved the worth of monetary vouchers for urine free from cocaine Participants were involved in a manualized psychosocial individual and group counselling Setting: outpatients. Duration: 16 weeks. Country of origin: USA
Outcomes	Primary outcomes: cocaine use (urine toxicology testing and self-report); retention in treatment. Secondary outcomes: side effects; opioid use based on urine toxicology screening and on self-reports; self-reported IV drug use; ASI composite scores (McLellan 1980); depression

Winstanley 2011 (*Continued*)

	symptoms (BDI; Beck 1961); anxiety symptoms (STAI; Spielberger 1983); self-reports of cocaine craving; clinicians' ratings of modified global assessment of cocaine severity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A stratified randomised procedure was used.
Allocation concealment (selection bias)	Low risk	Only the pharmacy staff (who did not have subject contact) was aware of random assignment and dosage
Blinding (performance bias and detection bias) Subjective	Low risk	All capsules were identical in weight and appearance and were dispensed in blister packages. Patients and medical staff were blinded to both the fluoxetine/placebo and methadone doses
Blinding (performance bias and detection bias) Objective	Low risk	All capsules were identical in weight and appearance and were dispensed in blister packages. Patients and medical staff were blinded to both the fluoxetine/placebo and methadone doses
Incomplete outcome data (attrition bias) All outcomes	Low risk	Strategies for handling missing data, within longitudinal data analyses (LDAs) were used. Reasons for drop out are given by medication group

ASI - Addiction Severity Index
BDI - Beck Depression Inventory
BE - Benzoylecgonine
BPRS - Brief Psychiatric Rating Scale
CCS - Cocaine Craving Scale
CCI - Cocaine Craving Intensity
CGI - Clinical Global Impression
DIS - Diagnostic Interview Schedule
DSM-III - Diagnostic and Statistic Manual (American Psychiatric Association), third edition
DSM-III-R - Diagnostic and Statistic Manual (American Psychiatric Association), third edition revised
DSM -IV - Diagnostic and Statistic Manual (American Psychiatric Association), fourth edition
ICD - International Classification of Disease
Hal-DIRS - Halikas-Crosby Drug Impairment Rating Scale
HARS - Hamilton Anxiety Rating Scale
HDRS - Hamilton Depression Rating Scale

HLMs - Hierarchical Linear Models
POMS - Profile of Mood States
SCID - Structured Clinical Interview for DSM
STAI - State Trait Inventory for Adults
QCI - Quantitative Cocaine Inventory

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Carroll 1995	Study design not in the inclusion criteria: it analyses results from a previous study (Carroll 1994) to investigate predictivity of depression.
Cornelius 1998	Study design not in the inclusion criteria: it uses data from another study on the efficacy of fluoxetine for depressed alcoholics to carry out secondary analysis
Ehrman 1996	Study design not in the inclusion criteria: subjects included in the study are a subset of those participating to another trial (Cornish 2001).
Feingold 2002	Study design not in the inclusion criteria: the paper reports the findings from the crossover component of an included trial (Oliveto 1999). Included subjects are a sub sample represented by those completing at least 16 weeks of treatment
Galloway 1996	Study design not in the inclusion criteria: non randomised open study; uses an historical control group
Gawin 1984 a	Study design not in the inclusion criteria: non randomised open clinical trial
Gonzalez 2003	Study design was not in the inclusion criteria: it analyses results from a previous study (Kosten 2003) to investigate predictivity of depression.
Haberny 1995	Study design not in the inclusion criteria. Outcome measures not in the inclusion criteria: it gives indication about selegiline safety by investigating interactions between selegiline and cocaine
Kampman 1999	Study design not in the inclusion criteria: it is an open, not randomised study; the control group started a treatment with placebo (multivitamins) in a different period of time
Kampman 2003	Objectives not in the inclusion criteria: it does not focus on the use of an antidepressant
Kampman 2005	Overview of other included studies (Ciraulo 2005 a; Ciraulo 2005 b; Winhusen 2005).
Kosten 1987	Study design not in the inclusion criteria: open, not randomised, study
Kosten 1992 b	Outcome measures not in the inclusion criteria: only subjective and physiological effects to infusion of cocaine 0.125 to 0.5 mg/kg and placebo were reported
Kosten 1992 c	Study design not in the inclusion criteria: it is a follow-up study using subjects enrolled in a previous trial (Gawin 1989).

(*Continued*)

Kosten 2005	Study design not in the inclusion criteria. It analyses results from a previous study (Oliveto 1999) to investigate predictivity of cocaine use.
Leal 1994	Study design not in the inclusion criteria: it analyses results from a previous study (Kosten 1992 a) to investigate predictivity of Antisocial Personality Disorder
Levin 2002	Study design not in the inclusion criteria: there is not control group
Levin 2008	Study design not in the inclusion criteria: it is not a clinical trial
McDowell 2000	Study design not in the inclusion criteria: it is not a controlled trial
Milligan 2004	Study design not in the inclusion criteria: it analyses results from one previous study (Carroll 1994) to investigate predictivity of ethnic differences in relation to treatment
Montoya 2002	Study design not in the inclusion criteria: open label study comparing two combinations of bupropion and bromocriptine
Oliveto 1995	Objectives not in the inclusion criteria: it focuses on "cocaine use"
Reid 2005	Objectives not in the inclusion criteria: It does not focus on the use of an antidepressant
Rowbotham 1984	Objectives not in the inclusion criteria: it assesses the interaction between trazodone and oral cocaine by examinating the effects of a single, 2 mg/Kg , oral dose of cocaine hydrochloride after pretreatment with a 100 mg oral dose of trazodone hydrochloride
Sofuoglu 2003	Study design not in the inclusion criteria: it analyses results from a previous study (Kosten 2003) to investigate predictivity of cocaine use.
Szerman 2005	Study design not in the inclusion criteria: there is not control group
Upadhyaya 2001	Objectives not in the inclusion criteria: open study evaluating venlafaxine treatment of patients with comorbid alcohol or cocaine abuse and attention-deficit/hyperactivity disorder
Ziedonis 1991	Study design not in the inclusion criteria: it analyses results from a previous study (Kosten 1992 a) to investigate predictivity of cocaine use.
Zueco Pérez 2002	Study design not in the inclusion criteria: there is not control group

Characteristics of studies awaiting assessment *[ordered by study ID]*

Gawin 1996

Methods	Randomised controlled double blind trial
Participants	81 participants meeting DSM-III-R criteria for cocaine dependence, crack smokers
Interventions	(1) desipramine, 27 participants; (2) flupenthixol, 27 participants; (3) placebo, 27 participants Minimal psychotherapy was provided to better isolate pure neuropharmacological effects Setting: Outpatients. Duration 6 weeks. Country of origin: USA
Outcomes	Retention in treatment; cocaine use; craving for cocaine, Beck depression scores, SCL-90 scores
Notes	This was an abstract of a poster presented at a conference. A published report on this trial was not found

Gonsai 2002

Methods	Randomised controlled double blind trial
Participants	60 participants depressed cocaine dependents.
Interventions	(1) sertraline hydrochloride, (200 mg/day); (2) placebo. Patients received cognitive behavioral treatment during weeks 4-12 Duration 12 weeks. Country of origin: USA
Outcomes	Primary outcomes: urine toxicology results for cocaine/metabolite or other illicit drugs. Secondary outcomes: scores on Hamilton Depression Rating Scale
Notes	This was an abstract of a poster presented at a conference. A published report on this trial was not found

Characteristics of ongoing studies *[ordered by study ID]*

Afshar 2006

Trial name or title	The Efficacy of Mirtazapine in Depressed Cocaine Dependent Subjects
Methods	Randomised controlled double blind trial
Participants	64 participants:18 - 64 years: both gender Inclusion Criteria: DSM-IV diagnosis of cocaine dependence; HDRS score of 12 or above and history of autonomous depression, defined as meeting DSM-IV criteria for major depression or dysthymic disorder during any lifetime period of abstinence of 30 days or longer; at least one urine toxicology positive for cocaine BE over the consecutive two-week baseline screening period during which 6 urine samples have been obtained; males and non-pregnant, non-nursing females, 18-64 years of age (inclusive); individuals able to give written informed consent and willing to comply with all study procedures Exclusion Criteria: Any Axis I diagnosis that, in the opinion of the Principal Investigator, may interfere with the course of the trial; physiological dependence on alcohol or opiates requiring medical detoxification; a

Afshar 2006 (*Continued*)

	medical or neurological illness that in the clinical judgment of the investigator would make study compliance difficult or contraindicate the use of mirtazapine; any clinically significant abnormal lab values or LFTs which are greater than 3 times the normal limit; the need or intention to use concurrently with or within four weeks prior to study drug administration, any of the following medications: monoamine oxidase inhibitors and/or sibutramine. Iin addition, other medications such as alpha2-agonists and medications which affect the enzymes CYP1A2, CYP2D6, CYP3A4 (as inhibitors, substrates, or inducers), and serotonin modulators should be used with caution. The research physician will decide on this issue; females of childbearing potential who do not agree to use a medically acceptable method of birth control (barrier, IUD, oral or depot contraceptive medication, or complete abstinence); positive pregnancy test; breastfeeding; known drug allergy or sensitivity to mirtazapine; participation in an investigational drug or device study within 1 month of enrolment in the present study; enrolment in an opiate-substitution (i.e., methadone, LAAM) treatment program within 45 days of enrolling in the present study; Individuals having taken LAAM, methadone or naltrexone within 14 days of enrolment in the present study; individuals who, in the clinical judgment of the Investigator, are actively and acutely suicidal; subjects, who in the opinion of the investigator, have a medical condition that may interfere with study assessments and/or put them at undue risk; subjects, who in the opinion of the investigator, will have difficulty complying with study procedures
Interventions	(1) mirtazapine; (2) placebo. Drug dose: mirtazapine 45 mg/day. Setting: outpatient. Duration: 12 weeks. Country of origin: USA
Outcomes	Primary outcomes: Efficacy will be determined by the quantitative analysis of urine for the cocaine metabolite BE during the full 12 weeks of treatment. Quantitative urine results from the two groups (Mirtazapine and Control) will be compared. Secondary outcomes: The Clinical Global Impression will be administered at baseline and during each week of treatment to determine efficacy
Starting date	September 2005
Contact information	Miriam Afshar, Boston University; Boston, Massachusetts, United States, 02118
Notes	Status: Study is ongoing but not recruiting

Cornish 1999a

Trial name or title	Gepirone Vs Placebo in Treatment of Cocaine Dependence
Methods	Placebo controlled trial
Participants	Information not available
Interventions	(1) gepirone; (2) placebo.
Outcomes	Information not available
Starting date	1999

Cornish 1999a (*Continued*)

Contact information	James Cornish, University of Pennsylvania, Philadelphia, Pennsylvania, United States
Notes	Status: completed

Cornish 1999b

Trial name or title	Ritanserin in Treatment of Cocaine Dependence - 1
Methods	Information not available
Participants	Estimated enrolment: 0; Age 28 - 47 years; Male
Interventions	Information not available
Outcomes	Information not available
Starting date	July 1992
Contact information	James Cornish, MD, University of Pennsylvania Philadelphia, Pennsylvania, United States, 19104 6178
Notes	Status: completed

Hatsukami 1999a

Trial name or title	Effects of nefazodone on treatment of female cocaine abusers
Methods	Placebo controlled double blind trial
Participants	Estimated Enrollment: 0; age 18 - 55 years; female Inclusion Criteria: Females, ages 18-55, minimum use of 8 days of the last 30, minimum of 8th grade education, current diagnosis of cocaine abuse/dependence Exclusion Criteria: Unstable medical illness, dx of MR, OBS, bipolar
Interventions	(1) nefazodone; (2) placebo. Not other information were available
Outcomes	Primary Outcome Measures: Craving; Drug use; Depression; Life functioning; HIV risk behaviours.
Starting date	December 1996
Contact information	Dorothy Hatsukami, PhD, University of Minnesota, Minneapolis, Minnesota, United States, 55455
Notes	This study evaluated the effect of nefazodone on reducing cocaine use and craving in both depressed and non depressed women and if there was a greater effect in depressed women Status: completed

Hatsukami 1999b

Trial name or title	Effect of nefazodone on relapse in females with cocaine abuse
Methods	Placebo controlled double blind trial
Participants	Estimated Enrollment: 0; age 18 - 55 years; female Inclusion Criteria: Female; ages 18-55; cocaine abuse/dependence; use of cocaine 7 days of the last 30 days or of the 30 days prior to current abstinence; less than 90 days current abstinence; at least an 8th grade education Exclusion Criteria: Unstable medical conditions; current use of Hismanal, Seldane, or Propulsid; dx of MR, OBS, bipolar, schizophrenia
Interventions	(1) nefazodone; (2) placebo. Not other information were available
Outcomes	Primary outcomes: retention; primary drug use; relapse. Secondary outcomes: depression.
Starting date	January 1999
Contact information	Dorothy Hatsukami, PhD, University of Minnesota, Minneapolis, Minnesota, United States, 55455
Notes	The purpose of this study is to determine the effect of nefazodone on relapse to cocaine in women and if a greater effect will be seen in the dependent condition. A relapse and coping skills questionnaire will be utilized to determine the various factors important to the relapse process Status: completed

Nunes 2005

Trial name or title	Placebo-Controlled Venlafaxine Treatment for Depressed Cocaine Abusers
Methods	Randomised placebo controlled double blind trial
Participants	150 participants; age 18 - 60 years; both gender Inclusion Criteria: meeting DSM-IV diagnosis criteria for current cocaine dependence; using cocaine at least one day in the month prior to study entry; meeting DSM-IV criteria for major depression or dysthymia, with depression either primary (predates earliest life-time substance abuse), depression persistent during 6 months of cocaine abstinence in the past, or depression for at least 3 months prior to study entry; if female, willing to use contraception throughout the study Exclusion Criteria: meeting DSM-IV diagnosis criteria for bipolar disorder, schizophrenia, or any psychotic disorder other than transient psychosis due to drug abuse; chronic organic mental disorder; significant risk of suicide, based on current mental state or history; untreated seizure disorder or history of substance-related seizures; unstable physical disorders that may make study participation dangerous, including hypertension, hepatitis (mildly elevated transaminase levels that are less than 4 times the upper limit or normal levels are acceptable), and diabetes; coronary vascular disease, as indicated by medical history, suspected by abnormal ECG, or history of heart symptoms; irregular heartbeat as indicated by QRS duration greater than 0.11; current use of other prescribed psychotropic medications; currently meeting DSM-IV diagnosis criteria for dependence on any drugs other than nicotine, marijuana, or alcohol; history of allergic or adverse reaction to desipramine or venlafaxine; prior history of failing to respond to venlafaxine; history of alcohol withdrawal syndrome in the year prior to study entry; current evidence of alcohol withdrawal, such as pulse rate greater

Nunes 2005 (*Continued*)

	than 115 beats per minute, blood pressure greater than 140/90 mm Hg, or visible tremors; pregnant or breastfeeding
Interventions	(1) venlafaxine; (2) placebo. Drug dose: venlafaxine up to 300 mg/day. Participants will also attend a therapy session once a week Setting: outpatient. Duration: 24 weeks. Country of origin: USA
Outcomes	Primary outcomes: cocaine use (measured by Clinical Global Impression-Objective Scale at Weeks 11 and 24); cocaine use (measured by urine screens at Weeks 1-12): depression (measured by Hamilton Depression Rating Scale at Weeks 11 and 24)
Starting date	October 1999
Contact information	Edward Nunes, Herbert Kleber, New York State Psychiatric Institute, New York, New York, United States, 10032
Notes	Status: completed

Oliveto 2006

Trial name or title	Clinical Efficacy of Sertraline Augmented With Gabapentin in Depressed, Recently Abstinent Cocaine-dependent Humans
Methods	Randomised controlled double blind trial
Participants	Age:18 to 65 years; both gender. Inclusion criteria: 18-65 years old; not currently enrolled in a treatment program; having a history of cocaine use, with street cocaine use by history being a minimum of 1 gram during the preceding 3 months; meeting DSM-IV criteria for cocaine dependence as assessed by the substance abuse section of the SCID; having laboratory confirmation of recent cocaine use (positive urine for cocaine or benzoylecgonine) during the month prior to study entry; scoring at least 15 on the HDRS; women of childbearing age must have a negative pregnancy test to enrol in this study and must agree to monthly pregnancy testing Exclusion criteria: current diagnosis of other drug or alcohol physical dependence (other than cocaine or tobacco); ill health (e.g., major cardiovascular, renal, endocrine, hepatic disorder); history of schizophrenia, or bipolar type I disorder; present or recent use of over-the-counter or prescription psychoactive drug or drug(s) that would be expected to have major interaction with drug to be tested; medical contraindication to receiving study medications (e.g., for sertraline, use of monoamine oxidase inhibitor within last two weeks; significant history of seizures; significant history of head trauma or serious neurological disorders); current suicidality or psychosis; liver function tests (i.e., liver enzymes) greater than three times normal levels; pregnancy
Interventions	(1) sertraline; (2) sertraline plus gabapentin; (3) placebo. Drug dose: Sertraline 200 mg/day; gabapentin 1200 mg/day. All subjects are expected to participate in weekly individual cognitive behavioral therapy Setting: residential three weeks, then outpatient. Duration: 12 weeks. Country of origin: USA

Oliveto 2006 (*Continued*)

Outcomes	Primary outcomes: urine toxicology results for cocaine/metabolite or other illicit drugs. Secondary outcomes: scores on HDRS.
Starting date	January 2006
Contact information	Alison Oliveto, PhD. University of Arkansas for Medical Sciences. Little Rock, Arkansas, United States, 72205 7911
Notes	Status: completed

Raby 2005

Trial name or title	A Placebo Controlled Trial of Mirtazapine for Patients With Depression and Cocaine Dependence
Methods	Randomised placebo controlled double blind trial
Participants	260 participants; both gender. Inclusion criteria: meeting DSM-IV criteria for current cocaine dependence; currently seeking treatment for cocaine dependence; using cocaine for at least one day per 2-week period in the month prior to study entry; meeting DSM-IV criteria for current major depression or dysthymia syndrome; scoring greater than 12 on the Baseline 21 Hamilton Depression Scale Exclusion criteria: meeting DSM-IV criteria for past mania (e.g., bipolar disorder), schizophrenia, or any psychotic disorder other than transient psychosis due to drug abuse; scoring less than 11 on the Baseline 21 HDRS; history of seizures; history of an allergic reaction to mirtazapine; chronic organic mental disorder; current suicidal risks or any history of suicidal behavior; pregnant, breastfeeding, or unwilling to use an adequate method of contraception for the duration of the study; unstable physical disorders, including high blood pressure, acute hepatitis, or diabetes; coronary vascular disease as indicated by history, or suspected by abnormal electrocardiogram, or history of cardiac symptoms; cardiac conduction system disease, as indicated by an electrocardiogram QRS duration greater than 0.11; history of failure to respond to a previous trial of mirtazapine; currently taking psychotropic medication; meeting DSM-IV criteria for opioid or sedative-hypnotic dependence; meeting DSM-IV criteria for alcohol dependence with evidence of clinically significant physiological dependence in need of medically supervised detoxification; current alcohol or marijuana dependence identified as the main problem for seeking treatment; individuals with alcohol or marijuana dependence (without significant physiological dependence) and cocaine dependence are eligible, as long as cocaine is identified as the primary substance problem for which they are seeking treatment; history of neutropenia or agranulocytosis with fever and an infection
Interventions	(1) mirtazapine; (2) placebo. Drug dose: not specified. Participants will be involved in motivational interviews and cognitive behavioral relapse prevention therapy; In addition, participants will earn low-value monetary vouchers contingent on cocaine abstinence Setting: outpatient. Duration: 8 weeks. Country of origin: USA
Outcomes	Mood and drug use
Starting date	2006

Raby 2005 (*Continued*)

Contact information	Lisa Sanfilippo, BA; sanfili@pi.cpmc.columbia.edu; Research Foundation for Mental Hygiene, Inc. New York, United States
Notes	Status: recruiting

Schmitz 2005a

Trial name or title	Pharmacotherapy Dosing Regimen in Cocaine and Opiate Dependent Individuals
Methods	Randomised placebo controlled double blind trial
Participants	200 participants; age 22 - 50 years; both gender. Inclusion criteria: meeting cocaine abuse and dependence criteria (as determined by the SCID); meeting opiate dependence criteria (as determined by the SCID); in good general physical and psychiatric health (except for possible acute drug use related problems) Exclusion criteria: meeting diagnostic criteria for other psychiatric disorders, including other forms of drug dependence (other than nicotine); current cardiovascular disease (as determined by an electrocardiogram); circumstances not allowing for completion of study (on probation or parole); ethical constraints of supervision not allowing confidentiality (on probation or parole)
Interventions	(1) Citalopram low dose plus methadone maintenance; (2) citalopram high dose plus methadone maintenance; (3) Placebo plus methadone maintenance Drug dose: (1) Citalopram 20 mg plus methadone 1.2 mg/kg; (2) Citalopram 40 mg plus methadone 1.2 mg/kg; (3) placebo plus methadone 1.2 mg/kg Setting: outpatient Duration: 24 weeks. Country of origin: USA
Outcomes	Primary outcomes: confirmed abstinence from cocaine. Secondary outcomes: retention; medication compliance.
Starting date	July 2006
Contact information	Laura B Madden-Fuentes, B.A. 713-500-2563 Laura.MaddenFuentes@uth.tmc.edu; Ann Garcia, MA 713-500-2804 Ann.D.Garcia@uth.tmc.edu University of Texas Health Science Center, Houston, Texas, United States, 77030
Notes	Status: recruiting

Schmitz 2005b

Trial name or title	ERP-8654 - Integrated Treatment for Cocaine and Mood Disorders
Methods	Randomised placebo controlled double blind trial
Participants	Estimated Enrollment: 140 cocaine dependent patients with comorbid major depressive disorder; age 18 - 55 years; both gender Inclusion criteria: generally physically healthy; aged 18-55; meeting cocaine dependence by DSM-IV criteria;

Schmitz 2005b (*Continued*)

	meeting major depressive disorder or substance-induced depression disorder by DSM-IV criteria; willing and able to participate in the 12 week treatment study and one year follow up Exclusion criteria: pregnant or breastfeeding; taking medications that interact with the study medication (MAO inhibitors, anticonvulsants, haloperidol, phenothiazines,selegiline, anaesthetics; having other psychiatric diagnoses requiring therapy or medication; being physically dependent on opiates or alcohol; currently being treated with bupropion hydrochloride
Interventions	(1) bupropion plus integrated CBT; (2) bupropion plus clinical management; (3) placebo plus integrated CBT; (4) placebo plus clinical management Setting: outpatient. Duration: 12 weeks. Country of origin: USA
Outcomes	Primary outcomes: urine toxicology for cocaine
Starting date	April 2001
Contact information	Joy Schmitz, PhD, University of Texas Health Sci Cntr Houston, Houston, Texas, United States, 77030
Notes	Status: completed

BE - Benzoylecgonine
DSM -IV - Diagnostic and Statistic Manual (American Psychiatric Association), fourth edition
HDRS - Hamilton Depression Rating Scale
SCID - Structured Clinical Interview for DSM

DATA AND ANALYSES

Comparison 1. Antidepressants vs placebo according to any definition

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dropout	31		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Dropouts: all studies	31	2819	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.93, 1.14]
1.2 Dropouts: excluding studies with high risk of bias	27	2417	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.91, 1.12]
2 Retention in treatment as mean number of weeks in treatment	8	705	Mean Difference (IV, Fixed, 95% CI)	0.34 [0.22, 0.47]
3 Abstinence, for at least three consecutive weeks	8	942	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.99, 1.51]
4 Abstinence as number of weeks of continuous abstinence	7	1062	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.21, 0.22]
5 Use of cocaine during the trial	4	251	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.91, 1.21]
6 Craving for cocaine	9		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Craving score: different scales of measure	9	636	Std. Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.13, 0.18]
6.2 Craving score: Mezinskis Scale, endpoint	3	312	Std. Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.11, 0.33]
7 Addiction Severity Index (ASI) score	7		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Medical	6	614	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.02, 0.07]
7.2 Employment	6	603	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.04, 0.05]
7.3 Alcohol	7	645	Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.02, 0.02]
7.4 Drugs	7	674	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.01, 0.01]
7.5 Legal	7	648	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.01, 0.04]
7.6 Family/ social	7	647	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.04, 0.01]
7.7 Psychiatric	7	646	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.02, 0.03]
8 Mood dichotomous measures	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Depression response, Clinician's Global rating (CGI)	2	152	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.49, 2.42]
8.2 >50% reduction in Hamilton Depression Rating Scale	2	321	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.89, 2.23]
9 Mood continuous measures	10		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 Hamilton Depression Rating Scale at the end of the treatment	6	420	Mean Difference (IV, Fixed, 95% CI)	-1.41 [-2.44, -0.37]
9.2 CGI depression severity score at the end of the treatment	3	390	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.35, 0.18]
9.3 Beck Depression Inventory (BDI) at the end of the treatment	2	98	Mean Difference (IV, Fixed, 95% CI)	0.78 [-1.42, 2.97]

9.4 Brief Psychiatric Rating Scale (BPRS) at the end of the treatment	2	48	Mean Difference (IV, Fixed, 95% CI)	-16.00 [-18.55, -17.45]
10 Adverse events	13		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Withdrawn due to adverse events	13	1396	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.91, 2.12]
10.2 Participants presenting al least one side effect	2	275	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [1.08, 1.77]

Comparison 2. Antidepressants vs placebo for operationally defined cocaine dependence

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dropout	22		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Dropouts: all studies	22	2150	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.91, 1.14]
1.2 Dropouts: excluding studies with high risk of bias	19	1765	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.86, 1.11]
2 Retention in treatment	7		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Retention in treatment (mean number of weeks): all studies	6	490	Mean Difference (IV, Fixed, 95% CI)	0.35 [0.22, 0.48]
2.2 Retention in treatment (mean number of weeks): excluding studies with high risk of bias	5	570	Mean Difference (IV, Fixed, 95% CI)	0.33 [0.20, 0.46]
3 Abstinence for at least three consecutive weeks	5	739	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.89, 1.41]
4 Abstinence as number of weeks of continuous abstinence	6	992	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.25, 0.19]
5 Use of cocaine during the trial	3	229	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.90, 1.20]
6 Withdrawn due to adverse events	11	1204	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.90, 2.19]

Comparison 3. Different class of antidepressants versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dropout	21		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Dropout: Tricyclics	15	1141	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.85, 1.18]
1.2 Dropout: SSRIs	6	527	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.70, 1.41]
2 Retention in treatment as mean number of weeks in treatment: tricyclics	3	159	Mean Difference (IV, Fixed, 95% CI)	1.10 [0.28, 1.91]
3 Abstinence for at least three consecutive weeks: tricyclics	5	367	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [1.10, 2.17]

4 Abstinence as average number of weeks of continuous abstinence: tricyclics	3	308	Mean Difference (IV, Fixed, 95% CI)	0.71 [-0.02, 1.44]
5 Use of cocaine during the trial: tricyclics	2	37	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.34, 2.11]
6 Craving for cocaine	5		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Craving score (different scales): SSRIs	3	93	Std. Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.64, 0.19]
6.2 Craving score (different scales): tricyclics	2	55	Std. Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.52, 0.54]
6.3 Craving score (Mezinskis Scale): SSRIs	2	65	Std. Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.45, 0.53]
7 Addidtion Severity Index (ASI) score, Drugs: SSRIs	2	65	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.03, 0.06]
8 Mood continuous measures	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 Beck Depression Inventory (BDI) at the end of the treatment: tricyclics	2	55	Mean Difference (IV, Random, 95% CI)	-1.27 [-7.05, 4.51]
8.2 Brief Psychiatric Rating Scale (BPRS) at the end of the treatment: tricyclics	2	44	Mean Difference (IV, Random, 95% CI)	-11.98 [-24.68, 0.73]
9 Adverse events	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Withdrawn due to adverse events: tricyclics	5	381	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.64, 2.43]
9.2 Withdrawn due to adverse events: SSRIs	3	251	Risk Ratio (M-H, Fixed, 95% CI)	3.55 [1.11, 11.34]

Comparison 4. Specific antidepressants versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dropout	21		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Dropouts: desipramine	13	1011	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.95, 1.20]
1.2 Dropouts: fluoxetine	3	430	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [1.08, 1.57]
1.3 Dropouts: bupropion	3	325	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.79, 1.25]
1.4 Dropouts: ritanserin	2	145	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.60, 2.14]
2 Retention in treatment as mean number of weeks in treatment: desipramine	3	159	Mean Difference (IV, Fixed, 95% CI)	1.10 [0.28, 1.91]
3 Abstinence for at least three consecutive weeks: desipramine	4	254	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [1.00, 2.03]
4 Abstinence as average number of weeks of continuous abstinence: desipramine	3	308	Mean Difference (IV, Fixed, 95% CI)	0.71 [-0.02, 1.44]
5 Use of cocaine during the trial: desipramine	2	37	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.34, 2.11]
6 Craving for cocaine	2	55	Mean Difference (IV, Fixed, 95% CI)	0.18 [-3.67, 4.03]
7 Mood continuous measures	4		Mean Difference (IV, Random, 95% CI)	Subtotals only

7.1 Beck Depression Inventory (BDI) at the end of the treatment: desipramine	2	55	Mean Difference (IV, Random, 95% CI)	-1.27 [-7.05, 4.51]
7.2 Brief Psychiatric Rating Scale (BPRS) at the end of the treatment: desipramine	2	44	Mean Difference (IV, Random, 95% CI)	-11.98 [-24.68, 0.73]
8 Adverse events	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Withdrawn due to adverse events: desipramine	4	268	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.68, 2.96]
8.2 Withdrawn due to adverse events: fluoxetine	2	218	Risk Ratio (M-H, Fixed, 95% CI)	3.60 [1.03, 12.62]
8.3 Participants presenting al least one adverse event: ritanserin	2	145	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.69, 1.16]

Comparison 5. Antidepressants versus different class of other medications

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dropout	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Dropouts: antidepressants versus dopamine agonists	4	171	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.80, 1.41]
1.2 Dropouts: antidepressants versus anticonvulsants	3	162	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.63, 1.17]
2 Craving for cocaine: antidepressants versus dopamine agonists	3	86	Std. Mean Difference (IV, Random, 95% CI)	-0.16 [-0.59, 0.26]
3 Withdrawn due to adverse events: antidepressants versus dopamine agonists	2	103	Risk Ratio (M-H, Fixed, 95% CI)	2.48 [0.38, 16.19]

Comparison 6. Different classes of antidepressants versus different classes of other medications

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dropout: SSRIs versus anticonvulsants	2	66	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.19, 3.29]
2 Use of cocaine continuous measures: SSRIs versus anticonvulsants	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Rate of Self-reported Cocaine Use (days/wk) at the end of the treatment	2	64	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-1.19, 0.96]

2.2 Benzoilecgonine (BE) concentration (endpoint ln of BE values or mean value)	2	66	Mean Difference (IV, Fixed, 95% CI)	-0.27 [-1.48, 0.95]
3 Craving for cocaine: SSRIs versus anticonvulsants	2	66	Std. Mean Difference (IV, Random, 95% CI)	0.02 [-0.79, 0.83]
4 Addiction Severity index (ASI) score, Drugs: SSRIs versus anticonvulsants	2	66	Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.05, 0.04]

Comparison 7. Desipramine versus Amantadine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dropouts	3	131	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.69, 1.23]
2 Abstinence, last week	2	43	Odds Ratio (M-H, Fixed, 95% CI)	2.30 [0.62, 8.55]
3 Craving for cocaine	2	46	Std. Mean Difference (IV, Random, 95% CI)	-0.16 [-0.74, 0.43]
4 Mood (BDI)	2	46	Mean Difference (IV, Fixed, 95% CI)	-0.17 [-1.93, 1.59]

Comparison 8. Antidepressants plus psychosocial interventions vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dropout	25		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Dropouts: associated psychotherapy	17	1845	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [1.01, 1.20]
1.2 Dropouts: associated counselling	8	589	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.72, 1.09]
2 Retention in treatment	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Retention in treatment (mean number of weeks): studies with psychotherapy	4	237	Mean Difference (IV, Fixed, 95% CI)	0.92 [0.16, 1.68]
2.2 Retention in treatment (mean number of weeks): studies with counselling	3	174	Mean Difference (IV, Fixed, 95% CI)	-0.55 [-1.68, 0.58]
3 Abstinence	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Abstinent for at least three consecutive weeks: studies with psychotherapy	5	544	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.89, 1.88]
3.2 Abstinent for at least three consecutive weeks: studies with counselling	2	188	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.84, 2.48]
4 Adverse events	12		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Withdrawn due to adverse events: studies with psychotherapy	7	701	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [0.91, 3.58]

4.2 Withdrawn due to adverse events: studies with counselling	6	485	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [0.74, 3.47]

Comparison 9. Antidepressants vs placebo participants also opioid dependence status

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dropouts	10	1006	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [1.05, 1.41]
2 Withdrawn due to adverse events	5	492	Risk Ratio (M-H, Fixed, 95% CI)	2.47 [1.03, 5.90]

Comparison 10. Antidepressants vs placebo according to length of trial

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dropout	31		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Dropouts: up to six weeks weeks of treatment	6	282	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.52, 1.25]
1.2 Dropouts: more than six weeks of treatment	25	2671	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.99, 1.20]
2 Retention in treatment: more than six weeks of treatment	6	577	Mean Difference (IV, Fixed, 95% CI)	0.33 [0.20, 0.46]
3 Abstinence for at least three consecutive weeks: more than six weeks of treatment	6	874	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.87, 1.39]
4 Withdrawn due to adverse events: more than six weeks of treatmentAdverse events	11	1298	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.87, 2.07]

Comparison 11. Antidepressants vs placebo (excluding medication with questionable or uncertain antidepressant activity)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dropouts	28	2547	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.92, 1.16]
2 Retention in treatment as mean number of weeks in treatment	7	664	Mean Difference (IV, Random, 95% CI)	0.29 [-0.41, 1.00]
3 Abstinence as number of weeks of continuous abstinence	6	883	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.17, 0.32]

Analysis 1.1. Comparison 1 Antidepressants vs placebo according to any definition, Outcome 1 Dropout.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 1 Antidepressants vs placebo according to any definition

Outcome: 1 Dropout

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Dropouts: all studies					
Arndt 1992	17/53	3/26		0.7 %	2.78 [0.89, 8.64]
Batki 1996	8/16	15/16		2.9 %	0.53 [0.32, 0.88]
Campbell 2003	29/49	34/50		5.7 %	0.87 [0.64, 1.18]
Ciraulo 2005 a	7/34	11/35		1.3 %	0.66 [0.29, 1.49]
Ciraulo 2005 b	10/20	7/20		1.6 %	1.43 [0.68, 3.00]
Ciraulo 2005 b	2/16	2/16		0.3 %	1.00 [0.16, 6.25]
Cornish 2001	10/40	9/40		1.4 %	1.11 [0.51, 2.44]
Elkashef 2006	53/150	40/150		4.9 %	1.33 [0.94, 1.87]
Gawin 1989	11/31	22/32		2.7 %	0.52 [0.30, 0.88]
Giannini 1986	2/10	0/10		0.1 %	5.00 [0.27, 92.62]
Giannini 1993	1/16	3/16		0.2 %	0.33 [0.04, 2.87]
Grabowsky 1995	4/11	5/10		0.9 %	0.73 [0.27, 1.97]
Grabowsky 1995	62/100	22/55		4.7 %	1.55 [1.08, 2.22]
Hall 1994	29/45	30/49		5.5 %	1.05 [0.77, 1.44]
Jenkins 1992	9/20	11/21		2.0 %	0.86 [0.46, 1.62]
Johnson 1997	6/33	5/32		0.8 %	1.16 [0.39, 3.44]
Jones 2004	83/101	76/98		9.6 %	1.06 [0.92, 1.22]
Kolar 1992	0/8	5/9		0.1 %	0.10 [0.01, 1.58]
Kosten 1992 a	8/30	4/31		0.8 %	2.07 [0.69, 6.15]
Kosten 2003	58/80	53/80		7.8 %	1.09 [0.89, 1.35]
Margolin 1995	11/74	13/75		1.6 %	0.86 [0.41, 1.79]
McDowell 2005	30/55	34/56		5.3 %	0.90 [0.65, 1.24]
McElroy 1989	5/9	5/6		1.8 %	0.67 [0.34, 1.32]
Nunes 1995	25/59	27/54		4.1 %	0.85 [0.57, 1.26]
O'Brien 1988	8/32	1/15		0.2 %	3.75 [0.51, 27.33]

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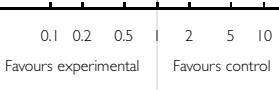
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Oliveto 1999	33/90	26/90		3.8 %	1.27 [0.83, 1.94]
Poling 2006	25/57	19/49		3.4 %	1.13 [0.72, 1.79]
Schmitz 2001	24/34	24/34		5.5 %	1.00 [0.74, 1.36]
Shoptaw 2008	30/37	28/33		7.7 %	0.96 [0.77, 1.18]
Tennant 1985	5/11	5/11		1.1 %	1.00 [0.40, 2.50]
Weddington 1991	27/32	19/28		5.8 %	1.24 [0.93, 1.67]
Winhusen 2005	1/16	5/17		0.2 %	0.21 [0.03, 1.63]
Winstanley 2011	54/94	38/92		5.7 %	1.39 [1.03, 1.88]
Subtotal (95% CI)	**1463**	**1356**		**100.0 %**	**1.03 [0.93, 1.14]**
Total events: 687 (Experimental), 601 (Control)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 48.55, df = 32 (P = 0.03); I^2 =34%					
Test for overall effect: Z = 0.60 (P = 0.55)					
2 Dropouts: excluding studies with high risk of bias					
Arndt 1992	17/53	3/26		0.8 %	2.78 [0.89, 8.64]
Batki 1996	8/16	15/16		3.2 %	0.53 [0.32, 0.88]
Campbell 2003	29/49	34/50		6.6 %	0.87 [0.64, 1.18]
Ciraulo 2005 a	7/34	11/35		1.4 %	0.66 [0.29, 1.49]
Ciraulo 2005 b	2/16	2/16		0.3 %	1.00 [0.16, 6.25]
Ciraulo 2005 b	10/20	7/20		1.7 %	1.43 [0.68, 3.00]
Cornish 2001	10/40	9/40		1.5 %	1.11 [0.51, 2.44]
Elkashef 2006	53/150	40/150		5.6 %	1.33 [0.94, 1.87]
Gawin 1989	11/31	22/32		3.0 %	0.52 [0.30, 0.88]
Giannini 1986	2/10	0/10		0.1 %	5.00 [0.27, 92.62]
Giannini 1993	1/16	3/16		0.2 %	0.33 [0.04, 2.87]
Hall 1994	29/45	30/49		6.3 %	1.05 [0.77, 1.44]
Jenkins 1992	9/20	11/21		2.2 %	0.86 [0.46, 1.62]
Johnson 1997	6/33	5/32		0.8 %	1.16 [0.39, 3.44]
Jones 2004	83/101	76/98		11.8 %	1.06 [0.92, 1.22]
Kosten 1992 a	8/30	4/31		0.8 %	2.07 [0.69, 6.15]
Kosten 2003	58/80	53/80		9.4 %	1.09 [0.89, 1.35]
McDowell 2005	30/55	34/56		6.1 %	0.90 [0.65, 1.24]
McElroy 1989	5/9	5/6		1.9 %	0.67 [0.34, 1.32]
Nunes 1995	25/59	27/54		4.6 %	0.85 [0.57, 1.26]



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Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
O'Brien 1988	8/32	1/15		0.3 %	3.75 [0.51, 27.33]
Oliveto 1999	33/90	26/90		4.2 %	1.27 [0.83, 1.94]
Poling 2006	25/57	19/49		3.7 %	1.13 [0.72, 1.79]
Schmitz 2001	24/34	24/34		6.4 %	1.00 [0.74, 1.36]
Shoptaw 2008	30/37	28/33		9.2 %	0.96 [0.77, 1.18]
Tennant 1985	5/11	5/11		1.1 %	1.00 [0.40, 2.50]
Winhusen 2005	1/16	5/17		0.2 %	0.21 [0.03, 1.63]
Winstanley 2011	54/94	38/92		6.6 %	1.39 [1.03, 1.88]
Subtotal (95% CI)	**1238**	**1179**		**100.0 %**	**1.01 [0.91, 1.12]**

Total events: 583 (Experimental), 537 (Control)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 38.87$, df = 27 (P = 0.07); $I^2 = 31\%$

Test for overall effect: Z = 0.16 (P = 0.88)

Analysis 1.2. Comparison 1 Antidepressants vs placebo according to any definition, Outcome 2 Retention in treatment as mean number of weeks in treatment.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 1 Antidepressants vs placebo according to any definition

Outcome: 2 Retention in treatment as mean number of weeks in treatment

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Cornish 2001	40	5.06 (2.74)	40	5.16 (2.73)		-0.10 [-1.30, 1.10]
Gawin 1989	24	5.41 (1.12)	24	4.37 (1.75)		1.04 [0.21, 1.87]
Hall 1994	45	10.67 (10.66)	49	8.31 (8.41)		2.36 [-1.54, 6.26]
Jenkins 1992	20	8 (3.74)	21	8.14 (3.72)		-0.14 [-2.42, 2.14]
Kolar 1992	8	12 (0)	9	9.33 (3.08)		0.0 [0.0, 0.0]
Lambert Passos 2005	105	6.18 (0.47)	105	5.84 (0.49)		0.34 [0.21, 0.47]
Shoptaw 2008	37	8.5 (5.8)	33	7.9 (5.2)		0.60 [-1.98, 3.18]
Winstanley 2011	73	19.92 (7.71)	72	22.9 (7.6)		-2.98 [-5.47, -0.49]
Total (95% CI)	**352**		**353**			**0.34 [0.22, 0.47]**

Heterogeneity: Chi^2 = 11.29, df = 6 (P = 0.08); I^2 =47%

Test for overall effect: Z = 5.31 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Antidepressants vs placebo according to any definition, Outcome 3 Abstinence, for at least three consecutive weeks.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 1 Antidepressants vs placebo according to any definition

Outcome: 3 Abstinence, for at least three consecutive weeks

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Campbell 2003	13/36	13/39		12.4 %	1.08 [0.58, 2.02]
Elkashef 2006	7/147	12/148		11.9 %	0.59 [0.24, 1.45]
Gawin 1989	14/24	4/24		4.0 %	3.50 [1.35, 9.11]
Giannini 1987 a	9/10	6/10		6.0 %	1.50 [0.87, 2.59]
Lambert Passos 2005	52/105	48/105		47.7 %	1.08 [0.82, 1.44]
McDowell 2005	11/55	11/56		10.8 %	1.02 [0.48, 2.15]
Nunes 1995	11/59	4/54		4.1 %	2.52 [0.85, 7.44]
Shoptaw 2008	6/37	3/33		3.1 %	1.78 [0.48, 6.57]
Total (95% CI)	**473**	**469**		**100.0 %**	**1.22 [0.99, 1.51]**

Total events: 123 (Experimental), 101 (Control)

Heterogeneity: Chi^2 = 10.81, df = 7 (P = 0.15); I^2 =35%

Test for overall effect: Z = 1.84 (P = 0.065)

Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Antidepressants vs placebo according to any definition, Outcome 4 Abstinence as number of weeks of continuous abstinence.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 1 Antidepressants vs placebo according to any definition

Outcome: 4 Abstinence as number of weeks of continuous abstinence

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Carroll 1994	54	3.19 (2.94)	56	2.75 (2.47)		4.5 %	0.44 [-0.58, 1.46]
Elkashef 2006	147	0.97 (1.17)	148	1.08 (1.28)		58.9 %	-0.11 [-0.39, 0.17]
Jones 2004	88	2.4 (1.51)	91	2.66 (1.56)		22.8 %	-0.26 [-0.71, 0.19]
Kosten 2003	80	2.8 (4.09)	80	1.74 (3.21)		3.6 %	1.06 [-0.08, 2.20]
Lambert Passos 2005	105	4.13 (3.48)	105	3.66 (3.48)		5.2 %	0.47 [-0.47, 1.41]
Shoptaw 2008	37	1.74 (2.84)	33	1.14 (1.34)		4.4 %	0.60 [-0.42, 1.62]
Weddington 1991	17	6.2 (4.53)	21	3.6 (3.66)		0.7 %	2.60 [-0.06, 5.26]
Total (95% CI)	**528**		**534**			**100.0 %**	**0.00 [-0.21, 0.22]**

Heterogeneity: Chi^2 = 11.87, df = 6 (P = 0.07); I^2 =49%

Test for overall effect: Z = 0.01 (P = 0.99)

Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Antidepressants vs placebo according to any definition, Outcome 5 Use of cocaine during the trial.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 1 Antidepressants vs placebo according to any definition

Outcome: 5 Use of cocaine during the trial

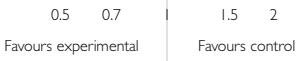
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Johnson 1997	22/33	15/32		17.6 %	1.42 [0.92, 2.21]
Margolin 1995	63/74	65/75		74.7 %	0.98 [0.86, 1.12]
McElroy 1989	2/9	3/6		4.2 %	0.44 [0.10, 1.92]
Tennant 1985	4/11	3/11		3.5 %	1.33 [0.39, 4.62]
Total (95% CI)	**127**	**124**		**100.0 %**	**1.05 [0.91, 1.21]**

Total events: 91 (Experimental), 86 (Control)

Heterogeneity: $Chi^2 = 4.29$, df = 3 (P = 0.23); I^2 =30%

Test for overall effect: Z = 0.66 (P = 0.51)

Test for subgroup differences: Not applicable



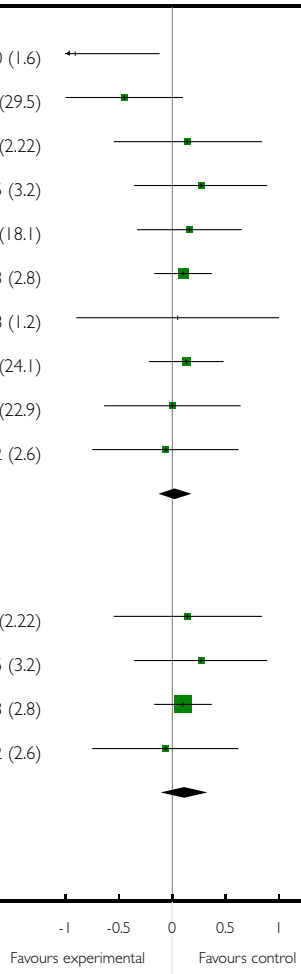
Analysis 1.6. Comparison 1 Antidepressants vs placebo according to any definition, Outcome 6 Craving for cocaine.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 1 Antidepressants vs placebo according to any definition

Outcome: 6 Craving for cocaine

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Craving score: different scales of measure							
Batki 1996	15	8.4 (1.8)	13	10 (1.6)		4.0 %	-0.91 [-1.69, -0.12]
Ciraulo 2005 a	27	30.54 (28.13)	25	43.61 (29.5)		8.0 %	-0.45 [-1.00, 0.10]
Ciraulo 2005 b	16	2.69 (1.96)	16	2.38 (2.22)		5.1 %	0.14 [-0.55, 0.84]
Ciraulo 2005 b	20	3.35 (2.66)	20	2.55 (3.2)		6.3 %	0.27 [-0.36, 0.89]
Cornish 2001	32	18.9 (19.7)	32	15.9 (18.1)		10.1 %	0.16 [-0.33, 0.65]
Elkashef 2006	97	3.6 (3.1)	110	3.3 (2.8)		32.7 %	0.10 [-0.17, 0.37]
Kolar 1992	8	3 (5.66)	9	2.8 (1.2)		2.7 %	0.05 [-0.90, 1.00]
Margolin 1995	63	26 (24.6)	62	22.8 (24.1)		19.8 %	0.13 [-0.22, 0.48]
Weddington 1991	17	5.4 (21.4)	21	5.5 (22.9)		6.0 %	0.00 [-0.64, 0.64]
Winhusen 2005	16	4 (3.5)	17	4.2 (2.6)		5.2 %	-0.06 [-0.75, 0.62]
Subtotal (95% CI)	**311**		**325**			**100.0 %**	**0.02 [-0.13, 0.18]**
Heterogeneity: Chi^2 = 9.93, df = 9 (P = 0.36); I^2 =9%							
Test for overall effect: Z = 0.31 (P = 0.75)							
2 Craving score: Mezinskis Scale, endpoint							
Ciraulo 2005 b	16	2.69 (1.96)	16	2.38 (2.22)		10.3 %	0.14 [-0.55, 0.84]
Ciraulo 2005 b	20	3.35 (2.66)	20	2.55 (3.2)		12.8 %	0.27 [-0.36, 0.89]
Elkashef 2006	97	3.6 (3.1)	110	3.3 (2.8)		66.3 %	0.10 [-0.17, 0.37]
Winhusen 2005	16	4 (3.5)	17	4.2 (2.6)		10.6 %	-0.06 [-0.75, 0.62]
Subtotal (95% CI)	**149**		**163**			**100.0 %**	**0.11 [-0.11, 0.33]**
Heterogeneity: Chi^2 = 0.50, df = 3 (P = 0.92); I^2 =0.0%							
Test for overall effect: Z = 0.96 (P = 0.34)							



Analysis 1.7. Comparison 1 Antidepressants vs placebo according to any definition, Outcome 7 Addiction Severity Index (ASI) score.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 1 Antidepressants vs placebo according to any definition

Outcome: 7 Addiction Severity Index (ASI) score

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Medical							
Carroll 1994	54	0.17 (0.26)	56	0.11 (0.2)		25.5 %	0.06 [-0.03, 0.15]
Ciraulo 2005 a	27	0.14 (0.27)	24	0.18 (0.27)		8.7 %	-0.04 [-0.19, 0.11]
Cornish 2001	29	0.39 (0.31)	29	0.21 (0.26)		8.9 %	0.18 [0.03, 0.33]
Elkashef 2006	119	0.18 (0.28)	118	0.17 (0.29)		36.6 %	0.01 [-0.06, 0.08]
Margolin 1995	63	0.17 (0.31)	62	0.19 (0.33)		15.3 %	-0.02 [-0.13, 0.09]
Winhusen 2005	16	0.21 (0.28)	17	0.26 (0.3)		4.9 %	-0.05 [-0.25, 0.15]
Subtotal (95% CI)	**308**		**306**			**100.0 %**	**0.03 [-0.02, 0.07]**
Heterogeneity: Chi² = 6.95, df = 5 (P = 0.22); I² =28%							
Test for overall effect: Z = 1.16 (P = 0.25)							
2 Employment							
Carroll 1994	54	0.47 (0.33)	56	0.48 (0.3)		15.3 %	-0.01 [-0.13, 0.11]
Ciraulo 2005 b	20	0.76 (0.28)	20	0.69 (0.23)		8.4 %	0.07 [-0.09, 0.23]
Cornish 2001	29	0.72 (0.21)	29	0.76 (0.22)		17.3 %	-0.04 [-0.15, 0.07]
Elkashef 2006	116	0.55 (0.31)	121	0.5 (0.31)		34.1 %	0.05 [-0.03, 0.13]
Margolin 1995	63	0.72 (0.29)	62	0.76 (0.29)		20.6 %	-0.04 [-0.14, 0.06]
Winhusen 2005	16	0.41 (0.34)	17	0.49 (0.31)		4.3 %	-0.08 [-0.30, 0.14]
Subtotal (95% CI)	**298**		**305**			**100.0 %**	**0.00 [-0.04, 0.05]**
Heterogeneity: Chi² = 3.89, df = 5 (P = 0.56); I² =0.0%							
Test for overall effect: Z = 0.12 (P = 0.90)							
3 Alcohol							
Carroll 1994	54	0.07 (0.14)	56	0.08 (0.09)		20.2 %	-0.01 [-0.05, 0.03]
Ciraulo 2005 a	27	0.12 (0.12)	24	0.11 (0.09)		11.8 %	0.01 [-0.05, 0.07]
Ciraulo 2005 b	20	0.17 (0.16)	20	0.17 (0.2)		3.1 %	0.0 [-0.11, 0.11]
Cornish 2001	29	0.11 (0.15)	29	0.1 (0.14)		7.1 %	0.01 [-0.06, 0.08]
Elkashef 2006	112	0.18 (0.19)	116	0.18 (0.17)		18.0 %	0.0 [-0.05, 0.05]
Margolin 1995	63	0.05 (0.07)	62	0.06 (0.11)		37.6 %	-0.01 [-0.04, 0.02]

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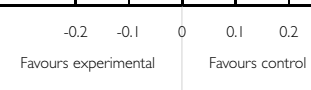
Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Winhusen 2005	16	0.18 (0.15)	17	0.18 (0.24)		2.1 %	0.0 [-0.14, 0.14]
Subtotal (95% CI)	**321**		**324**			**100.0 %**	**0.00 [-0.02, 0.02]**
Heterogeneity: Chi² = 0.60, df = 6 (P = 1.00); I² =0.0%							
Test for overall effect: Z = 0.38 (P = 0.70)							
4 Drugs							
Carroll 1994	54	0.02 (0.03)	56	0.02 (0.02)		73.8 %	0.0 [-0.01, 0.01]
Ciraulo 2005 a	27	0.18 (0.1)	24	0.12 (0.1)		2.2 %	0.06 [0.01, 0.11]
Ciraulo 2005 b	16	0.16 (0.07)	16	0.13 (0.09)		2.2 %	0.03 [-0.03, 0.09]
Ciraulo 2005 b	20	0.15 (0.1)	20	0.2 (0.09)		1.9 %	-0.05 [-0.11, 0.01]
Cornish 2001	29	0.13 (0.07)	28	0.11 (0.08)		4.4 %	0.02 [-0.02, 0.06]
Elkashef 2006	112	0.19 (0.1)	114	0.18 (0.1)		9.9 %	0.01 [-0.02, 0.04]
Margolin 1995	63	0.27 (0.11)	62	0.29 (0.11)		4.5 %	-0.02 [-0.06, 0.02]
Winhusen 2005	16	0.19 (0.12)	17	0.21 (0.12)		1.0 %	-0.02 [-0.10, 0.06]
Subtotal (95% CI)	**337**		**337**			**100.0 %**	**0.00 [-0.01, 0.01]**
Heterogeneity: Chi² = 11.10, df = 7 (P = 0.13); I² =37%							
Test for overall effect: Z = 0.43 (P = 0.67)							
5 Legal							
Carroll 1994	54	0.07 (0.14)	56	0.05 (0.12)		18.6 %	0.02 [-0.03, 0.07]
Ciraulo 2005 a	27	0.1 (0.18)	24	0.03 (0.09)		7.5 %	0.07 [-0.01, 0.15]
Ciraulo 2005 b	20	0.09 (0.17)	20	0.06 (0.14)		4.7 %	0.03 [-0.07, 0.13]
Cornish 2001	29	0.04 (0.12)	29	0.06 (0.16)		8.3 %	-0.02 [-0.09, 0.05]
Elkashef 2006	114	0.05 (0.11)	117	0.06 (0.15)		38.5 %	-0.01 [-0.04, 0.02]
Margolin 1995	63	0.09 (0.18)	62	0.03 (0.08)		18.6 %	0.06 [0.01, 0.11]
Winhusen 2005	16	0.07 (0.15)	17	0.1 (0.17)		3.7 %	-0.03 [-0.14, 0.08]
Subtotal (95% CI)	**323**		**325**			**100.0 %**	**0.01 [-0.01, 0.04]**
Heterogeneity: Chi² = 9.01, df = 6 (P = 0.17); I² =33%							
Test for overall effect: Z = 1.39 (P = 0.16)							
6 Family/ social							
Carroll 1994	54	0.22 (0.21)	56	0.17 (0.18)		13.8 %	0.05 [-0.02, 0.12]
Ciraulo 2005 a	27	0.19 (0.14)	24	0.26 (0.16)		10.8 %	-0.07 [-0.15, 0.01]
Ciraulo 2005 b	20	0.13 (0.11)	20	0.13 (0.09)		19.1 %	0.0 [-0.06, 0.06]
Cornish 2001	29	0.16 (0.21)	29	0.16 (0.17)		7.7 %	0.0 [-0.10, 0.10]
Elkashef 2006	114	0.13 (0.18)	118	0.17 (0.2)		30.9 %	-0.04 [-0.09, 0.01]
Margolin 1995	63	0.12 (0.21)	62	0.15 (0.19)		15.0 %	-0.03 [-0.10, 0.04]
Winhusen 2005	15	0.26 (0.25)	16	0.24 (0.22)		2.7 %	0.02 [-0.15, 0.19]



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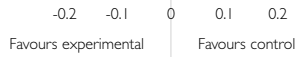
Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Subtotal (95% CI)	**322**		**325**			**100.0 %**	**-0.02 [-0.04, 0.01]**
Heterogeneity: Chi^2 = 6.36, df = 6 (P = 0.38); I^2 =6%							
Test for overall effect: Z = 1.22 (P = 0.22)							
7 Psychiatric							
Carroll 1994	54	0.11 (0.17)	56	0.11 (0.18)		14.6 %	0.0 [-0.07, 0.07]
Ciraulo 2005 a	27	0.21 (0.24)	24	0.22 (0.18)		4.7 %	-0.01 [-0.13, 0.11]
Ciraulo 2005 b	20	0.05 (0.12)	20	0.07 (0.17)		7.5 %	-0.02 [-0.11, 0.07]
Cornish 2001	29	0.09 (0.15)	29	0.09 (0.16)		9.8 %	0.0 [-0.08, 0.08]
Elkashef 2006	113	0.1 (0.16)	116	0.07 (0.13)		43.8 %	0.03 [-0.01, 0.07]
Margolin 1995	63	0.09 (0.16)	62	0.12 (0.21)		14.6 %	-0.03 [-0.10, 0.04]
Winhusen 2005	16	0.1 (0.16)	17	0.13 (0.17)		4.9 %	-0.03 [-0.14, 0.08]
Subtotal (95% CI)	**322**		**324**			**100.0 %**	**0.01 [-0.02, 0.03]**
Heterogeneity: Chi^2 = 3.54, df = 6 (P = 0.74); I^2 =0.0%							
Test for overall effect: Z = 0.42 (P = 0.68)							

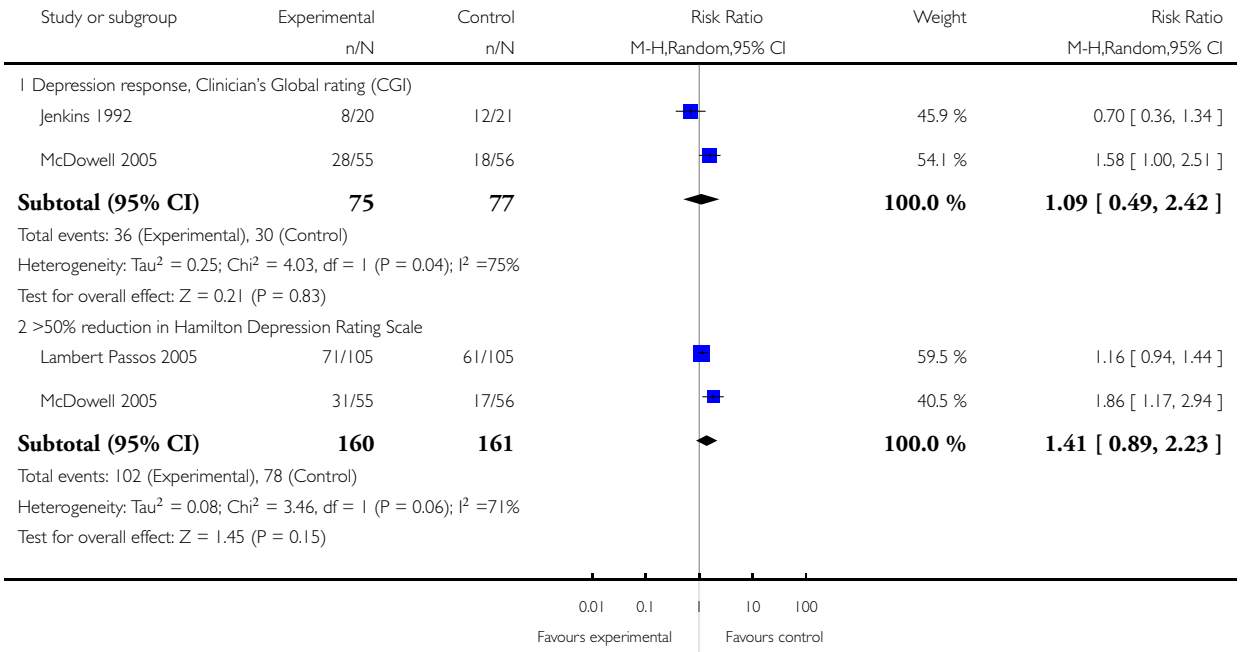


Analysis 1.8. Comparison 1 Antidepressants vs placebo according to any definition, Outcome 8 Mood dichotomous measures.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 1 Antidepressants vs placebo according to any definition

Outcome: 8 Mood dichotomous measures



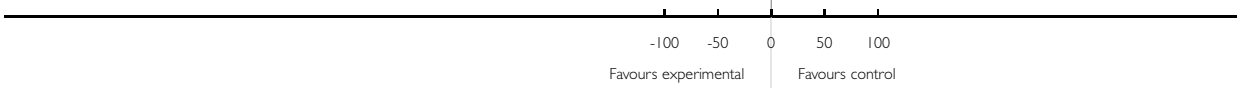
Analysis 1.9. Comparison 1 Antidepressants vs placebo according to any definition, Outcome 9 Mood continuous measures.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 1 Antidepressants vs placebo according to any definition

Outcome: 9 Mood continuous measures

Study or subgroup	Favours experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Hamilton Depression Rating Scale at the end of the treatment							
Ciraulo 2005 a	27	9.42 (6.44)	24	10.47 (10.3)		4.7 %	-1.05 [-5.83, 3.73]
Ciraulo 2005 b	20	1.75 (2.36)	20	2.9 (4.29)		23.5 %	-1.15 [-3.30, 1.00]
Cornish 2001	29	4.5 (4.8)	31	5.4 (4.3)		20.2 %	-0.90 [-3.21, 1.41]
Margolin 1995	63	4.6 (4.7)	62	6.2 (6.7)		26.2 %	-1.60 [-3.63, 0.43]
McDowell 2005	55	8.93 (6.72)	56	11.28 (7.4)		15.6 %	-2.35 [-4.98, 0.28]
Winhusen 2005	16	5.8 (4.1)	17	7 (5.6)		9.7 %	-1.20 [-4.54, 2.14]
Subtotal (95% CI)	**210**		**210**			**100.0 %**	**-1.41 [-2.44, -0.37]**
Heterogeneity: Chi² = 0.81, df = 5 (P = 0.98); I² =0.0%							
Test for overall effect: Z = 2.65 (P = 0.0081)							
2 CGI depression severity score at the end of the treatment							
Ciraulo 2005 b	16	2.94 (1.12)	16	3.06 (1.06)		12.5 %	-0.12 [-0.88, 0.64]
Ciraulo 2005 b	20	3.95 (1.23)	20	3.65 (1.35)		11.2 %	0.30 [-0.50, 1.10]
Elkashef 2006	97	3.4 (1.4)	110	3.3 (1.3)		52.4 %	0.10 [-0.27, 0.47]
McDowell 2005	55	2.78 (1.42)	56	3.43 (1.52)		23.9 %	-0.65 [-1.20, -0.10]
Subtotal (95% CI)	**188**		**202**			**100.0 %**	**-0.08 [-0.35, 0.18]**
Heterogeneity: Chi² = 5.96, df = 3 (P = 0.11); I² =50%							
Test for overall effect: Z = 0.62 (P = 0.54)							
3 Beck Depression Inventory (BDI) at the end of the treatment							
Cornish 2001	29	6.3 (5.4)	31	6.4 (7)		48.5 %	-0.10 [-3.25, 3.05]
Weddington 1991	17	3.6 (4.94)	21	2 (4.58)		51.5 %	1.60 [-1.46, 4.66]
Subtotal (95% CI)	**46**		**52**			**100.0 %**	**0.78 [-1.42, 2.97]**
Heterogeneity: Chi² = 0.58, df = 1 (P = 0.45); I² =0.0%							
Test for overall effect: Z = 0.69 (P = 0.49)							
4 Brief Psychiatric Rating Scale (BPRS) at the end of the treatment							
Giannini 1987 a	10	7.88 (0.63)	10	25.88 (0.63)		99.4 %	-18.00 [-18.55, -17.45]
Giannini 1993	15	36.8 (10.1)	13	54.2 (9.37)		0.6 %	-17.40 [-24.62, -10.18]
Subtotal (95% CI)	**25**		**23**			**100.0 %**	**-18.00 [-18.55, -17.45]**
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² =0.0%							
Test for overall effect: Z = 64.06 (P < 0.00001)							

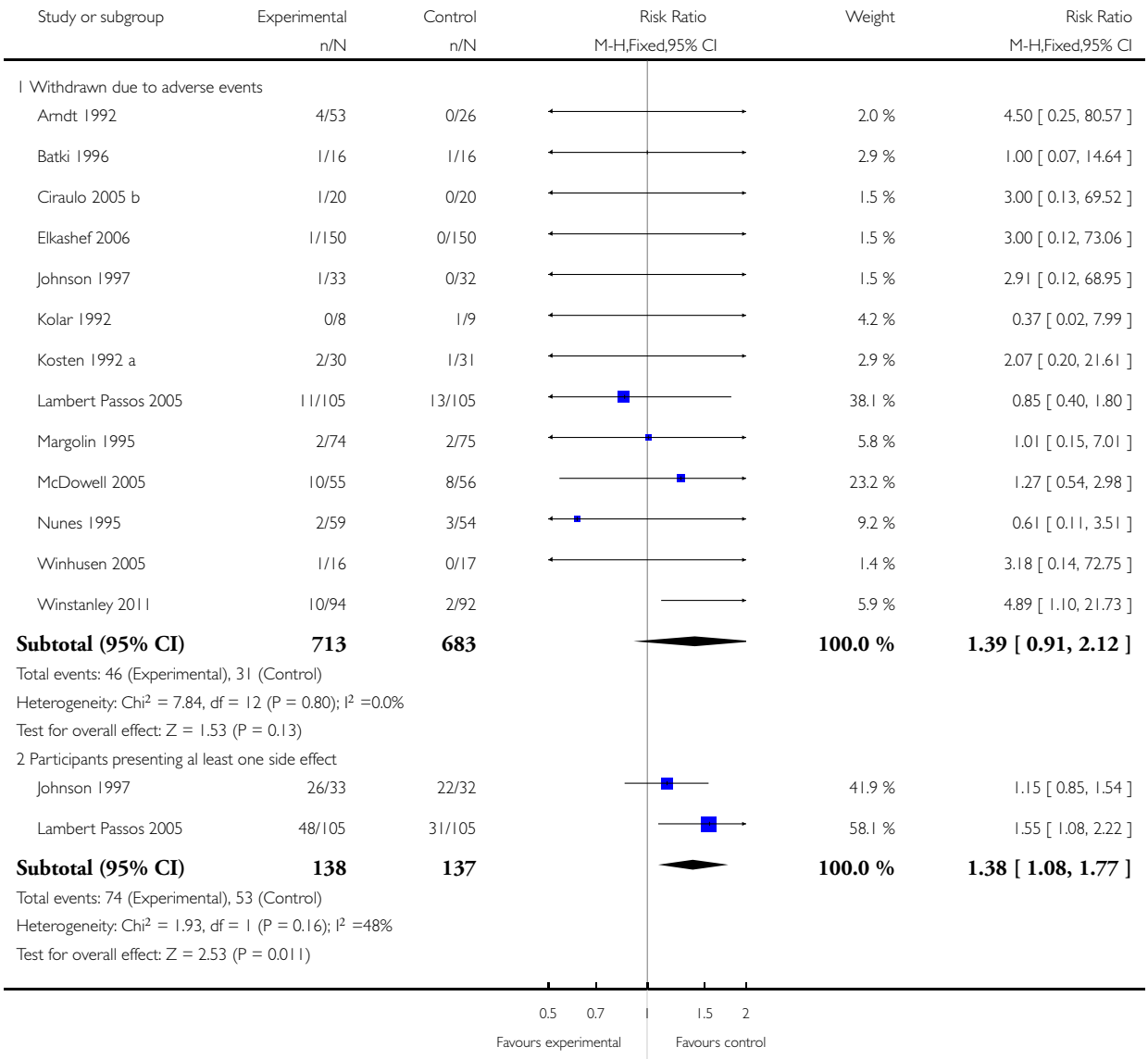


Analysis 1.10. Comparison 1 Antidepressants vs placebo according to any definition, Outcome 10 Adverse events.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 1 Antidepressants vs placebo according to any definition

Outcome: 10 Adverse events

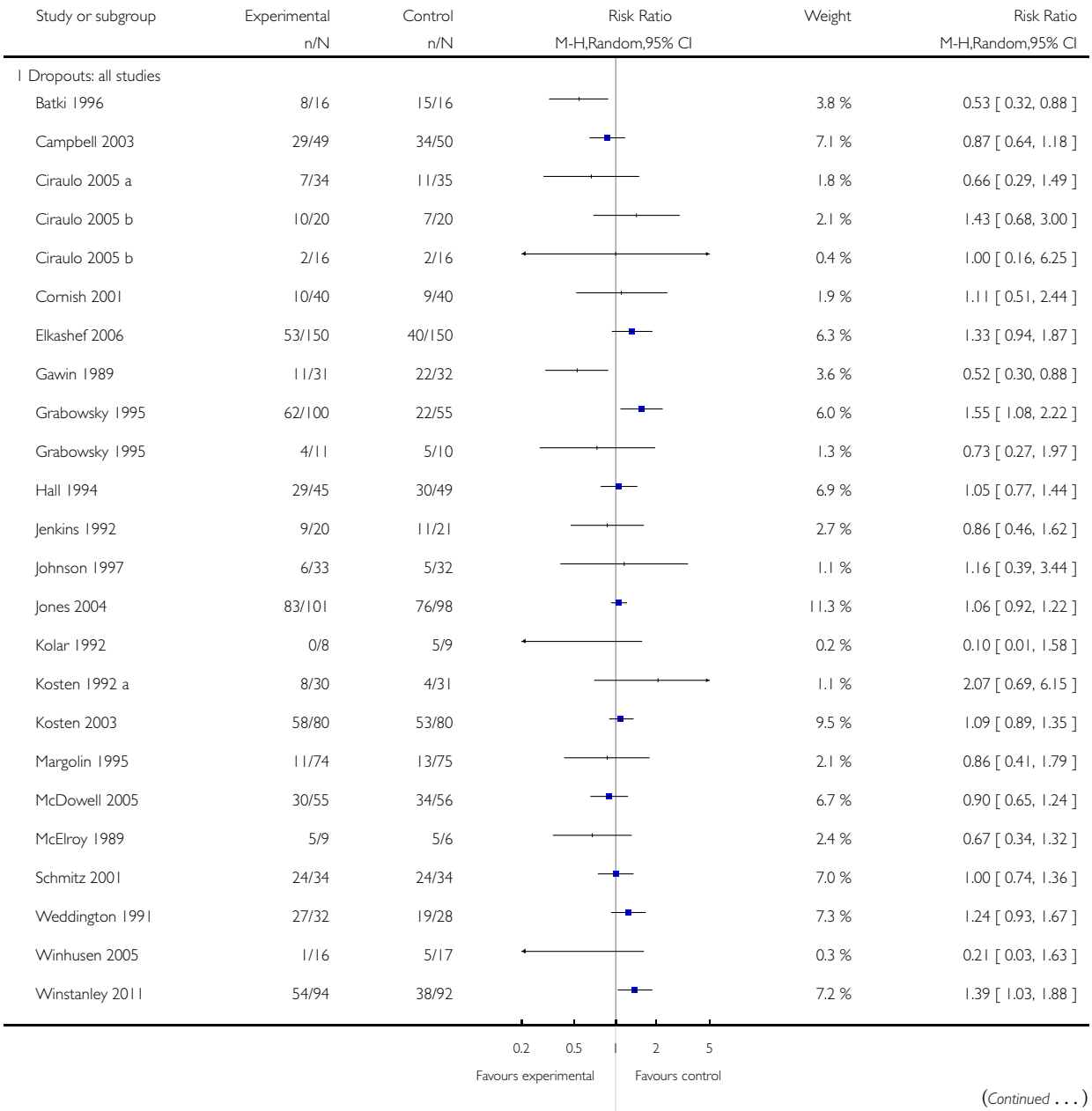


Analysis 2.1. Comparison 2 Antidepressants vs placebo for operationally defined cocaine dependence, Outcome 1 Dropout.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 2 Antidepressants vs placebo for operationally defined cocaine dependence

Outcome: 1 Dropout



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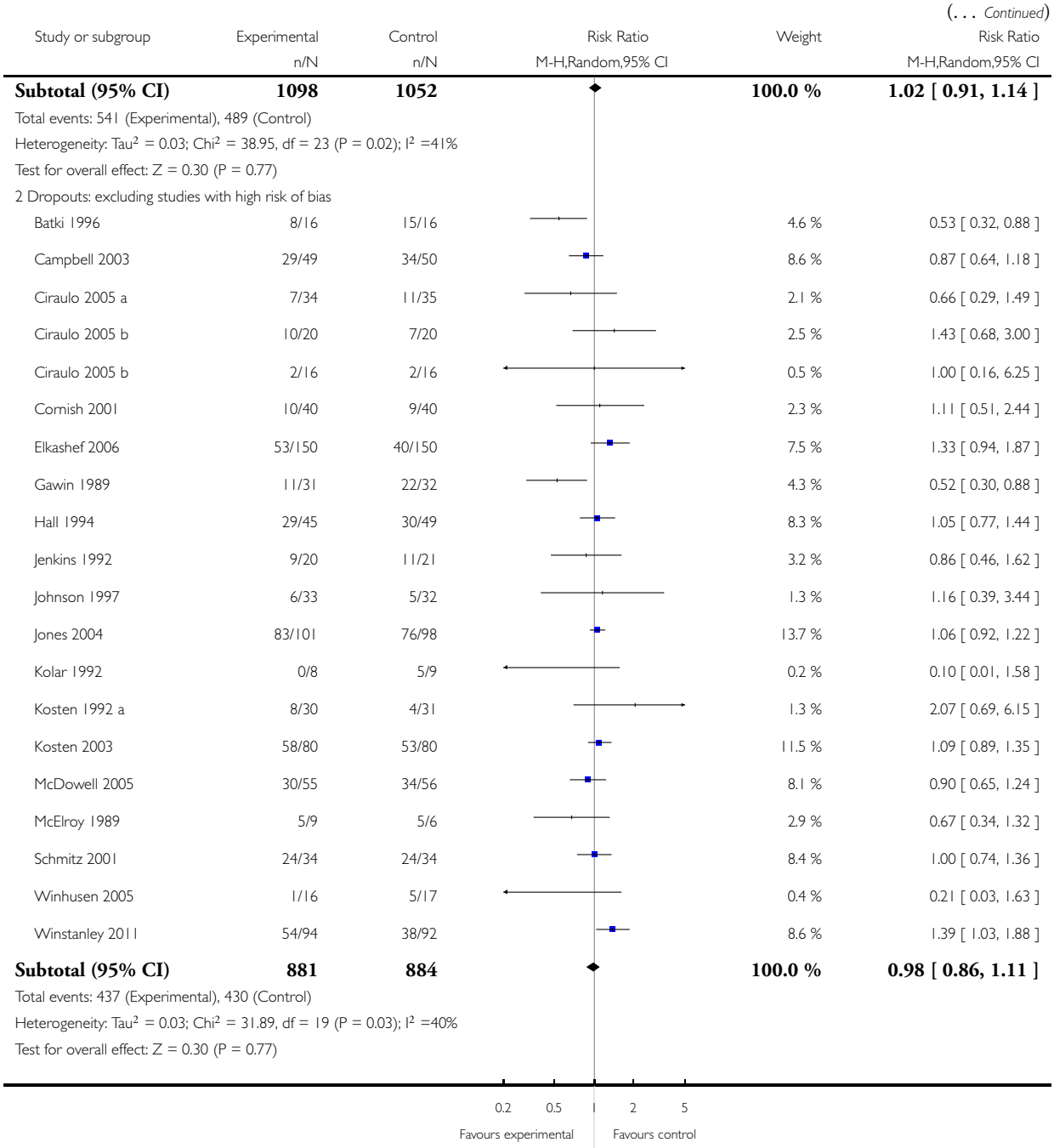


Analysis 2.2. Comparison 2 Antidepressants vs placebo for operationally defined cocaine dependence, Outcome 2 Retention in treatment.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 2 Antidepressants vs placebo for operationally defined cocaine dependence

Outcome: 2 Retention in treatment

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Retention in treatment (mean number of weeks): all studies						
Cornish 2001	40	5.06 (2.74)	40	5.16 (2.73)		-0.10 [-1.30, 1.10]
Gawin 1989	24	5.41 (1.12)	24	4.37 (1.75)		1.04 [0.21, 1.87]
Hall 1994	45	10.67 (10.66)	49	8.31 (8.41)		2.36 [-1.54, 6.26]
Jenkins 1992	20	8 (3.74)	21	8.14 (3.72)		-0.14 [-2.42, 2.14]
Kolar 1992	8	12 (0)	9	9.33 (3.08)		0.0 [0.0, 0.0]
Lambert Passos 2005	105	6.18 (0.47)	105	5.84 (0.49)		0.34 [0.21, 0.47]
Subtotal (95% CI)	**242**		**248**			**0.35 [0.22, 0.48]**
Heterogeneity: Chi^2 = 4.40, df = 4 (P = 0.35); I^2 =9%						
Test for overall effect: Z = 5.42 (P < 0.00001)						
2 Retention in treatment (mean number of weeks): excluding studies with high risk of bias						
Cornish 2001	40	5.06 (2.74)	40	5.16 (2.73)		-0.10 [-1.30, 1.10]
Hall 1994	45	10.67 (10.66)	49	8.31 (8.41)		2.36 [-1.54, 6.26]
Jenkins 1992	20	8 (3.74)	21	8.14 (3.72)		-0.14 [-2.42, 2.14]
Lambert Passos 2005	105	6.18 (0.47)	105	5.84 (0.49)		0.34 [0.21, 0.47]
Winstanley 2011	73	19.92 (7.71)	72	22.9 (7.6)		-2.98 [-5.47, -0.49]
Subtotal (95% CI)	**283**		**287**			**0.33 [0.20, 0.46]**
Heterogeneity: Chi^2 = 8.49, df = 4 (P = 0.08); I^2 =53%						
Test for overall effect: Z = 4.98 (P < 0.00001)						

Analysis 2.3. Comparison 2 Antidepressants vs placebo for operationally defined cocaine dependence, Outcome 3 Abstinence for at least three consecutive weeks.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 2 Antidepressants vs placebo for operationally defined cocaine dependence

Outcome: 3 Abstinence for at least three consecutive weeks

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Campbell 2003	13/36	13/39		14.3 %	1.08 [0.58, 2.02]
Elkashef 2006	7/147	12/148		13.7 %	0.59 [0.24, 1.45]
Gawin 1989	14/24	4/24		4.6 %	3.50 [1.35, 9.11]
Lambert Passos 2005	52/105	48/105		55.0 %	1.08 [0.82, 1.44]
McDowell 2005	11/55	11/56		12.5 %	1.02 [0.48, 2.15]
Total (95% CI)	**367**	**372**		**100.0 %**	**1.12 [0.89, 1.41]**

Total events: 97 (Experimental), 88 (Control)

Heterogeneity: Chi^2 = 7.54, df = 4 (P = 0.11); I^2 =47%

Test for overall effect: Z = 0.95 (P = 0.34)

Test for subgroup differences: Not applicable

Analysis 2.4. Comparison 2 Antidepressants vs placebo for operationally defined cocaine dependence, Outcome 4 Abstinence as number of weeks of continuous abstinence.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 2 Antidepressants vs placebo for operationally defined cocaine dependence

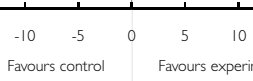
Outcome: 4 Abstinence as number of weeks of continuous abstinence

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Carroll 1994	54	3.19 (2.94)	56	2.75 (2.47)		4.7 %	0.44 [-0.58, 1.46]
Elkashef 2006	147	0.97 (1.17)	148	1.08 (1.28)		61.6 %	-0.11 [-0.39, 0.17]
Jones 2004	88	2.4 (1.51)	91	2.66 (1.56)		23.9 %	-0.26 [-0.71, 0.19]
Kosten 2003	80	2.8 (4.09)	80	1.74 (3.21)		3.7 %	1.06 [-0.08, 2.20]
Lambert Passos 2005	105	4.13 (3.48)	105	3.66 (3.48)		5.4 %	0.47 [-0.47, 1.41]
Weddington 1991	17	6.2 (4.53)	21	3.6 (3.66)		0.7 %	2.60 [-0.06, 5.26]
Total (95% CI)	**491**		**501**			**100.0 %**	**-0.03 [-0.25, 0.19]**

Heterogeneity: Chi^2 = 10.49, df = 5 (P = 0.06); I^2 =52%

Test for overall effect: Z = 0.24 (P = 0.81)

Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2 Antidepressants vs placebo for operationally defined cocaine dependence, Outcome 5 Use of cocaine during the trial.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 2 Antidepressants vs placebo for operationally defined cocaine dependence

Outcome: 5 Use of cocaine during the trial

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Johnson 1997	22/33	15/32		18.3 %	1.42 [0.92, 2.21]
Margolin 1995	63/74	65/75		77.4 %	0.98 [0.86, 1.12]
McElroy 1989	2/9	3/6		4.3 %	0.44 [0.10, 1.92]
Total (95% CI)	**116**	**113**		**100.0 %**	**1.04 [0.90, 1.20]**

Total events: 87 (Experimental), 83 (Control)

Heterogeneity: $Chi^2 = 3.97$, df = 2 (P = 0.14); $I^2 = 50\%$

Test for overall effect: Z = 0.53 (P = 0.59)

Test for subgroup differences: Not applicable

Analysis 2.6. Comparison 2 Antidepressants vs placebo for operationally defined cocaine dependence, Outcome 6 Withdrawn due to adverse events.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 2 Antidepressants vs placebo for operationally defined cocaine dependence

Outcome: 6 Withdrawn due to adverse events

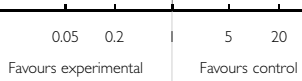
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Batki 1996	1/16	1/16		3.3 %	1.00 [0.07, 14.64]
Ciraulo 2005 b	1/20	0/20		1.6 %	3.00 [0.13, 69.52]
Elkashef 2006	1/150	0/150		1.6 %	3.00 [0.12, 73.06]
Johnson 1997	1/33	0/32		1.7 %	2.91 [0.12, 68.95]
Kolar 1992	0/8	1/9		4.7 %	0.37 [0.02, 7.99]
Kosten 1992 a	2/30	1/31		3.2 %	2.07 [0.20, 21.61]
Lambert Passos 2005	11/105	13/105		42.9 %	0.85 [0.40, 1.80]
Margolin 1995	2/74	2/75		6.5 %	1.01 [0.15, 7.01]
McDowell 2005	10/55	8/56		26.1 %	1.27 [0.54, 2.98]
Winhusen 2005	1/16	0/17		1.6 %	3.18 [0.14, 72.75]
Winstanley 2011	10/94	2/92		6.7 %	4.89 [1.10, 21.73]
Total (95% CI)	**601**	**603**		**100.0 %**	**1.40 [0.90, 2.19]**

Total events: 40 (Experimental), 28 (Control)

Heterogeneity: $Chi^2 = 6.37$, df = 10 (P = 0.78); $I^2 = 0.0\%$

Test for overall effect: Z = 1.50 (P = 0.13)

Test for subgroup differences: Not applicable

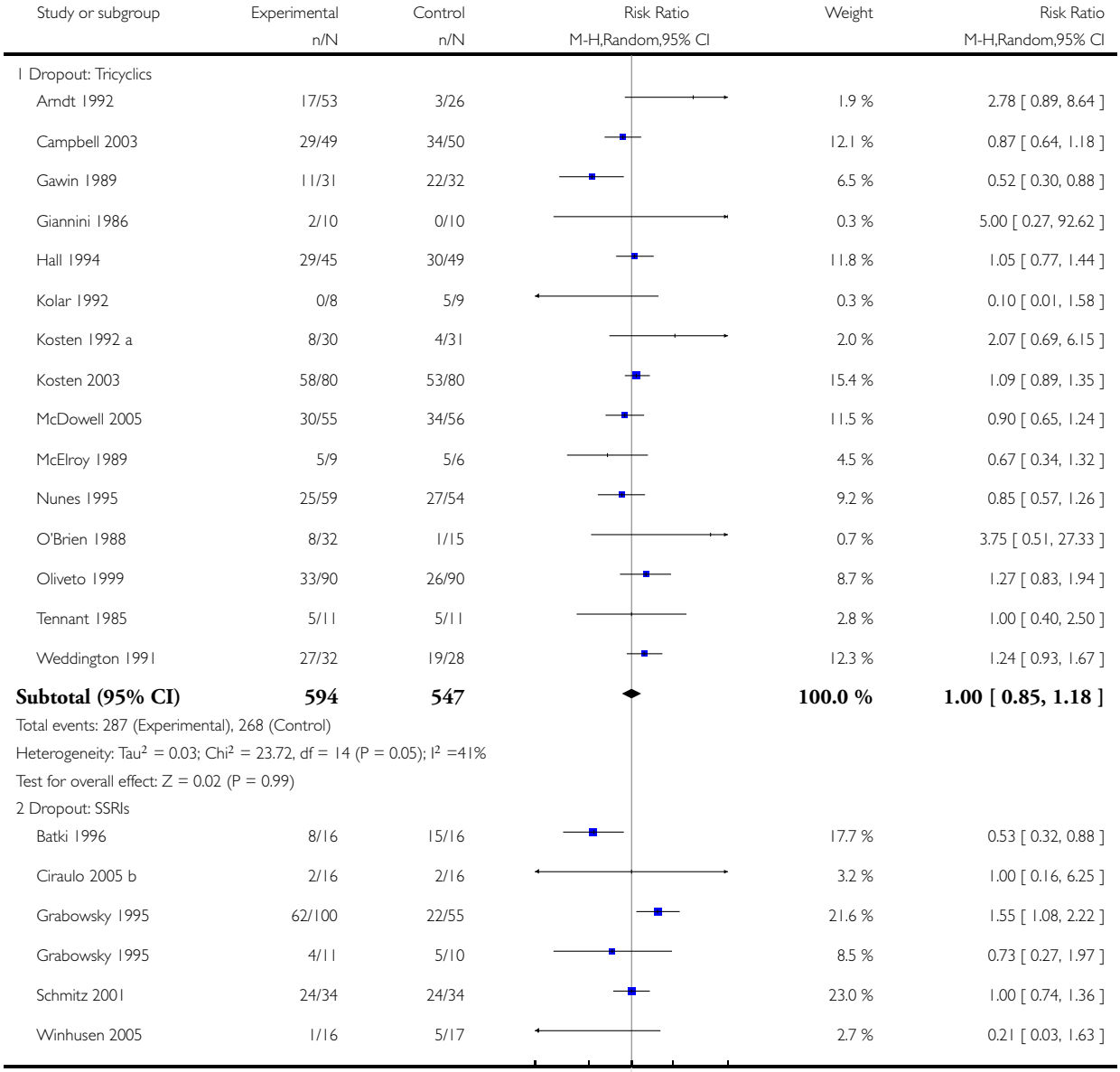


Analysis 3.1. Comparison 3 Different class of antidepressants versus placebo, Outcome 1 Dropout.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 3 Different class of antidepressants versus placebo

Outcome: 1 Dropout



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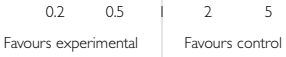
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Winstanley 2011	54/94	38/92		23.2 %	1.39 [1.03, 1.88]
Subtotal (95% CI)	**287**	**240**		**100.0 %**	**0.99 [0.70, 1.41]**
Total events: 155 (Experimental), 111 (Control)					
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 17.39$, df = 6 (P = 0.01); $I^2 = 65\%$					
Test for overall effect: Z = 0.05 (P = 0.96)					



Analysis 3.2. Comparison 3 Different class of antidepressants versus placebo, Outcome 2 Retention in treatment as mean number of weeks in treatment: tricyclics.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 3 Different class of antidepressants versus placebo

Outcome: 2 Retention in treatment as mean number of weeks in treatment: tricyclics

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Gawin 1989	24	5.41 (1.12)	24	4.37 (1.75)		1.04 [0.21, 1.87]
Hall 1994	45	10.67 (10.66)	49	8.31 (8.41)		2.36 [-1.54, 6.26]
Kolar 1992	8	12 (0)	9	9.33 (3.08)		0.0 [0.0, 0.0]
Total (95% CI)	**77**		**82**			**1.10 [0.28, 1.91]**
Heterogeneity: $Chi^2 = 0.42$, df = 1 (P = 0.52); $I^2 = 0.0\%$						
Test for overall effect: Z = 2.65 (P = 0.0082)						
Test for subgroup differences: Not applicable						

Analysis 3.3. Comparison 3 Different class of antidepressants versus placebo, Outcome 3 Abstinence for at least three consecutive weeks: tricyclics.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 3 Different class of antidepressants versus placebo

Outcome: 3 Abstinence for at least three consecutive weeks: tricyclics

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Campbell 2003	13/36	13/39		33.2 %	1.08 [0.58, 2.02]
Gawin 1989	14/24	4/24		10.7 %	3.50 [1.35, 9.11]
Giannini 1987 a	9/10	6/10		16.0 %	1.50 [0.87, 2.59]
McDowell 2005	11/55	11/56		29.0 %	1.02 [0.48, 2.15]
Nunes 1995	11/59	4/54		11.1 %	2.52 [0.85, 7.44]
Total (95% CI)	**184**	**183**		**100.0 %**	**1.55 [1.10, 2.17]**

Total events: 58 (Experimental), 38 (Control)

Heterogeneity: Chi^2 = 6.05, df = 4 (P = 0.20); I^2 =34%

Test for overall effect: Z = 2.52 (P = 0.012)

Test for subgroup differences: Not applicable

Analysis 3.4. Comparison 3 Different class of antidepressants versus placebo, Outcome 4 Abstinence as average number of weeks of continuous abstinence: tricyclics.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 3 Different class of antidepressants versus placebo

Outcome: 4 Abstinence as average number of weeks of continuous abstinence: tricyclics

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Carroll 1994	54	3.19 (2.94)	56	2.75 (2.47)		51.2 %	0.44 [-0.58, 1.46]
Kosten 2003	80	2.8 (4.09)	80	2.1 (3.15)		41.3 %	0.70 [-0.43, 1.83]
Weddington 1991	17	6.2 (4.53)	21	3.6 (3.66)		7.5 %	2.60 [-0.06, 5.26]
Total (95% CI)	**151**		**157**			**100.0 %**	**0.71 [-0.02, 1.44]**

Heterogeneity: Chi² = 2.21, df = 2 (P = 0.33); I² =9%

Test for overall effect: Z = 1.91 (P = 0.056)

Test for subgroup differences: Not applicable

Analysis 3.5. Comparison 3 Different class of antidepressants versus placebo, Outcome 5 Use of cocaine during the trial: tricyclics.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 3 Different class of antidepressants versus placebo

Outcome: 5 Use of cocaine during the trial: tricyclics

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
McElroy 1989	2/9	3/6		54.5 %	0.44 [0.10, 1.92]
Tennant 1985	4/11	3/11		45.5 %	1.33 [0.39, 4.62]
Total (95% CI)	**20**	**17**		**100.0 %**	**0.85 [0.34, 2.11]**

Total events: 6 (Experimental), 6 (Control)

Heterogeneity: Chi² = 1.26, df = 1 (P = 0.26); I² =21%

Test for overall effect: Z = 0.35 (P = 0.72)

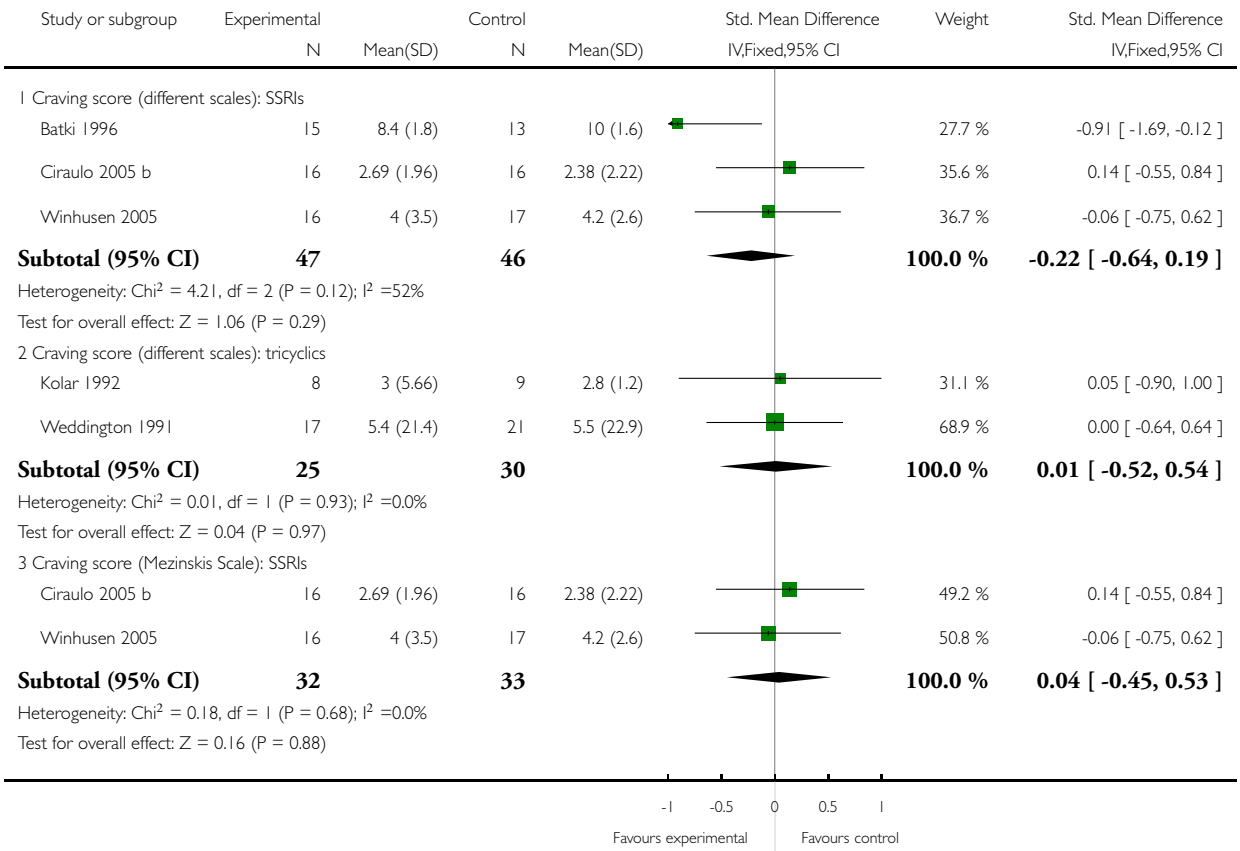
Test for subgroup differences: Not applicable

Analysis 3.6. Comparison 3 Different class of antidepressants versus placebo, Outcome 6 Craving for cocaine.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 3 Different class of antidepressants versus placebo

Outcome: 6 Craving for cocaine



Analysis 3.7. Comparison 3 Different class of antidepressants versus placebo, Outcome 7 Addidtion Severity Index (ASI) score, Drugs: SSRIs.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 3 Different class of antidepressants versus placebo

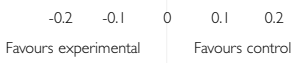
Outcome: 7 Addidtion Severity Index (ASI) score, Drugs: SSRIs

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Ciraulo 2005 b	16	0.16 (0.07)	16	0.13 (0.09)		68.3 %	0.03 [-0.03, 0.09]
Winhusen 2005	16	0.19 (0.12)	17	0.21 (0.12)		31.7 %	-0.02 [-0.10, 0.06]
Total (95% CI)	**32**		**33**			**100.0 %**	**0.01 [-0.03, 0.06]**

Heterogeneity: $Chi^2 = 0.98$, df = 1 (P = 0.32); $I^2 = 0.0\%$

Test for overall effect: Z = 0.60 (P = 0.55)

Test for subgroup differences: Not applicable



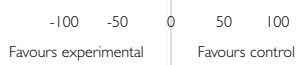
Analysis 3.8. Comparison 3 Different class of antidepressants versus placebo, Outcome 8 Mood continuous measures.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 3 Different class of antidepressants versus placebo

Outcome: 8 Mood continuous measures

Study or subgroup	Favours experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Beck Depression Inventory (BDI) at the end of the treatment: tricyclics							
Kolar 1992	8	1 (1.13)	9	5.3 (5.4)		48.6 %	-4.30 [-7.91, -0.69]
Weddington 1991	17	3.6 (4.94)	21	2 (4.58)		51.4 %	1.60 [-1.46, 4.66]
Subtotal (95% CI)	**25**		**30**			**100.0 %**	**-1.27 [-7.05, 4.51]**
Heterogeneity: $Tau^2 = 14.49$; $Chi^2 = 5.97$, df = 1 (P = 0.01); $I^2 = 83\%$							
Test for overall effect: Z = 0.43 (P = 0.67)							
2 Brief Psychiatric Rating Scale (BPRS) at the end of the treatment: tricyclics							
Giannini 1987 b	12	13 (8.65)	12	18 (8.65)		46.3 %	-5.00 [-11.92, 1.92]
Giannini 1987 a	10	7.88 (0.63)	10	25.88 (0.63)		53.7 %	-18.00 [-18.55, -17.45]



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Study or subgroup	Favours experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Subtotal (95% CI)	**22**		**22**			**100.0 %**	**-11.98 [-24.68, 0.73]**
Heterogeneity: Tau^2 = 78.23; Chi^2 = 13.47, df = 1 (P = 0.00024); I^2 =93%							
Test for overall effect: Z = 1.85 (P = 0.065)							

-100 -50 0 50 100

Favours experimental Favours control

Analysis 3.9. Comparison 3 Different class of antidepressants versus placebo, Outcome 9 Adverse events.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 3 Different class of antidepressants versus placebo

Outcome: 9 Adverse events

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Withdrawn due to adverse events: tricyclics					
Arndt 1992	4/53	0/26		4.7 %	4.50 [0.25, 80.57]
Kolar 1992	0/8	1/9		10.1 %	0.37 [0.02, 7.99]
Kosten 1992 a	2/30	1/31		7.0 %	2.07 [0.20, 21.61]
McDowell 2005	10/55	8/56		56.1 %	1.27 [0.54, 2.98]
Nunes 1995	2/59	3/54		22.2 %	0.61 [0.11, 3.51]
Subtotal (95% CI)	**205**	**176**		**100.0 %**	**1.24 [0.64, 2.43]**
Total events: 18 (Experimental), 13 (Control)					
Heterogeneity: Chi^2 = 2.18, df = 4 (P = 0.70); I^2 =0.0%					
Test for overall effect: Z = 0.64 (P = 0.52)					
2 Withdrawn due to adverse events: SSRIs					
Batki 1996	1/16	1/16		28.5 %	1.00 [0.07, 14.64]
Winhusen 2005	1/16	0/17		13.8 %	3.18 [0.14, 72.75]
Winstanley 2011	10/94	2/92		57.6 %	4.89 [1.10, 21.73]
Subtotal (95% CI)	**126**	**125**		**100.0 %**	**3.55 [1.11, 11.34]**
Total events: 12 (Experimental), 3 (Control)					
Heterogeneity: Chi^2 = 1.04, df = 2 (P = 0.59); I^2 =0.0%					
Test for overall effect: Z = 2.13 (P = 0.033)					
Test for subgroup differences: Chi^2 = 2.35, df = 1 (P = 0.13), I^2 =57%					

0.01 0.1 1 10 100

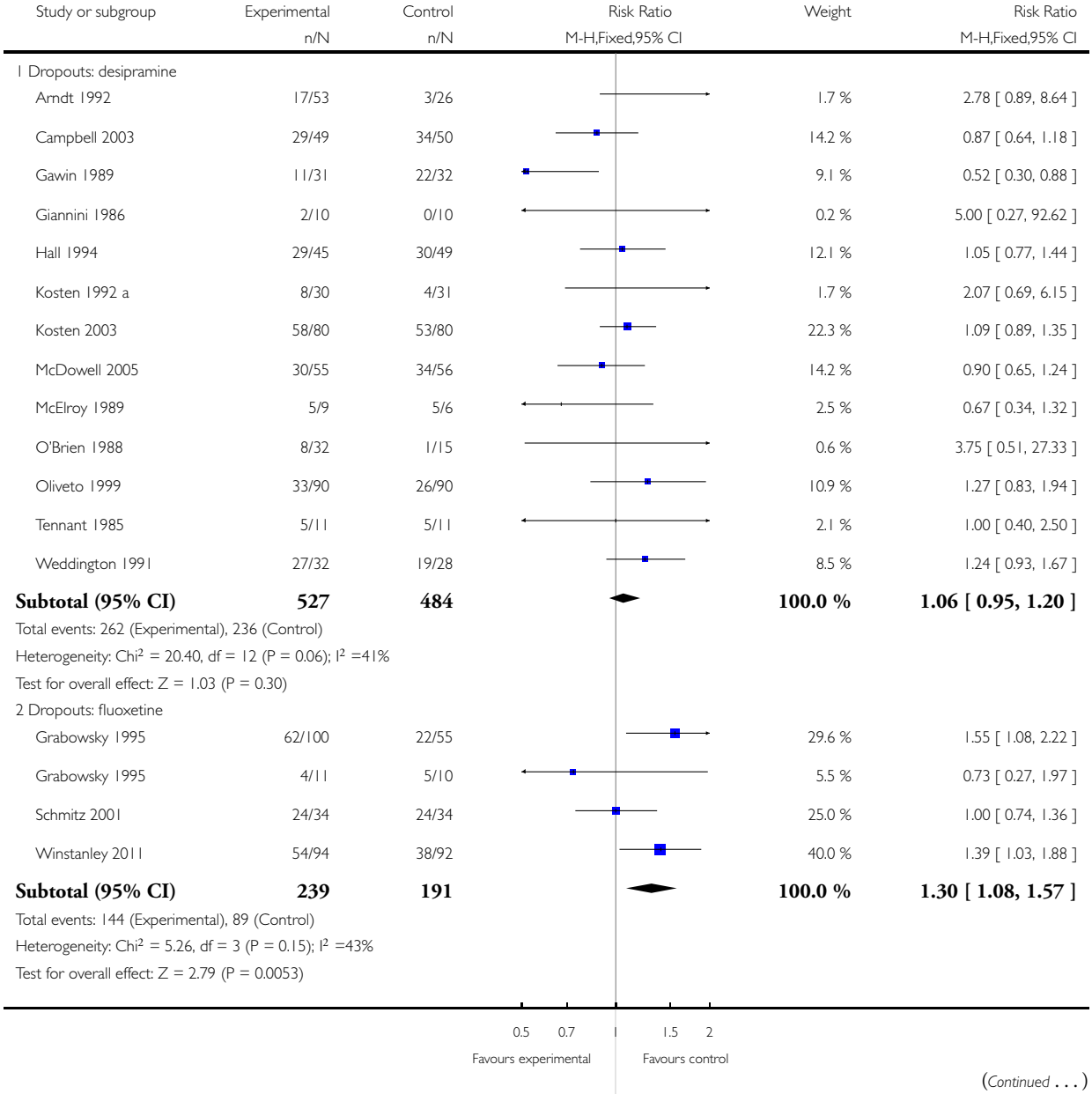
Favours experimental Favours control

Analysis 4.1. Comparison 4 Specific antidepressants versus placebo, Outcome 1 Dropout.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 4 Specific antidepressants versus placebo

Outcome: 1 Dropout



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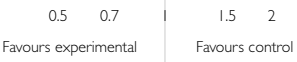
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
3 Dropouts: bupropion					
Margolin 1995	11/74	13/75		20.5 %	0.86 [0.41, 1.79]
Poling 2006	25/57	19/49		32.5 %	1.13 [0.72, 1.79]
Shoptaw 2008	30/37	28/33		47.0 %	0.96 [0.77, 1.18]
Subtotal (95% CI)	**168**	**157**		**100.0 %**	**0.99 [0.79, 1.25]**
Total events: 66 (Experimental), 60 (Control)					
Heterogeneity: Chi^2 = 0.59, df = 2 (P = 0.75); I^2 =0.0%					
Test for overall effect: Z = 0.06 (P = 0.95)					
4 Dropouts: ritanserin					
Cornish 2001	10/40	9/40		63.9 %	1.11 [0.51, 2.44]
Johnson 1997	6/33	5/32		36.1 %	1.16 [0.39, 3.44]
Subtotal (95% CI)	**73**	**72**		**100.0 %**	**1.13 [0.60, 2.14]**
Total events: 16 (Experimental), 14 (Control)					
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%					
Test for overall effect: Z = 0.38 (P = 0.71)					



Analysis 4.2. Comparison 4 Specific antidepressants versus placebo, Outcome 2 Retention in treatment as mean number of weeks in treatment: desipramine.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 4 Specific antidepressants versus placebo

Outcome: 2 Retention in treatment as mean number of weeks in treatment: desipramine

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Gawin 1989	24	5.41 (1.12)	24	4.37 (1.75)		1.04 [0.21, 1.87]
Hall 1994	45	10.67 (10.66)	49	8.31 (8.41)		2.36 [-1.54, 6.26]
Kolar 1992	8	12 (0)	9	9.33 (3.08)		0.0 [0.0, 0.0]
Total (95% CI)	**77**		**82**			**1.10 [0.28, 1.91]**
Heterogeneity: Chi^2 = 0.42, df = 1 (P = 0.52); I^2 =0.0%						
Test for overall effect: Z = 2.65 (P = 0.0082)						
Test for subgroup differences: Not applicable						

Analysis 4.3. Comparison 4 Specific antidepressants versus placebo, Outcome 3 Abstinence for at least three consecutive weeks: desipramine.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 4 Specific antidepressants versus placebo

Outcome: 3 Abstinence for at least three consecutive weeks: desipramine

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Campbell 2003	13/36	13/39		37.4 %	1.08 [0.58, 2.02]
Gawin 1989	14/24	4/24		12.0 %	3.50 [1.35, 9.11]
Giannini 1987 a	9/10	6/10		18.0 %	1.50 [0.87, 2.59]
McDowell 2005	11/55	11/56		32.7 %	1.02 [0.48, 2.15]
Total (95% CI)	**125**	**129**		**100.0 %**	**1.43 [1.00, 2.03]**

Total events: 47 (Experimental), 34 (Control)

Heterogeneity: $Chi^2 = 4.95$, df = 3 (P = 0.18); $I^2 = 39\%$

Test for overall effect: Z = 1.96 (P = 0.050)

Test for subgroup differences: Not applicable

Analysis 4.4. Comparison 4 Specific antidepressants versus placebo, Outcome 4 Abstinence as average number of weeks of continuous abstinence: desipramine.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 4 Specific antidepressants versus placebo

Outcome: 4 Abstinence as average number of weeks of continuous abstinence: desipramine

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Carroll 1994	54	3.19 (2.94)	56	2.75 (2.47)		51.2 %	0.44 [-0.58, 1.46]
Kosten 2003	80	2.8 (4.09)	80	2.1 (3.15)		41.3 %	0.70 [-0.43, 1.83]
Weddington 1991	17	6.2 (4.53)	21	3.6 (3.66)		7.5 %	2.60 [-0.06, 5.26]
Total (95% CI)	**151**		**157**			**100.0 %**	**0.71 [-0.02, 1.44]**

Heterogeneity: Chi² = 2.21, df = 2 (P = 0.33); I² =9%

Test for overall effect: Z = 1.91 (P = 0.056)

Test for subgroup differences: Not applicable

Analysis 4.5. Comparison 4 Specific antidepressants versus placebo, Outcome 5 Use of cocaine during the trial: desipramine.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 4 Specific antidepressants versus placebo

Outcome: 5 Use of cocaine during the trial: desipramine

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
McElroy 1989	2/9	3/6		54.5 %	0.44 [0.10, 1.92]
Tennant 1985	4/11	3/11		45.5 %	1.33 [0.39, 4.62]
Total (95% CI)	**20**	**17**		**100.0 %**	**0.85 [0.34, 2.11]**

Total events: 6 (Experimental), 6 (Control)

Heterogeneity: Chi² = 1.26, df = 1 (P = 0.26); I² =21%

Test for overall effect: Z = 0.35 (P = 0.72)

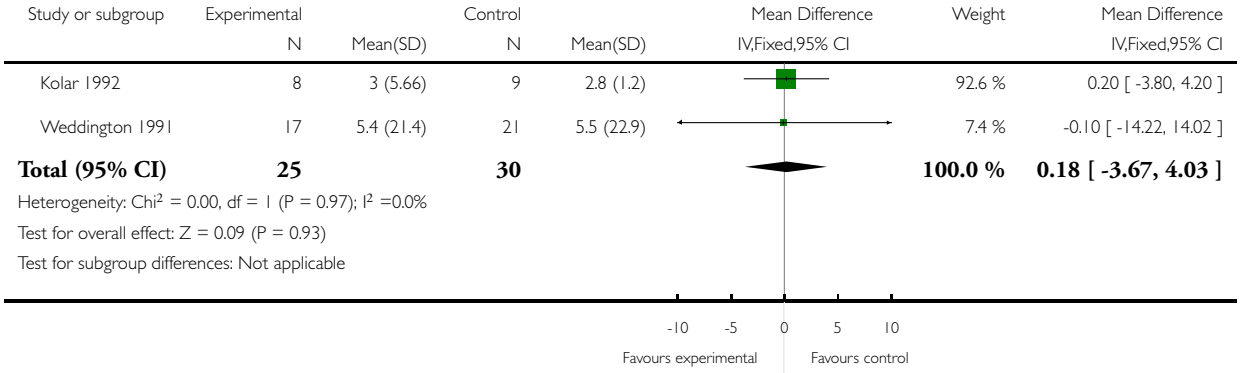
Test for subgroup differences: Not applicable

Analysis 4.6. Comparison 4 Specific antidepressants versus placebo, Outcome 6 Craving for cocaine.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 4 Specific antidepressants versus placebo

Outcome: 6 Craving for cocaine

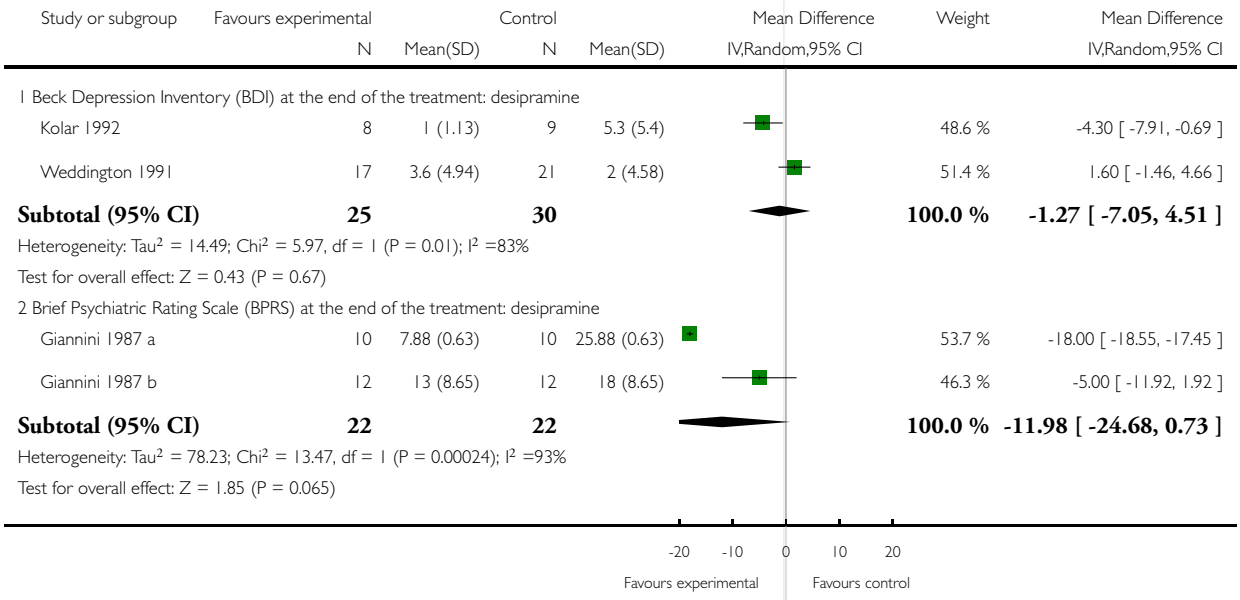


Analysis 4.7. Comparison 4 Specific antidepressants versus placebo, Outcome 7 Mood continuous measures.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 4 Specific antidepressants versus placebo

Outcome: 7 Mood continuous measures

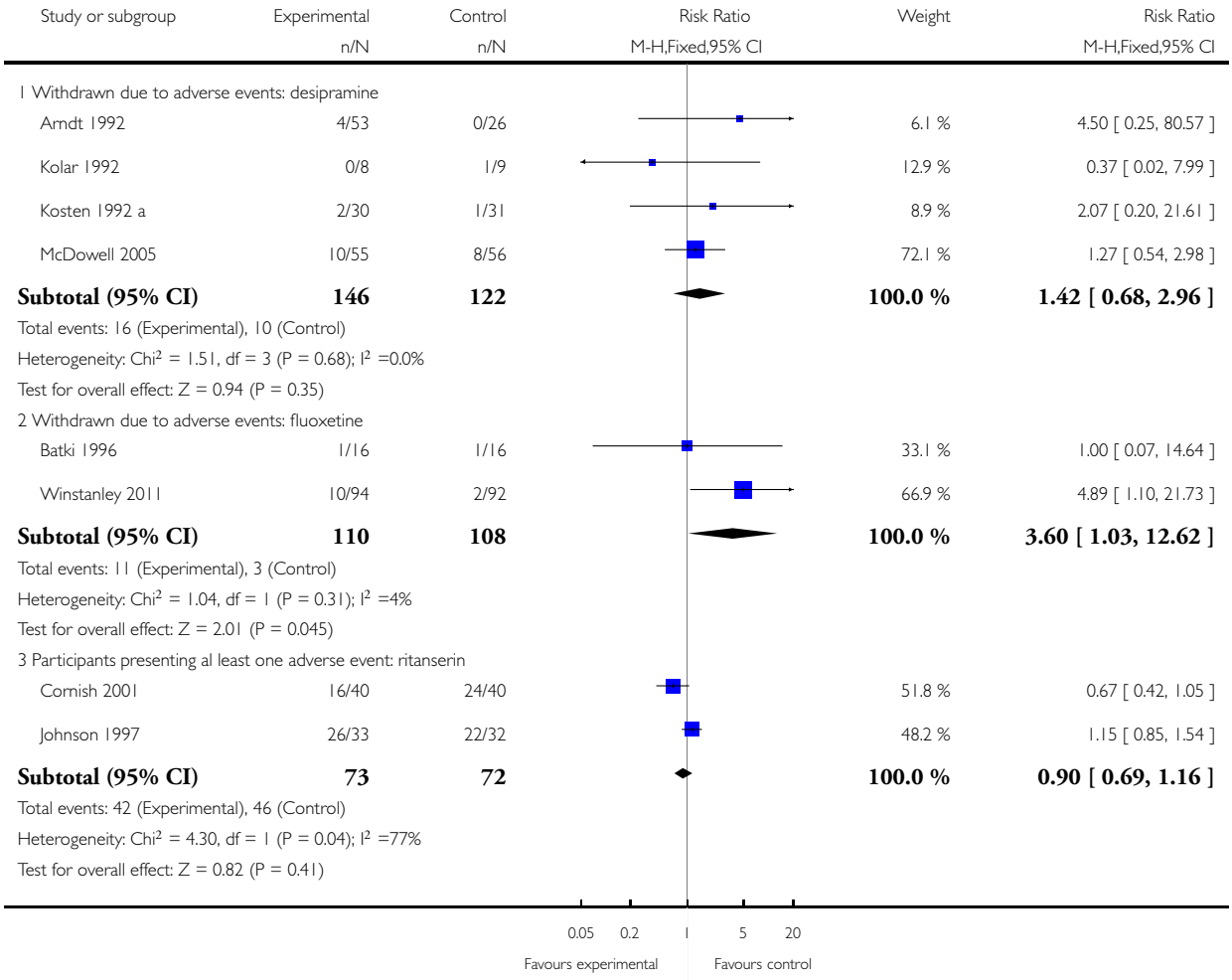


Analysis 4.8. Comparison 4 Specific antidepressants versus placebo, Outcome 8 Adverse events.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 4 Specific antidepressants versus placebo

Outcome: 8 Adverse events

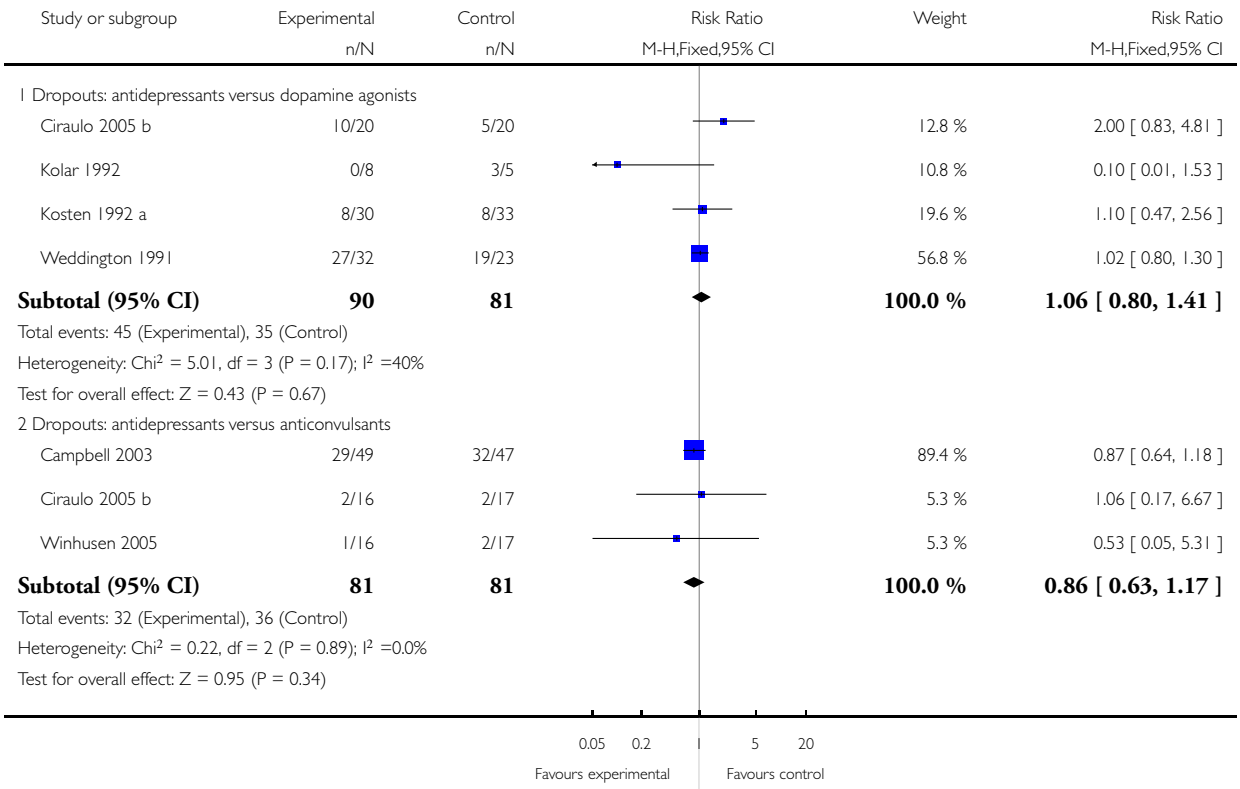


Analysis 5.1. Comparison 5 Antidepressants versus different class of other medications, Outcome 1 Dropout.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 5 Antidepressants versus different class of other medications

Outcome: 1 Dropout



Analysis 5.2. Comparison 5 Antidepressants versus different class of other medications, Outcome 2 Craving for cocaine: antidepressants versus dopamine agonists.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 5 Antidepressants versus different class of other medications

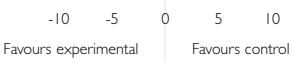
Outcome: 2 Craving for cocaine: antidepressants versus dopamine agonists

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Ciraulo 2005 b	20	3.35 (2.66)	20	3.85 (3.05)		47.0 %	-0.17 [-0.79, 0.45]
Kolar 1992	8	3 (5.66)	5	5 (2.68)		14.2 %	-0.39 [-1.52, 0.74]
Weddington 1991	17	5.4 (21.4)	16	7 (22.4)		38.9 %	-0.07 [-0.75, 0.61]
Total (95% CI)	**45**		**41**			**100.0 %**	**-0.16 [-0.59, 0.26]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.22$, df = 2 (P = 0.90); $I^2 = 0.0\%$

Test for overall effect: Z = 0.75 (P = 0.45)

Test for subgroup differences: Not applicable



Analysis 5.3. Comparison 5 Antidepressants versus different class of other medications, Outcome 3 Withdrawn due to adverse events: antidepressants versus dopamine agonists.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 5 Antidepressants versus different class of other medications

Outcome: 3 Withdrawn due to adverse events: antidepressants versus dopamine agonists

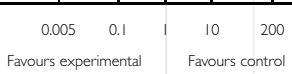
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ciraulo 2005 b	1/20	0/20		34.4 %	3.00 [0.13, 69.52]
Kosten 1992 a	2/30	1/33		65.6 %	2.20 [0.21, 23.04]
Total (95% CI)	**50**	**53**		**100.0 %**	**2.48 [0.38, 16.19]**

Total events: 3 (Experimental), 1 (Control)

Heterogeneity: $Chi^2 = 0.02$, df = 1 (P = 0.88); $I^2 = 0.0\%$

Test for overall effect: Z = 0.95 (P = 0.34)

Test for subgroup differences: Not applicable



Analysis 6.1. Comparison 6 Different classes of antidepressants versus different classes of other medications, Outcome 1 Dropout: SSRIs versus anticonvulsants.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 6 Different classes of antidepressants versus different classes of other medications

Outcome: 1 Dropout: SSRIs versus anticonvulsants

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ciraulo 2005 b	2/16	2/17		50.0 %	1.06 [0.17, 6.67]
Winhusen 2005	1/16	2/17		50.0 %	0.53 [0.05, 5.31]
Total (95% CI)	**32**	**34**		**100.0 %**	**0.80 [0.19, 3.29]**

Total events: 3 (Experimental), 4 (Control)

Heterogeneity: $Chi^2 = 0.21$, df = 1 (P = 0.64); $I^2 = 0.0\%$

Test for overall effect: Z = 0.31 (P = 0.75)

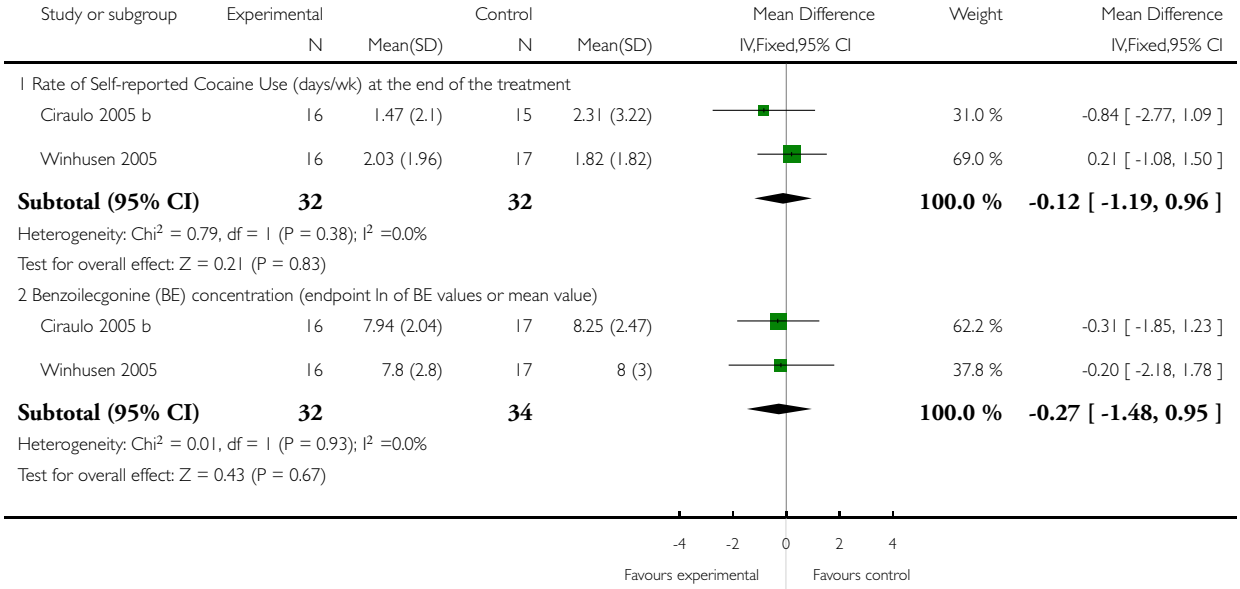
Test for subgroup differences: Not applicable

Analysis 6.2. Comparison 6 Different classes of antidepressants versus different classes of other medications, Outcome 2 Use of cocaine continuous measures: SSRIs versus anticonvulsants.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 6 Different classes of antidepressants versus different classes of other medications

Outcome: 2 Use of cocaine continuous measures: SSRIs versus anticonvulsants



Analysis 6.3. Comparison 6 Different classes of antidepressants versus different classes of other medications, Outcome 3 Craving for cocaine: SSRIs versus anticonvulsants.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 6 Different classes of antidepressants versus different classes of other medications

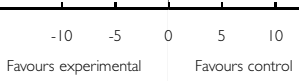
Outcome: 3 Craving for cocaine: SSRIs versus anticonvulsants

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Ciraulo 2005 b	16	2.69 (1.96)	17	3.76 (3.17)		50.0 %	-0.39 [-1.08, 0.30]
Winhusen 2005	16	4 (3.5)	17	2.7 (2.3)		50.0 %	0.43 [-0.26, 1.12]
Total (95% CI)	**32**		**34**			**100.0 %**	**0.02 [-0.79, 0.83]**

Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 2.73$, df = 1 (P = 0.10); $I^2 = 63\%$

Test for overall effect: Z = 0.05 (P = 0.96)

Test for subgroup differences: Not applicable



Analysis 6.4. Comparison 6 Different classes of antidepressants versus different classes of other medications, Outcome 4 Addiction Severity index (ASI) score, Drugs: SSRIs versus anticonvulsants.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 6 Different classes of antidepressants versus different classes of other medications

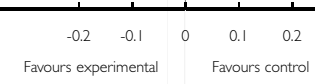
Outcome: 4 Addiction Severity index (ASI) score, Drugs: SSRIs versus anticonvulsants

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Ciraulo 2005 b	16	0.16 (0.07)	17	0.15 (0.1)		57.1 %	0.01 [-0.05, 0.07]
Winhusen 2005	16	0.19 (0.12)	17	0.21 (0.07)		42.9 %	-0.02 [-0.09, 0.05]
Total (95% CI)	**32**		**34**			**100.0 %**	**0.00 [-0.05, 0.04]**

Heterogeneity: $Chi^2 = 0.43$, df = 1 (P = 0.51); $I^2 = 0.0\%$

Test for overall effect: Z = 0.13 (P = 0.90)

Test for subgroup differences: Not applicable



Analysis 7.1. Comparison 7 Desipramine versus Amantadine, Outcome 1 Dropouts.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 7 Desipramine versus Amantadine

Outcome: 1 Dropouts

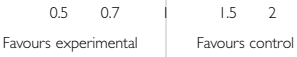
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kolar 1992	0/8	3/5		12.4 %	0.10 [0.01, 1.53]
Kosten 1992 a	8/30	8/33		22.5 %	1.10 [0.47, 2.56]
Weddington 1991	27/32	19/23		65.2 %	1.02 [0.80, 1.30]
Total (95% CI)	**70**	**61**		**100.0 %**	**0.92 [0.69, 1.23]**

Total events: 35 (Experimental), 30 (Control)

Heterogeneity: Chi^2 = 3.40, df = 2 (P = 0.18); I^2 =41%

Test for overall effect: Z = 0.54 (P = 0.59)

Test for subgroup differences: Not applicable



Analysis 7.2. Comparison 7 Desipramine versus Amantadine, Outcome 2 Abstinence, last week.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 7 Desipramine versus Amantadine

Outcome: 2 Abstinence, last week

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Kolar 1992	7/8	1/2		6.8 %	7.00 [0.22, 226.00]
Weddington 1991	8/17	5/16		93.2 %	1.96 [0.47, 8.11]
Total (95% CI)	**25**	**18**		**100.0 %**	**2.30 [0.62, 8.55]**

Total events: 15 (Experimental), 6 (Control)

Heterogeneity: Chi^2 = 0.44, df = 1 (P = 0.51); I^2 =0.0%

Test for overall effect: Z = 1.24 (P = 0.21)

Test for subgroup differences: Not applicable

Analysis 7.3. Comparison 7 Desipramine versus Amantadine, Outcome 3 Craving for cocaine.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 7 Desipramine versus Amantadine

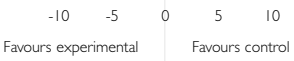
Outcome: 3 Craving for cocaine

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Kolar 1992	8	3 (5.66)	5	5 (2.68)		26.7 %	-0.39 [-1.52, 0.74]
Weddington 1991	17	5.4 (21.4)	16	7 (22.4)		73.3 %	-0.07 [-0.75, 0.61]
Total (95% CI)	**25**		**21**			**100.0 %**	**-0.16 [-0.74, 0.43]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.22$, df = 1 (P = 0.64); $I^2 = 0.0\%$

Test for overall effect: Z = 0.52 (P = 0.60)

Test for subgroup differences: Not applicable



Analysis 7.4. Comparison 7 Desipramine versus Amantadine, Outcome 4 Mood (BDI).

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 7 Desipramine versus Amantadine

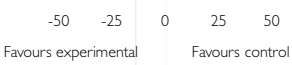
Outcome: 4 Mood (BDI)

Study or subgroup	Favours experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kolar 1992	8	1 (1.13)	5	1.6 (2.24)		69.5 %	-0.60 [-2.71, 1.51]
Weddington 1991	17	3.6 (4.94)	16	2.8 (4.4)		30.5 %	0.80 [-2.39, 3.99]
Total (95% CI)	**25**		**21**			**100.0 %**	**-0.17 [-1.93, 1.59]**

Heterogeneity: $Chi^2 = 0.51$, df = 1 (P = 0.47); $I^2 = 0.0\%$

Test for overall effect: Z = 0.19 (P = 0.85)

Test for subgroup differences: Not applicable

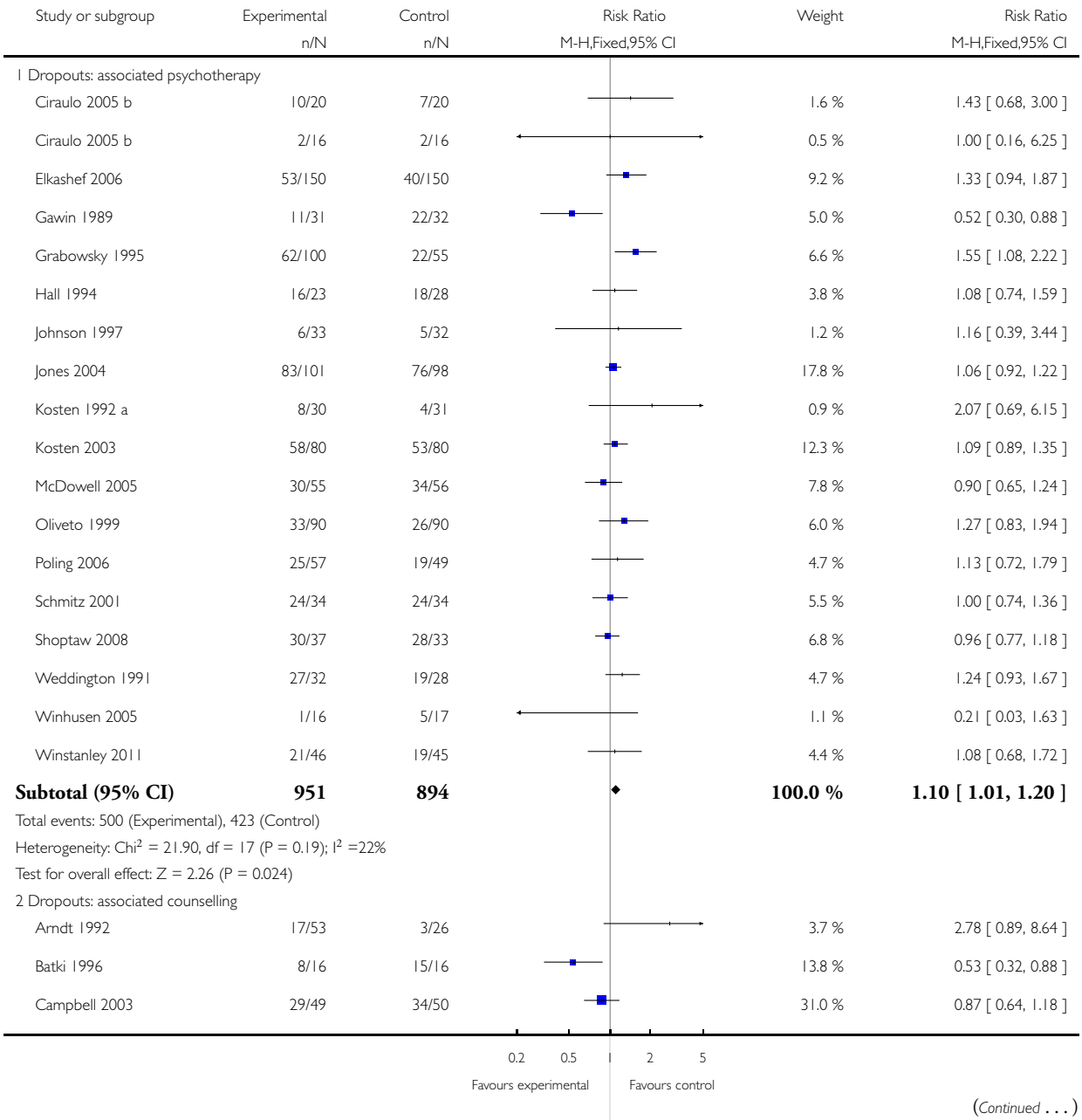


Analysis 8.1. Comparison 8 Antidepressants plus psychosocial interventions vs placebo, Outcome 1 Dropout.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 8 Antidepressants plus psychosocial interventions vs placebo

Outcome: 1 Dropout



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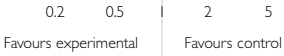
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cornish 2001	10/40	9/40		8.3 %	1.11 [0.51, 2.44]
Giannini 1986	2/10	0/10		0.5 %	5.00 [0.27, 92.62]
Kolar 1992	0/8	5/9		4.8 %	0.10 [0.01, 1.58]
Margolin 1995	11/74	13/75		11.9 %	0.86 [0.41, 1.79]
Nunes 1995	25/59	27/54		26.0 %	0.85 [0.57, 1.26]
Subtotal (95% CI)	**309**	**280**		**100.0 %**	**0.89 [0.72, 1.09]**
Total events: 102 (Experimental), 106 (Control)					
Heterogeneity: Chi² = 11.94, df = 7 (P = 0.10); I² =41%					
Test for overall effect: Z = 1.11 (P = 0.27)					
Test for subgroup differences: Chi² = 3.56, df = 1 (P = 0.06), I² =72%					



Analysis 8.2. Comparison 8 Antidepressants plus psychosocial interventions vs placebo, Outcome 2 Retention in treatment.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 8 Antidepressants plus psychosocial interventions vs placebo

Outcome: 2 Retention in treatment

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Retention in treatment (mean number of weeks): studies with psychotherapy						
Gawin 1989	24	5.41 (1.12)	24	4.37 (1.75)		1.04 [0.21, 1.87]
Hall 1994	23	11.06 (10.09)	28	7.86 (7.79)		3.20 [-1.83, 8.23]
Shoptaw 2008	37	8.5 (5.8)	33	7.9 (5.2)		0.60 [-1.98, 3.18]
Winstanley 2011	35	22 (7.5)	33	23.6 (6.9)		-1.60 [-5.02, 1.82]
Subtotal (95% CI)	**119**		**118**			**0.92 [0.16, 1.68]**
Heterogeneity: Chi² = 3.01, df = 3 (P = 0.39); I² =0%						
Test for overall effect: Z = 2.37 (P = 0.018)						
2 Retention in treatment (mean number of weeks): studies with counselling						
Cornish 2001	40	5.06 (2.74)	40	5.16 (2.73)		-0.10 [-1.30, 1.10]

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Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Kolar 1992	8	12 (0)	9	9.33 (3.08)		0.0 [0.0, 0.0]
Winstanley 2011	38	18 (7.5)	39	22.4 (8.2)		-4.40 [-7.91, -0.89]
Subtotal (95% CI)	**86**		**88**			**-0.55 [-1.68, 0.58]**
Heterogeneity: Chi^2 = 5.17, df = 1 (P = 0.02); I^2 =81%						
Test for overall effect: Z = 0.95 (P = 0.34)						

-1 -0.5 0 0.5 1

Favours control Favours experimental

Analysis 8.3. Comparison 8 Antidepressants plus psychosocial interventions vs placebo, Outcome 3 Abstinence.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 8 Antidepressants plus psychosocial interventions vs placebo

Outcome: 3 Abstinence

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Abstinent for at least three consecutive weeks: studies with psychotherapy					
Elkashef 2006	7/147	12/148		33.2 %	0.59 [0.24, 1.45]
Gawin 1989	14/24	4/24		11.1 %	3.50 [1.35, 9.11]
Giannini 1987 a	9/10	6/10		16.7 %	1.50 [0.87, 2.59]
McDowell 2005	11/55	11/56		30.3 %	1.02 [0.48, 2.15]
Shoptaw 2008	6/37	3/33		8.8 %	1.78 [0.48, 6.57]
Subtotal (95% CI)	**273**	**271**		**100.0 %**	**1.30 [0.89, 1.88]**
Total events: 47 (Experimental), 36 (Control)					
Heterogeneity: Chi^2 = 7.99, df = 4 (P = 0.09); I^2 =50%					
Test for overall effect: Z = 1.37 (P = 0.17)					
2 Abstinent for at least three consecutive weeks: studies with counselling					
Campbell 2003	13/36	13/39		74.9 %	1.08 [0.58, 2.02]
Nunes 1995	11/59	4/54		25.1 %	2.52 [0.85, 7.44]
Subtotal (95% CI)	**95**	**93**		**100.0 %**	**1.44 [0.84, 2.48]**
Total events: 24 (Experimental), 17 (Control)					
Heterogeneity: Chi^2 = 1.83, df = 1 (P = 0.18); I^2 =45%					
Test for overall effect: Z = 1.33 (P = 0.18)					
Test for subgroup differences: Chi^2 = 0.10, df = 1 (P = 0.75), I^2 =0.0%					

0.1 0.2 0.5 1 2 5 10

Favours control Favours experimental

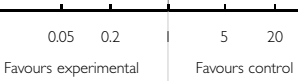
Analysis 8.4. Comparison 8 Antidepressants plus psychosocial interventions vs placebo, Outcome 4 Adverse events.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 8 Antidepressants plus psychosocial interventions vs placebo

Outcome: 4 Adverse events

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Withdrawn due to adverse events: studies with psychotherapy					
Ciraulo 2005 b	1/20	0/20		4.4 %	3.00 [0.13, 69.52]
Elkashef 2006	1/150	0/150		4.4 %	3.00 [0.12, 73.06]
Johnson 1997	1/33	0/32		4.4 %	2.91 [0.12, 68.95]
Kosten 1992 a	2/30	1/31		8.6 %	2.07 [0.20, 21.61]
McDowell 2005	10/55	8/56		69.5 %	1.27 [0.54, 2.98]
Winhusen 2005	1/16	0/17		4.3 %	3.18 [0.14, 72.75]
Winstanley 2011	2/46	0/45		4.4 %	4.89 [0.24, 99.18]
Subtotal (95% CI)	**350**	**351**		**100.0 %**	**1.81 [0.91, 3.58]**
Total events: 18 (Experimental), 9 (Control)					
Heterogeneity: Chi^2 = 1.49, df = 6 (P = 0.96); I^2 =0.0%					
Test for overall effect: Z = 1.69 (P = 0.090)					
2 Withdrawn due to adverse events: studies with counselling					
Arndt 1992	4/53	0/26		6.5 %	4.50 [0.25, 80.57]
Batki 1996	1/16	1/16		9.8 %	1.00 [0.07, 14.64]
Kolar 1992	0/8	1/9		13.9 %	0.37 [0.02, 7.99]
Margolin 1995	2/74	2/75		19.4 %	1.01 [0.15, 7.01]
Nunes 1995	2/59	3/54		30.6 %	0.61 [0.11, 3.51]
Winstanley 2011	8/48	2/47		19.8 %	3.92 [0.88, 17.49]
Subtotal (95% CI)	**258**	**227**		**100.0 %**	**1.60 [0.74, 3.47]**
Total events: 17 (Experimental), 9 (Control)					
Heterogeneity: Chi^2 = 4.24, df = 5 (P = 0.52); I^2 =0.0%					
Test for overall effect: Z = 1.19 (P = 0.23)					
Test for subgroup differences: Chi^2 = 0.05, df = 1 (P = 0.82), I^2 =0.0%					



Analysis 9.1. Comparison 9 Antidepressants vs placebo participants also opioid dependence status, Outcome 1 Dropouts.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 9 Antidepressants vs placebo participants also opioid dependence status

Outcome: 1 Dropouts

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Arndt 1992	17/53	3/26		2.4 %	2.78 [0.89, 8.64]
Grabowsky 1995	4/11	5/10		3.1 %	0.73 [0.27, 1.97]
Kolar 1992	0/8	5/9		3.1 %	0.10 [0.01, 1.58]
Kosten 1992 a	8/30	4/31		2.3 %	2.07 [0.69, 6.15]
Kosten 2003	58/80	53/80		31.1 %	1.09 [0.89, 1.35]
Margolin 1995	11/74	13/75		7.6 %	0.86 [0.41, 1.79]
O'Brien 1988	8/32	1/15		0.8 %	3.75 [0.51, 27.33]
Oliveto 1999	33/90	26/90		15.2 %	1.27 [0.83, 1.94]
Poling 2006	25/57	19/49		12.0 %	1.13 [0.72, 1.79]
Winstanley 2011	54/94	38/92		22.5 %	1.39 [1.03, 1.88]
Total (95% CI)	**529**	**477**		**100.0 %**	**1.22 [1.05, 1.41]**

Total events: 218 (Experimental), 167 (Control)

Heterogeneity: Chi^2 = 11.12, df = 9 (P = 0.27); I^2 =19%

Test for overall effect: Z = 2.53 (P = 0.011)

Test for subgroup differences: Not applicable

Analysis 9.2. Comparison 9 Antidepressants vs placebo participants also opioid dependence status, Outcome 2 Withdrawn due to adverse events.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 9 Antidepressants vs placebo participants also opioid dependence status

Outcome: 2 Withdrawn due to adverse events

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Arndt 1992	4/53	0/26		9.4 %	4.50 [0.25, 80.57]
Kolar 1992	0/8	1/9		20.1 %	0.37 [0.02, 7.99]
Kosten 1992 a	2/30	1/31		13.9 %	2.07 [0.20, 21.61]
Margolin 1995	2/74	2/75		28.1 %	1.01 [0.15, 7.01]
Winstanley 2011	10/94	2/92		28.6 %	4.89 [1.10, 21.73]
Total (95% CI)	**259**	**233**		**100.0 %**	**2.47 [1.03, 5.90]**

Total events: 18 (Experimental), 6 (Control)

Heterogeneity: $Chi^2 = 3.28$, df = 4 (P = 0.51); $I^2 = 0.0\%$

Test for overall effect: Z = 2.03 (P = 0.042)

Test for subgroup differences: Not applicable

Analysis 10.1. Comparison 10 Antidepressants vs placebo according to length of trial, Outcome 1 Dropout.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 10 Antidepressants vs placebo according to length of trial

Outcome: 1 Dropout

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Dropouts: up to six weeks weeks of treatment					
Cornish 2001	10/40	9/40		23.0 %	1.11 [0.51, 2.44]
Gawin 1989	11/31	22/32		38.6 %	0.52 [0.30, 0.88]
Giannini 1986	2/10	0/10		2.2 %	5.00 [0.27, 92.62]
Giannini 1993	1/16	3/16		4.0 %	0.33 [0.04, 2.87]
Johnson 1997	6/33	5/32		13.9 %	1.16 [0.39, 3.44]
Tennant 1985	5/11	5/11		18.3 %	1.00 [0.40, 2.50]
Subtotal (95% CI)	**141**	**141**		**100.0 %**	**0.80 [0.52, 1.25]**
Total events: 35 (Experimental), 44 (Control)					
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 6.16$, df = 5 (P = 0.29); $I^2 = 19\%$					
Test for overall effect: Z = 0.97 (P = 0.33)					
2 Dropouts: more than six weeks of treatment					
Arndt 1992	17/53	3/26		0.7 %	2.78 [0.89, 8.64]
Batki 1996	8/16	15/16		2.8 %	0.53 [0.32, 0.88]
Campbell 2003	29/49	34/50		5.6 %	0.87 [0.64, 1.18]
Ciraulo 2005 a	7/34	11/35		1.3 %	0.66 [0.29, 1.49]
Ciraulo 2005 b	2/16	2/16		0.3 %	1.00 [0.16, 6.25]
Ciraulo 2005 b	10/20	7/20		1.5 %	1.43 [0.68, 3.00]
Elkashef 2006	53/150	40/150		4.8 %	1.33 [0.94, 1.87]
Grabowsky 1995	62/100	22/55		4.5 %	1.55 [1.08, 2.22]
Grabowsky 1995	62/100	22/55		4.5 %	1.55 [1.08, 2.22]
Hall 1994	29/45	30/49		5.3 %	1.05 [0.77, 1.44]
Jenkins 1992	9/20	11/21		2.0 %	0.86 [0.46, 1.62]
Jones 2004	83/101	76/98		9.4 %	1.06 [0.92, 1.22]
Kolar 1992	0/8	5/9		0.1 %	0.10 [0.01, 1.58]
Kosten 1992 a	8/30	4/31		0.8 %	2.07 [0.69, 6.15]
Kosten 2003	58/80	53/80		7.7 %	1.09 [0.89, 1.35]

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Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Margolin 1995	11/74	13/75		1.5 %	0.86 [0.41, 1.79]
McDowell 2005	30/55	34/56		5.2 %	0.90 [0.65, 1.24]
McElroy 1989	5/9	5/6		1.7 %	0.67 [0.34, 1.32]
Nunes 1995	25/59	27/54		4.0 %	0.85 [0.57, 1.26]
O'Brien 1988	8/32	1/15		0.2 %	3.75 [0.51, 27.33]
Oliveto 1999	33/90	26/90		3.7 %	1.27 [0.83, 1.94]
Poling 2006	25/57	19/49		3.3 %	1.13 [0.72, 1.79]
Schmitz 2001	24/34	24/34		5.4 %	1.00 [0.74, 1.36]
Shoptaw 2008	30/37	28/33		7.5 %	0.96 [0.77, 1.18]
Weddington 1991	27/32	19/28		5.6 %	1.24 [0.93, 1.67]
Winhusen 2005	15/16	12/17		5.0 %	1.33 [0.95, 1.85]
Winstanley 2011	54/94	38/92		5.6 %	1.39 [1.03, 1.88]
Subtotal (95% CI)	**1411**	**1260**		**100.0 %**	**1.09 [0.99, 1.20]**

Total events: 724 (Experimental), 581 (Control)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 42.76$, df = 26 (P = 0.02); $I^2 = 39\%$

Test for overall effect: Z = 1.72 (P = 0.086)

Test for subgroup differences: $Chi^2 = 1.74$, df = 1 (P = 0.19), $I^2 = 43\%$

Analysis 10.2. Comparison 10 Antidepressants vs placebo according to length of trial, Outcome 2 Retention in treatment: more than six weeks of treatment.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 10 Antidepressants vs placebo according to length of trial

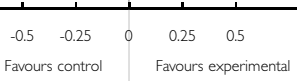
Outcome: 2 Retention in treatment: more than six weeks of treatment

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Hall 1994	45	10.67 (10.66)	49	8.31 (8.41)		2.36 [-1.54, 6.26]
Jenkins 1992	20	8 (3.74)	21	8.14 (3.72)		-0.14 [-2.42, 2.14]
Kolar 1992	8	12 (0)	9	9.33 (3.08)		0.0 [0.0, 0.0]
Lambert Passos 2005	105	6.18 (0.47)	105	5.84 (0.49)		0.34 [0.21, 0.47]
Shoptaw 2008	37	8.5 (5.8)	33	7.9 (5.2)		0.60 [-1.98, 3.18]
Winstanley 2011	73	19.92 (7.71)	72	22.9 (7.6)		-2.98 [-5.47, -0.49]
Total (95% CI)	**288**		**289**			**0.33 [0.20, 0.46]**

Heterogeneity: $Chi^2 = 8.04$, df = 4 (P = 0.09); $I^2 = 50\%$

Test for overall effect: Z = 5.04 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 10.3. Comparison 10 Antidepressants vs placebo according to length of trial, Outcome 3 Abstinence for at least three consecutive weeks: more than six weeks of treatment.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 10 Antidepressants vs placebo according to length of trial

Outcome: 3 Abstinence for at least three consecutive weeks: more than six weeks of treatment

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Campbell 2003	13/36	13/39		13.8 %	1.08 [0.58, 2.02]
Elkashef 2006	7/147	12/148		13.2 %	0.59 [0.24, 1.45]
Lambert Passos 2005	52/105	48/105		52.9 %	1.08 [0.82, 1.44]
McDowell 2005	11/55	11/56		12.0 %	1.02 [0.48, 2.15]
Nunes 1995	11/59	4/54		4.6 %	2.52 [0.85, 7.44]
Shoptaw 2008	6/37	3/33		3.5 %	1.78 [0.48, 6.57]
Total (95% CI)	**439**	**435**		**100.0 %**	**1.10 [0.87, 1.39]**

Total events: 100 (Experimental), 91 (Control)

Heterogeneity: Chi^2 = 4.68, df = 5 (P = 0.46); I^2 =0.0%

Test for overall effect: Z = 0.81 (P = 0.42)

Test for subgroup differences: Not applicable

Analysis 10.4. Comparison 10 Antidepressants vs placebo according to length of trial, Outcome 4 Withdrawn due to adverse events: more than six weeks of treatmentAdverse events.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 10 Antidepressants vs placebo according to length of trial

Outcome: 4 Withdrawn due to adverse events: more than six weeks of treatmentAdverse events

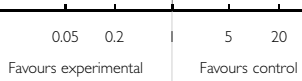
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Arndt 1992	4/53	0/26		2.0 %	4.50 [0.25, 80.57]
Batki 1996	1/16	1/16		3.0 %	1.00 [0.07, 14.64]
Ciraulo 2005 b	1/20	0/20		1.5 %	3.00 [0.13, 69.52]
Elkashef 2006	1/150	0/150		1.5 %	3.00 [0.12, 73.06]
Kolar 1992	0/8	1/9		4.3 %	0.37 [0.02, 7.99]
Kosten 1992 a	2/30	1/31		3.0 %	2.07 [0.20, 21.61]
Lambert Passos 2005	11/105	13/105		39.2 %	0.85 [0.40, 1.80]
Margolin 1995	2/74	2/75		6.0 %	1.01 [0.15, 7.01]
McDowell 2005	10/55	8/56		23.9 %	1.27 [0.54, 2.98]
Nunes 1995	2/59	3/54		9.5 %	0.61 [0.11, 3.51]
Winstanley 2011	10/94	2/92		6.1 %	4.89 [1.10, 21.73]
Total (95% CI)	**664**	**634**		**100.0 %**	**1.34 [0.87, 2.07]**

Total events: 44 (Experimental), 31 (Control)

Heterogeneity: $Chi^2 = 7.22$, df = 10 (P = 0.70); $I^2 = 0.0\%$

Test for overall effect: Z = 1.34 (P = 0.18)

Test for subgroup differences: Not applicable



Analysis 11.1. Comparison 11 Antidepressants vs placebo (excluding medication with questionable or uncertain antidepressant activity), Outcome 1 Dropouts.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 11 Antidepressants vs placebo (excluding medication with questionable or uncertain antidepressant activity)

Outcome: 1 Dropouts

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Arndt 1992	17/53	3/26		0.9 %	2.78 [0.89, 8.64]
Batki 1996	8/16	15/16		3.5 %	0.53 [0.32, 0.88]
Campbell 2003	29/49	34/50		6.2 %	0.87 [0.64, 1.18]
Ciraulo 2005 a	7/34	11/35		1.6 %	0.66 [0.29, 1.49]
Ciraulo 2005 b	10/20	7/20		2.0 %	1.43 [0.68, 3.00]
Ciraulo 2005 b	2/16	2/16		0.4 %	1.00 [0.16, 6.25]
Cornish 2001	10/40	9/40		1.8 %	1.11 [0.51, 2.44]
Elkashef 2006	53/150	40/150		5.5 %	1.33 [0.94, 1.87]
Gawin 1989	11/31	22/32		3.3 %	0.52 [0.30, 0.88]
Giannini 1986	2/10	0/10		0.2 %	5.00 [0.27, 92.62]
Grabowsky 1995	62/100	22/55		5.3 %	1.55 [1.08, 2.22]
Grabowsky 1995	4/11	5/10		1.2 %	0.73 [0.27, 1.97]
Hall 1994	29/45	30/49		6.1 %	1.05 [0.77, 1.44]
Johnson 1997	6/33	5/32		1.0 %	1.16 [0.39, 3.44]
Kolar 1992	0/8	5/9		0.2 %	0.10 [0.01, 1.58]
Kosten 1992 a	8/30	4/31		1.0 %	2.07 [0.69, 6.15]
Kosten 2003	58/80	53/80		8.1 %	1.09 [0.89, 1.35]
Margolin 1995	11/74	13/75		2.0 %	0.86 [0.41, 1.79]
McDowell 2005	30/55	34/56		5.9 %	0.90 [0.65, 1.24]
McElroy 1989	5/9	5/6		2.2 %	0.67 [0.34, 1.32]
Nunes 1995	25/59	27/54		4.7 %	0.85 [0.57, 1.26]
O'Brien 1988	8/32	1/15		0.3 %	3.75 [0.51, 27.33]
Oliveto 1999	33/90	26/90		4.4 %	1.27 [0.83, 1.94]
Poling 2006	25/57	19/49		4.0 %	1.13 [0.72, 1.79]
Schmitz 2001	24/34	24/34		6.1 %	1.00 [0.74, 1.36]

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Shoptaw 2008	30/37	28/33		8.0 %	0.96 [0.77, 1.18]
Tennant 1985	5/11	5/11		1.4 %	1.00 [0.40, 2.50]
Weddington 1991	27/32	19/28		6.3 %	1.24 [0.93, 1.67]
Winhusen 2005	1/16	5/17		0.3 %	0.21 [0.03, 1.63]
Winstanley 2011	54/94	38/92		6.3 %	1.39 [1.03, 1.88]
Total (95% CI)	**1326**	**1221**		**100.0 %**	**1.03 [0.92, 1.16]**

Total events: 594 (Experimental), 511 (Control)

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 47.24$, df = 29 (P = 0.02); $I^2 = 39\%$

Test for overall effect: Z = 0.54 (P = 0.59)

Test for subgroup differences: Not applicable

Analysis 11.2. Comparison 11 Antidepressants vs placebo (excluding medication with questionable or uncertain antidepressant activity), Outcome 2 Retention in treatment as mean number of weeks in treatment.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 11 Antidepressants vs placebo (excluding medication with questionable or uncertain antidepressant activity)

Outcome: 2 Retention in treatment as mean number of weeks in treatment

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Cornish 2001	40	5.06 (2.74)	40	5.16 (2.73)		-0.10 [-1.30, 1.10]
Gawin 1989	24	5.41 (1.12)	24	4.37 (1.75)		1.04 [0.21, 1.87]
Hall 1994	45	10.67 (10.66)	49	8.31 (8.41)		2.36 [-1.54, 6.26]
Kolar 1992	8	12 (0)	9	9.33 (3.08)		0.0 [0.0, 0.0]
Lambert Passos 2005	105	6.18 (0.47)	105	5.84 (0.49)		0.34 [0.21, 0.47]
Shoptaw 2008	37	8.5 (5.8)	33	7.9 (5.2)		0.60 [-1.98, 3.18]
Winstanley 2011	73	19.92 (7.71)	72	22.9 (7.6)		-2.98 [-5.47, -0.49]
Total (95% CI)	**332**		**332**			**0.29 [-0.41, 1.00]**

Heterogeneity: $Tau^2 = 0.33$; $Chi^2 = 11.12$, df = 5 (P = 0.05); $I^2 = 55\%$

Test for overall effect: Z = 0.81 (P = 0.42)

Test for subgroup differences: Not applicable

Analysis 11.3. Comparison 11 Antidepressants vs placebo (excluding medication with questionable or uncertain antidepressant activity), Outcome 3 Abstinence as number of weeks of continuous abstinence.

Review: Antidepressants for cocaine dependence and problematic cocaine use

Comparison: 11 Antidepressants vs placebo (excluding medication with questionable or uncertain antidepressant activity)

Outcome: 3 Abstinence as number of weeks of continuous abstinence

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Carroll 1994	54	3.19 (2.94)	56	2.75 (2.47)		5.8 %	0.44 [-0.58, 1.46]
Elkashef 2006	147	0.97 (1.17)	148	1.08 (1.28)		76.3 %	-0.11 [-0.39, 0.17]
Kosten 2003	80	2.8 (4.09)	80	1.74 (3.21)		4.6 %	1.06 [-0.08, 2.20]
Lambert Passos 2005	105	4.13 (3.48)	105	3.66 (3.48)		6.7 %	0.47 [-0.47, 1.41]
Shoptaw 2008	37	1.74 (2.84)	33	1.14 (1.34)		5.7 %	0.60 [-0.42, 1.62]
Weddington 1991	17	6.2 (4.53)	21	3.6 (3.66)		0.8 %	2.60 [-0.06, 5.26]
Total (95% CI)	**440**		**443**			**100.0 %**	**0.08 [-0.17, 0.32]**

Heterogeneity: Chi^2 = 10.19, df = 5 (P = 0.07); I^2 =51%

Test for overall effect: Z = 0.63 (P = 0.53)

Test for subgroup differences: Not applicable

APPENDICES

Appendix 1. PubMed search strategy

1. cocaine-related disorders[MeSH Terms]
2. (((addict*[Title/Abstract]) OR abuse*[Title/Abstract]) OR dependen*[Title/Abstract]) OR disorder*[Title/Abstract]
3. #1 OR #2
4. Cocaine [mesh] OR Cocaine [tiab]
5. #3 AND #4
6. "antidepressive agents"[MeSH Terms]
7. Monoamine Oxidase Inhibitors[MeSH Terms]
8. "serotonin uptake inhibitors"[MeSH Terms]
9. Antidepress* OR "**Monoamine-oxidase inhibitors" OR MAOIs** OR acetylcarnitine OR agomelatine OR alaproclate OR amersergide OR amiflamine OR amineptine OR amitriptyline OR **amoxapine** OR befloxatone OR benactyzine OR brofaromine

OR bupropion OR butriptyline OR caroxazone OR chlorphenamidine OR chlorpoxiten OR cilosamine OR cimoxatone OR **citalopram** OR **clomipramine** OR clorgyline OR clorimipramine OR clovoxamine OR cyclobenzaprine OR deanol OR demexiptiline OR deprenyl OR **desipramine** OR dibenzepin OR diclofensine OR **dothiepin** OR desmethyldoxepin OR **doxepin** OR dosulepin OR duloxetine OR escitalopram OR etoperidone OR femoxetine OR fenfluramine OR fluotracen OR **fluoxetine** OR fluparoxan OR **fluvoxamine** OR idazoxan OR **imipramine** OR iprindole OR iproniazid OR **isocarboxazid** OR litoxetine OR lithium OR **lofepramine** OR **maprotiline** OR medifoxamine OR melitracen OR metapramine OR mianserin OR milnacipran OR minaprine OR mirtazapine OR **moclobemide** OR nefazodone OR nialamide OR nomifensine OR **nortriptyline** OR noxiptiline OR norzimelidine OR opipramol OR oxaflozane OR oxaprotiline OR pargyline OR **paroxetine** OR **phenelzine** OR pizotyline OR piribedil OR pirlindole OR pivagabine OR prosulpride OR protriptyline OR quinupramine OR quipazine OR reboxetine OR rolipram OR "Selective Serotonin Reuptake Inhibitors" OR SSRI OR selegiline OR **sertraline** OR setiptiline OR sulpiride OR teniloxine OR tetrindole OR thozalinone OR **tianeptine** OR toloxatone OR tomoxetine OR **tranylcypromine** OR **trazodone** OR **trimipramine** OR 5-Hydroxytryptophan OR venlafaxine OR desvenlafaxine OR **viloxazine** OR viqualine OR zimeldine

10. #6 OR #7 OR #8 or #9
11. randomized controlled trial[Publication Type]
12. controlled clinical trial[Publication Type]
13. random* [tiab]
14. placebo* [tiab]
15. drug therapy[MeSH Subheading]
16. trial[Title/Abstract]
17. groups[Title/Abstract]
18. #11 OR #12 OR #13 or #14 or #15 or #16 OR #17
19. animals[MeSH Terms]) NOT humans[MeSH Terms]
20. #18 NOT #19
21. #5 AND #10 AND #20

Appendix 2. Search strategy for EMBASE and CINAHL

1. cocaine dependence/exp
2. ((cocaine) and (addict* or disorder* or dependen* or abuse*))
3. 1 OR 2
4. cocaine'/exp OR cocaine
5. cocaine derivative'/exp
6. 4 or 5
7. antidepressant/exp
8. citalopram OR escitalopram OR paroxetine OR fluoxetine OR fluvoxamine OR sertraline OR trazodone OR nefazodone OR venlafaxine OR desvenlafaxine OR duloxetine OR reboxetine OR bupropion OR amoxapine OR amitriptyline OR maprotiline OR nortriptyline OR desipramine OR trimipramine OR imipramine OR protriptyline OR doxepin OR clomipramine OR mirtazapine OR mianserin OR moclobemide OR phenelzine OR tranylcypromine OR agomelatine or Acetylcarnitine or Alaproclate or Amersergide or Amiflamine or Amineptine or Amisulpride OR Befloxatone or Benactyzine or Brofaromine or Butriptyline or Caroxazone or Chlorpoxiten or Cilosamine or Cimoxatone or Clorgyline or Clorimipramine or Clovoxamine or Deanol or Demexiptiline or Deprenyl or Dibenzipin or Diclofensine or Dothiepin or Etoperidone or Femoxetine or Fluotracen or Fluparoxan or Idazoxan or Iprindole or Iproniazid or isocarboxazid or Litoxetine or Lofepramine or Medifoxamine or Melitracen or Metapramine or Milnacipran or Minaprine or Nialamide or Nomifensine or Noxiptiline or Opipramol or Oxaflozane or Oxaprotiline or Pargyline or Piribedil or Pirlindole or Pivagabine or Prosulpride or Protriptyline or Quinupramine or Rolipram or SSRI or Setiptiline or Sulpiride or Teniloxine or Tetrindole or Thiazesim or Thozalinone or Tianeptine or Toloxatone or Tomoxetine or Viloxazine or Viqualine or Zimeldine
9. 7 or 8
10. random* OR control* OR prospective* OR volunteer*
11. (singl* OR doubl* OR trebl* OR tripl* AND (blind* OR mask*))
12. cross-over OR crossover*
13. 'randomized controlled trial'/exp
14. 'phase 2 clinical trial'/exp

15. 'phase 3 clinical trial'/exp
16. 'double blind procedure'/exp
17. 'single blind procedure'/exp
18. 'crossover procedure'/exp
19. 'latin square design'/exp
20. 'placebo'/exp
21. 'multicenter study'/exp
22. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. 3 AND 6 AND 9 AND 22
24. limit 23 to humans

Appendix 3. Search strategy for CENTRAL

1. cocaine-related disorders [mesh]
2. ((cocaine) NEXT (addict* or disorder* or dependen* or abuse*)):TI;AB
3. 1 OR 2
4. cocaine [mesh]
5. cocaine or crack:TI;AB
6. 4 or 5
7. antidepressant*:TI,AB
8. Antidepressive Agents[Mesh]
9. citalopram OR escitalopram OR paroxetine OR fluoxetine OR fluvoxamine OR sertraline OR trazodone OR nefazodone OR venlafaxine OR desvenlafaxine OR duloxetine OR reboxetine OR bupropion OR amoxapine OR amitriptyline OR maprotiline OR nortriptyline OR desipramine OR trimipramine OR imipramine OR protriptyline OR doxepin OR clomipramine OR mirtazapine OR mianserin OR moclobemide OR phenelzine OR tranylcypromine OR agomelatine or Acetylcarnitine or Alaproclate or Amersergide or Amiflamine or Amineptine or Amisulpride OR Befloxatone or Benactyzine or Brofaromine or Butriptyline or Caroxazone or Chlorpoxiten or Cilosamine or Cimoxatone or Clorgyline or Clorimipramine or Clovoxamine or Deanol or Demexiptiline or Deprenyl or Dibenzipin or Diclofensine or Dothiepin or Etoperidone or Femoxetine or Fluotracen or Fluparoxan or Idazoxan or Iprindole or Iproniazid or isocarboxazid or Litoxetine or Lofepramine or Medifoxamine or Melitracen or Metapramine or Milnacipran or Minaprine or Nialamide or Nomifensine or Noxiptiline or Opipramol or Oxaflozane or Oxaprotiline or Pargyline or Piribedil or Pirlindole or Pivagabine or Prosulpride or Protriptyline or Quinupramine or Rolipram or SSRI or Setiptiline or Sulpiride or Teniloxine or Tetrindole or Thiazesim or Thozalinone or Tianeptine or Toloxatone or Tomoxetine or Viloxazine or Viqualine or Zimeldine
10. 7 or 8 or 9
11. 3 AND 6 AND 10

Appendix 4. Search strategy for ongoing registries (clinicaltrials.gov, controlledtrials.com

Cocaine AND antidepressants

Appendix 5. Criteria for assessing risk of bias in RCTs and CCTs

	Item	Judgment	Description
1	Was the method of randomization adequate?	Low Risk	The investigators describe a random component in the sequence generation process such as: random number table; computer random

(*Continued*)

			number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization
		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; availability of the intervention
		Unclear Risk	Insufficient information about the sequence generation process to permit judgement of 'Yes' or 'No'
2	Was the treatment allocation concealed?	Low Risk	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
		High Risk	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
		Unclear Risk	Insufficient information to permit judgement of 'Yes' or 'No'. 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	Was knowledge of the allocated interventions adequately prevented during the study? (blinding of patients, provider, outcome assessor) Objective outcomes	Low Risk	Blinding of participants, providers and outcome assessor and unlikely that the blinding could have been broken; Either participants or providers were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias No blinding, but the objective outcome measurement are not likely to be influenced by lack of blinding
4	Was knowledge of the allocated interventions adequately prevented during the study? (blinding of patients, provider, outcome assessor) Subjective outcomes	Low Risk	Blinding of participants, providers and outcome assessor and unlikely that the blinding could have been broken; Either participants or providers were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias
		High Risk	No blinding or incomplete blinding, and the outcome or outcome measurement 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;

(*Continued*)

			Either participants or outcome assessor were not blinded, and the non-blinding of others likely to introduce bias
		Unclear Risk	Insufficient information to permit judgement of 'Yes' or 'No';
5	Were incomplete outcome data adequately addressed? For all outcomes except retention in treatment or drop out	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 reporting of attrition/exclusions to permit judgement of 'Yes' or 'No' (e.g. number randomised not stated, no reasons for missing data provided; number of drop out not reported for each group);

Appendix 6. Treatments regimes in the included studies

Desipramine: used in 17 trials (Arndt 1992; Campbell 2003; Carroll 1994; Gawin 1989; Giannini 1986; Giannini 1987 a; Giannini 1987 b; Hall 1994; Kolar 1992; Kosten 1992 a; Kosten 2003; McDowell 2005; McElroy 1989; O'Brien 1988; Oliveto 1999; Tennant 1985; Weddington 1991). Dose ranged from 75 to 300 mg/day.
Fluoxetine: used in 5 trials (Batki 1996; Covi 1993; Grabowsky 1995; Schmitz 2001; Winstanley 2011), doses ranging from 20 to 60 mg/day. Two distinct doses (20 and 40 mg/day) of fluoxetine, corresponding to different arms were adopted in Grabowsky 1995. Three distinct doses (20, 40 and 60 mg/day) of fluoxetine, corresponding to different arms were adopted in Covi 1993.
Bupropion (300 mg/day): used in three trials (Margolin 1995; Poling 2006; Shoptaw 2008).
Nefazodone (up to 400 mg/day): used in two trials (Ciraulo 2005 a; Lambert Passos 2005).
Ritanserin (10mg/day): used in two trials (Cornish 2001; Johnson 1997).
One trial each:

- **Buspirone** (30 mg/day) (Giannini 1993),
- **Gepirone** (16 mg/day) (Jenkins 1992),
- **Paroxetine** (20 mg/day) (Ciraulo 2005 b),
- **Citalopram** (20 mg/day) (Moeller 2007),
- **Venlafaxine** (up to 150 mg) (Ciraulo 2005 b),
- **Selegiline** (20 cm^2 patch containing 1.0 mg/cm^2 of selegiline per day) (Elkashef 2006),
- **Tryptophan** (8 g/day) (Jones 2004),
- **Sertraline** (110 mg/day) (Winhusen 2005),
- **Imipramine** (150-300 mg/day) (Nunes 1995).

Appendix 7. Psychosocial treatments offered in association with antidepressants in the included studies

- Cognitive Behavioral Psychotherapy or Relapse Prevention Therapy (Carroll 1994; Ciraulo 2005 a; Ciraulo 2005 b; Grabowsky 1995; Hall 1994; Johnson 1997; Jones 2004; Kosten 1992 a; McDowell 2005; Moeller 2007; Oliveto 1999; Schmitz 2001; Shoptaw 2008; Winhusen 2005);
- Interpersonal Psychotherapy (Covi 1993; Gawin 1989; Weddington 1991);
- Counselling (Arndt 1992; Batki 1996; Campbell 2003; Ciraulo 2005 a; Cornish 2001; Elkashef 2006; Giannini 1986; Kolar 1992; Lambert Passos 2005; Margolin 1995; Nunes 1995; Winstanley 2011);
- Contigiency Management (Kosten 2003; Poling 2006; Winstanley 2011);
- Not Otherwise Specified Psychotherapy (Giannini 1987 a; Giannini 1987 b).
- Jenkins 1992; McElroy 1989; O'Brien 1988; Tennant 1985 did not specified on the availability of psychotherapy.

Appendix 8. Rating instruments utilised in the included studies

1. Addiction Severity Index (ASI) (McLellan 1980; McLellan 1985; McLellan 1991; McLellan 1992), utilized in: Arndt 1992; Campbell 2003; Carroll 1994; Ciraulo 2005 a; Ciraulo 2005 b; Cornish 2001; Covi 1993; Elkashef 2006; Grabowsky 1995; Hall 1994; Jenkins 1992; Johnson 1997; Kosten 1992 a; Kosten 2003; Margolin 1995; O'Brien 1988; Oliveto 1999; Poling 2006; Schmitz 2001; Shoptaw 2008; Winhusen 2005; Winstanley 2011;
2. Structured Clinical Interview for DSM-IV (SCID) (First 1995; First 1996; Spitzer 1985; Spitzer 1987Spitzer 1988; Spitzer 1990; Spitzer 1992), utilized in: Batki 1996; Carroll 1994; Ciraulo 2005 a; Ciraulo 2005 b; Grabowsky 1995; Jenkins 1992; Johnson 1997; Jones 2004; Kosten 1992 a; Kosten 2003; McDowell 2005; Margolin 1995; Moeller 2007; Nunes 1995; Oliveto 1999; Poling 2006; Schmitz 2001; Shoptaw 2008; Winstanley 2011;
3. Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott 1978), utilized in: Gawin 1989; Kolar 1992; Weddington 1991;
4. Diagnostic Interview Schedule (Robins 1981; Blouin 1988; Robins 1989), utilized in: Arndt 1992; Covi 1993; Hall 1994;
5. Psychiatric Diagnostic Interview (PDI-R) (Othmer 1987; Othmer 1989), utilized in: Campbell 2003;
6. Composite International Diagnostic Interview (CIDI) (Robbins 1988), utilized in: Lambert Passos 2005;
7. Research Diagnostic Criteria (Spitzer 1978), utilized in: Weddington 1991;
8. Brief Psychiatric Rating Scale (BPRS), utilized in: Giannini 1987 a; Giannini 1987 b;

9. Determination of Attention Deficit Disorder Utah Criteria (Wender 1981), utilized in: Weddington 1991;
10. Global Assessment Scale (Endicott 1976), utilized in: Gawin 1989; Jenkins 1992;
11. Shipley Institute of Living Scale (Shipley 1984), utilized in: Covi 1993; Weddington 1991;
12. 13-items Quantitative Cocaine inventory, utilized in: Arndt 1992;
13. Yale Quantitative Cocaine Inventory (QCI) (Batki 1993), utilized in: Batki 1996;
14. Quantitative cocaine weekly inventory (Gawin 1986), utilized in: Nunes 1995;
15. Substance Use Report (SUR), utilized in: Ciraulo 2005 a; Ciraulo 2005 b; Elkashef 2006; Jones 2004; Winhusen 2005;
16. Drug use inventory, utilized in: Oliveto 1999;
17. Opioid intoxication and withdrawal symptoms checklist, utilized in: Oliveto 1999;
18. Drug and alcohol Use History (Hall 1991), utilized in: Hall 1994;
19. Self-reported cocaine use and craving with time-line follow back method (Sobell 1980), utilized in: McDowell 2005;
20. Self-reported estimates of cocaine consumption, utilized in: Johnson 1997;
21. Self-reported cocaine, opiate use and opiate withdrawal, utilized in: Kosten 2003;
22. Drug Impairment Rating Scale (Hal-DIRS) (Halikas 1991), utilized in: Campbell 2003;
23. Cocaine Craving Scale (Halikas 1991, Mezinskis 2001), utilized in: Carroll 1994; Ciraulo 2005 a; Ciraulo 2005 b; Elkashef 2006; Winhusen 2005;
24. Cocaine Use Inventory and Craving Scale (Gawin 1984 b), utilized in: Gawin 1989; Jenkins 1992;
25. Craving Visual Analogue Scale (VAS), utilized in: Cornish 2001; Covi 1993; Johnson 1997; Kosten 1992 a; Lambert Passos 2005; Margolin 1995; McElroy 1989; Nunes 1995; Shoptaw 2008; Weddington 1991;
26. Self-Efficacy About Cocaine Scale (modified from Candiotte 1981), utilized in: Hall 1994;
27. Desire to Use Drugs Inventory (DUDI), utilized in: Grabowsky 1995;
28. Brief Substance Craving Scale (Mezinskis 1998), utilized in: Winhusen 2005;
29. Commitment to abstinence (Hall 1991), utilized in: Hall 1994;
30. Withdrawal Scale (Hall 1991), utilized in: Hall 1994;
31. Functional Social Support (Cohen 1985), utilized in: Hall 1994;
32. Symptoms Checklist-90-R (SCL-90-R) (Derogatis 1973), utilized in: Covi 1993; Kolar 1992;
33. Checklist of Recent Life Events (Billings 1982), utilized in: Hall 1994; Weddington 1991;
34. Center for Epidemiological Studies Depression Scale (CES-D) (Radloff 1977; Weissman 1977), utilized in: Kosten 2003; Poling 2006;
35. Beck Depression Inventory (BDI) (Beck 1972; Beck 1988), utilized in: Arndt 1992; Cornish 2001; Grabowsky 1995; Kolar 1992; McElroy 1989; O'Brien 1988; Oliveto 1999; Schmitz 2001; Shoptaw 2008; Weddington 1991; Winstanley 2011;
36. Hamilton Depression Rating Scale (HDRS) (Hamilton 1960; Hamilton 1967; Williams 1988), utilized in: Batki 1996; Carroll 1994; Ciraulo 2005 a; Ciraulo 2005 b; Cornish 2001; Elkashef 2006; Giannini 1986; Grabowsky 1995; Jenkins 1992; Kosten 2003; Lambert Passos 2005; Margolin 1995; McElroy 1989; McDowell 2005; Moeller 2007; Nunes 1995; Schmitz 2001; Winhusen 2005;
37. Hamilton Anxiety Rating Scale (HARS) (Hamilton 1959; Hamilton 1967; Bruss 1994), utilized in: Batki 1996; Carroll 1994; Ciraulo 2005 a; Ciraulo 2005 b; Grabowsky 1995; Jenkins 1992; Moeller 2007; Winhusen 2005;
38. State-Trait Inventory for Adults (STAI) (Spielberger 1983), utilized in: Winstanley 2011;
39. Clinical Global Impression (CGI) (Guy 1976; Tracy 2000), utilized in: Carroll 1994; Ciraulo 2005 a; Ciraulo 2005 b; Elkashef 2006; Jenkins 1992; Johnson 1997; Margolin 1995; McDowell 2005; Winhusen 2005;
40. Profile of Mood States (POMS) (McNair 1971), utilized in: Cornish 2001; Covi 1993; Grabowsky 1995;
41. Weekly Symptom Checklist for adverse effects, utilized in: Jones 2004;
42. Side Effects Checklist, utilized in: Kosten 1992 a; Weddington 1991; Winstanley 2011;
43. Risk Assessment Score (Navaline 1994), utilized in: Carroll 1994; Ciraulo 2005 a; Ciraulo 2005 b; Winhusen 2005;

WHAT'S NEW

Last assessed as up-to-date: 9 November 2011.

Date	Event	Description
9 November 2011	New search has been performed	substantially updated
9 November 2011	New citation required and conclusions have changed	the review is substantially changed: new authors, new searches, new studies, conclusions changed

HISTORY

Protocol first published: Issue 1, 2001

Review first published: Issue 4, 2001

Date	Event	Description
15 February 2011	New search has been performed	Change of the authors, new search, new studies
21 April 2008	Amended	Converted to new review format.
6 July 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

One author (Vecchi) developed search strategy. Two authors (Pani, Trogu) inspected the search hits by reading titles and abstracts. Each potentially relevant study located in the search was obtained in full text and assessed for inclusion independently by two authors (Pani, Trogu). Doubts were resolved by discussion between all the authors. Two author (Pani, Trogu) assessed study quality. Data were extracted independently by two authors (Pani, Trogu). Any disagreement was discussed between all the authors. Amato commented and emended the review.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- Universidade Federal de Pelotas, Brazil.
- Department of Epidemiology, ASL RM E, Italy.

External sources

- lnstitute of Psychiatry - London, UK.
- World Health Organization, Switzerland.

INDEX TERMS

Medical Subject Headings (MeSH)

Antidepressive Agents [*therapeutic use]; Cocaine-Related Disorders [*drug therapy; rehabilitation]; Randomized Controlled Trials as Topic

MeSH check words

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