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Dopamine agonists for the treatment of cocaine dependence (Review)

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[Intervention Review]

Dopamine agonists for the treatment of cocaine dependence

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ABSTRACT

Background

Cocaine misuse is a disorder for which no pharmacological treatment of proven efficacy exists. Advances in neurobiology could guide future medication development.

Objectives

To investigate the efficacy and acceptability of dopamine agonists alone or in combination with any psychosocial intervention for the treatment of of people who misuse cocaine.

Search methods

We run the search on 12 January 2015. We searched the Cochrane Drugs and Alcohol Group (CDAG) Specialized Register, PubMed, EMBASE, CINAHL, PsycINFO, ICTRP, clinicaltrials.gov and screened reference lists.

Selection criteria

Randomised controlled trials (RCTs) and controlled clinical trials (CCTs) comparing dopamine agonists alone or associated with psychosocial intervention with placebo, no treatment or other pharmacological interventions.

Data collection and analysis

We used standard Cochrane methodological procedures.

Main results

Twenty four studies, including 2147 participants, met the inclusion criteria. Comparing any dopamine agonist versus placebo, we found no differences for any of the outcomes considered: dropout (moderate quality of evidence), abstinence (low quality of evidence), severity of dependence (low quality of evidence), adverse events (moderate quality of evidence). This was also observed when single dopamine agonists were compared against placebo. Comparing amantadine versus antidepressants, we found low quality of evidence that antidepressants performed better for abstinence (RR 0.25, 95% CI 0.12 to 0.53) based on two studies with 44 participants. No differences were found for dropout or adverse events, for both moderate quality of evidence.

The major flaws of the included studies concerned selection bias because most studies did not report information about sequence generation (80%) and allocation concealment methods (86%): half of the included studies were judged at unclear risk of performance bias and 62.5% at unclear risk of detection bias for what concerns subjective outcomes.

Authors' conclusions

Current evidence from RCTs does not support the use of dopamine agonists for treating cocaine misuse. This absence of evidence may leave to clinicians the alternative of balancing the possible benefits against the potential adverse effects of the treatment. Even the potential benefit of combining a dopamine agonist with a more potent psychosocial intervention, which was suggested by the previous Cochrane Review (Soares 2003), is not supported by the results of this Cochrane Review update.

PLAIN LANGUAGE SUMMARY

Dopamine agonists for the treatment of people who misuse cocaine

Background

A pharmacological agent with proven efficacy does not exist for treatment of cocaine misuse. 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 misuse 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. In this Cochrane Review we looked at the evidence on the efficacy and acceptability of dopamine agonists as a treatment, used either alone or in combination with any psychosocial intervention, for people addicted to cocaine.

Study characteristics

We searched scientific databases and internet resources to identify randomised controlled trials (where participants are allocated at random to any dopamine agonist drug or placebo or another type of drug aimed to reduce use of cocaine. We also assessed dropout from treatment and frequency of side effects. We included adults of any gender, age or ethnicity.

Key results

We included 24 studies with 2147 participants, who were all addicted to cocaine. Most were men (82.%)with an average age of 37 years. The mean duration of the included trials was seven weeks (range 1.5 to 16 weeks) Twenty-two studies were conducted in USA, one in Brazil and one in Spain; all but four were outpatients.

The included trials studied the following drugs: amantadine, bromocriptine, L dopa/Carbidopa, pergolide, cabergoline hydergine, and pramipexole. All compared dopamine agonist versus placebo. Four studies compared amantidine versus antidepressants.

No differences were found between the drugs and placebo for any of the outcomes considered: dropout (moderate quality of evidence), abstinence (low quality of evidence), severity of dependence (low quality of evidence), adverse events (moderate quality of evidence). Antidepressants was found to be better than the dopamine agonist amantidine for abstinence, but this was based on two studies with very few participants and low quality of evidence. There is no current evidence supporting the clinical use of dopamine agonist medications in the treatment of cocaine misuse. The evidence is current to 12 January 2015.

Summary of findings for the main comparison. Any dopamine agonist versus placebo for the treatment of cocaine dependence

Any dopamine agonist versus placebo for the treatment of cocaine dependence

Patient or population: patients with the treatment of cocaine dependence
Settings: Outpatient
Intervention: any dopamine agonist versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Any dopamine agonist versus placebo				
Dropouts Follow-up: mean 6 weeks	**Study population**		**RR 1.04** (0.94 to 1.14)	1656 (20 studies)	⊕⊕⊕⊖ **moderate** [1]	
	456 per 1000	**474 per 1000** (428 to 519)				
	Moderate					
	400 per 1000	**416 per 1000** (376 to 456)				
Adverse events as N of participants with at least one adverse event Follow-up: mean 6 weeks	**Study population**		**RR 1.27** (0.66 to 2.44)	252 (7 studies)	⊕⊕⊕⊖ **moderate** [1]	
	272 per 1000	**345 per 1000** (180 to 664)				
	Moderate					
	200 per 1000	**254 per 1000** (132 to 488)				
Abstinence (objective) Participants abstinent at the end of treatment (N) Follow-up: mean 6 weeks	**Study population**		**RR 1.12** (0.85 to 1.47)	731 (11 studies)	⊕⊕⊖⊖ **low** [1,2]	
	308 per 1000	**345 per 1000** (262 to 453)				
	Moderate					

	355 per 1000	**398 per 1000** (302 to 522)				
Abstinence at follow-up (objective) N of subjects abstinent at follow-up Follow-up: mean 4 months	**Study population**		**RR 1.1** (0.61 to 1.98)	136 (4 studies)	⊕⊕⊝⊝ **low** [1,2]	
	625 per 1000	**688 per 1000** (381 to 1000)				
	Moderate					
	541 per 1000	**595 per 1000** (330 to 1000)				
Severity of dependence (difference before and after) Follow-up: mean 6 weeks		The mean severity of dependence (difference before and after) in the intervention groups was **1.69 standard deviations higher** (0.17 to 3.2 higher)		202 (4 studies)	⊕⊕⊝⊝ **low** [1,2]	SMD 1.69 (0.17 to 3.2)

*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% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **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]Most studies were classified as at unclear risk of bias for sequence generation and method of allocation concealment.
[2]Significant heterogeneity.

Summary of findings 2. Amantadine versus placebo for the treatment of cocaine dependence

Amantadine versus placebo for the treatment of cocaine dependence

Patient or population: patients with the treatment of cocaine dependence
Settings: Outpatient
Intervention: amantadine versus placebo

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)

	Assumed risk	Corresponding risk			
	Control	**Amantadine versus placebo**			
Dropouts Follow-up: mean 6 weeks	**Study population**		**RR 0.98** (0.77 to 1.26)	484 (9 studies)	⊕⊕⊕⊖ **moderate** [1]
	378 per 1000	**371 per 1000** (291 to 476)			
	Moderate				
	286 per 1000	**280 per 1000** (220 to 360)			
Adverse events as N of participants with at least one adverse event Follow-up: mean 6 weeks	**Study population**		**RR 1.19** (0.69 to 2.06)	128 (4 studies)	⊕⊕⊕⊖ **moderate** [1]
	329 per 1000	**391 per 1000** (227 to 677)			
	Moderate				
	300 per 1000	**357 per 1000** (207 to 618)			
Abstinence (objective) N of subjects abstinent at the end of the study Follow-up: mean 6 weeks	**Study population**		**RR 1.13** (0.59 to 2.13)	275 (5 studies)	⊕⊕⊖⊖ **low** [1,2]
	307 per 1000	**347 per 1000** (181 to 654)			
	Moderate				
	355 per 1000	**401 per 1000** (209 to 756)			
Abstinence at follow-up (objective) N of subjects abstinent at follow-up Follow-up: mean 4 months	**Study population**		**RR 1.49** (1.03 to 2.15)	76 (3 studies)	⊕⊕⊕⊖ **moderate** [1]
	512 per 1000	**763 per 1000** (528 to 1000)			
	Moderate				
	526 per 1000	**784 per 1000** (542 to 1000)			

*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% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **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]Most were classified as at unclear risk of bias for sequence generation and method of allocation concealment.
[2]Significant heterogeneity.

Summary of findings 3. Amantidine versus antidepressants for the treatment of cocaine dependence

Amantidine versus antidepressants for the treatment of cocaine dependence

Patient or population: patients with the treatment of cocaine dependence
Settings: Outpatient
Intervention: amantidine versus antidepressants

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Amantidine versus antidepressants			
Dropouts Follow-up: mean 6 weeks	**Study population**		**RR 0.86** (0.48 to 1.53)	153 (4 studies)	⊕⊕⊕⊖ **moderate** [1]
	329 per 1000	**283 per 1000** (158 to 504)			
	Moderate				
	267 per 1000	**230 per 1000** (128 to 409)			
Adverse events as N of participants with at least one adverse event Follow-up: mean 6 weeks	**Study population**		**RR 0.56** (0.18 to 1.77)	44 (2 studies)	⊕⊕⊖⊖ **low** [1,2]
	320 per 1000	**179 per 1000** (58 to 566)			

	Moderate				
	335 per 1000	**188 per 1000** (60 to 593)			
Abstinence (objective) N of subjects abstinent at the end of the study Follow-up: mean 6 weeks	**Study population**		**RR 0.25** (0.12 to 0.53)	68 (2 studies)	⊕⊕⊝⊝ **low** [1,2]
	775 per 1000	**194 per 1000** (93 to 411)			
	Moderate				
	859 per 1000	**215 per 1000** (103 to 455)			

*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% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **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]Most studies were classified as at unclear risk of bias for sequence generation and method of allocation concealment.
[2]Only 2 studies with 44 participants.

BACKGROUND

Description of the condition

Cocaine is an alkaloid derived from the leaf of erythroxylon coca. People commonly use it as a 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 (UNODC 2014). There is a wide and well documented range of consequences associated with acute and chronic use of this drug, such as medical, psychological and social problems, including the spread of infectious diseases (e.g. AIDS, hepatitis and tuberculosis), crime, violence and neonatal drug exposure (Higgins 1994). Both injection and non-injection cocaine use can increase the risk of HIV infection through high risk injecting and sexual behaviours (Sorensen 1991).

The illicit use of cocaine has become a persistent health problem worldwide.

The annual prevalence of cocaine use on a global estimate is 0.4% (0.3 to 0.4%), with a higher annual prevalence in Oceania (1.5%) and North America (1.8%), and a lower annual prevalence in Asia (0.05%). The number of first-time users has declined in recent years due to a decrease in the global availability of cocaine, related to a one-quarter reduction in the cultivation of coca bush (UNODC 2014)

Although cocaine prevalence figures are much lower than comparable figures for cannabis, the prevalence of use among young adults can be higher than the population average.

In Europe, lifetime prevalence for cocaine among 15- to 64-year-olds is 4.2% and ranges from 0.4% to 9.0%, with the highest levels being found in Spain (8.8%) and in United Kingdom (UK) (9.0%); recent use among 15- to 34-year-olds is 1.7% with Spain and UK having rates over 3% (EMCDDA 2014).

In the USA, 0.6% of the population (1.5 million) currently uses cocaine and the lifetime prevalence for cocaine use is about 13.7% (SAMHSA 2014).

Description of the intervention

Cocaine dependence remains a disorder for which no pharmacological treatment of proven efficacy exists, although considerable advances in the neurobiology of this addiction could guide future medication development. The effect of this drug seems to rely on its ability to increase the availability of monoamines (dopamine, serotonin and noradrenaline) in the brain. An increase in dopamine levels in specific areas of the meso-limbic system, such as the nucleus accumbens, has been associated with the rewarding effect of drugs and self-administration behaviour in animal and human (Di Chiara 1988; Drevets 1999; Drevets 2001; Volkow 2003a). Specifically, the speed with which addictive drugs enter the brain and elevates dopamine levels in the nucleus accumbens seems to be positively correlated with addictive potential (Volkow 1995; Volkow 2003b; Kimmel 2007). Among addictive drugs, cocaine is the most directly involved in the activation of dopaminergic system, since acute cocaine-induced increase of extracellular dopamine is due to the inhibition of its presynaptic reuptake through the blockade of its transporter (Self 1995; Gold 1997; Wise 2005). On the contrary, chronic cocaine abuse leads to down-regulation of dopaminergic systems (Volkow 1997; Gardner 1999; Volkow 1999a; Volkow 2006; Martinez 2009; Volkow 2010). Depression following post-cocaine use and cocaine craving may be linked to this down-regulation.

How the intervention might work

These pre-clinical findings are the theoretical foundations on which the use of dopamine agonists for the treatment of cocaine dependence is based. Given this knowledge, manipulation of dopamine transmission in the reward circuitry of the brain has been looked as the mainstay of the development of new medications for the treatment of cocaine addiction. More specifically, dopamine agonists or antagonists, acting on brain dopamine transporter or brain dopamine receptors, have been tested.

Use of dopamine agonists is based primarily on two reasons:

- Slow-onset long acting dopamine agonists will have less addictive potential (Volkow 1999b; Volkow 2003b);
- Dopamine agonists will ameliorate dopaminergic dysfunction, counter-acting mesolimbic dopaminergic down regulation consequent to chronic use of cocaine, thereby reducing craving and the risk of relapse (Gardner 1999; Volkow 1999a; Volkow 2006; Volkow 2010).

Under this assumption, dopamine agonists may alleviate cocaine abstinence symptomatology, reduce craving and the risk of relapse.

Why it is important to do this review

Although effective pharmacotherapy is available for people who are heroin (Faggiano 2003; Mattick 2008; Mattick 2009) or alcohol dependent (Amato 2010; Rösner 2010a; Rösner 2010b), none currently exists for people who are cocaine dependent. This is 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 2015), antidepressants (Pani 2011) and psychostimulants (Castells 2010) for people with cocaine dependence but none found support for the efficacy of these treatments. Moreover, a Cochrane Review assessing the efficacy and safety of disulphiram (Pani 2010) has shown low evidence supporting its clinical use for the treatment of cocaine dependence.

One Cochrane Review has been published on the efficacy of psychosocial treatments for psychostimulants dependence (Knapp 2007). It shows that existing treatments demonstrate modest outcomes at best. Therefore, 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 dopamine agonists for cocaine dependence was published in 2003 (Soares 2003) and updated in 2011 (Amato 2011). Moreover, the review on psychostimulants, which actually are dopamine agonists (Castells 2010), did not consider medications devoid of psychostimulant effect. Therefore,

a review update is required to examine the effect of dopamine agonists that do not have psychostimulant effects..

OBJECTIVES

To investigate the efficacy and acceptability of dopamine agonists alone or in combination with any psychosocial intervention for the treatment of of people who misuse cocaine.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and controlled clinical trials (CCTs) which focused on the use of dopamine agonists for people who misuse cocaine.

Types of participants

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

Types of interventions

Experimental

- Any dopamine agonist alone or in combination with any psychosocial intervention. We excluded psychostimulants.

Control

- Placebo;
- Other pharmacological interventions;
- Any psychosocial intervention.

Furthermore, we considered different factors as confounders and accounted for them in the analyses whenever possible:

- Setting (inpatient or outpatient treatment);
- Starting dose/rate and pattern of dose reduction;
- Scheduled duration of treatment;
- Severity of dependence (duration of use, route of administration, frequency of consumption);
- 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 as number of participants who did not complete the treatment;
2. Acceptability of the treatment as number of participants experiencing adverse effect;
3. Dropouts due to adverse effects;
4. Abstinence self reported or number of participants with urine samples negative for cocaine, or both;
5. Results at follow-up as number of participants abstinent at follow-up.

Secondary outcomes

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

Search methods for identification of studies

Electronic searches

In Appendix 1 we have detailed the search methods used in the previous version of this review (Amato 2011). Amato 2011 included searches up to June 2011.

For this update, we searched the following electronic databases up to 13 January 2015:

1. CDAG Specialized Register (January 2015);
2. CENTRAL (the Cochrane Library, Issue 1, January 2015);
3. MEDLINE (PubMed) (June 2011 to 12 January 2015);
4. EMBASE (Elsevier, EMBASE.com) (June 2011 to 12 January 2015);
5. CINAHL (EBSCO Host) (June 2011 to 12 January 2015);
6. Web of Science (June 2011 to 12 January 2015).

In addition, we searched for ongoing clinical trials and unpublished studies via internet searches on the following websites on 12 January 2015:

- ClinicalTrials.gov: www.clinicaltrials.gov;
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) www.who.int/ictrp/en/.

See Appendix 2 for the search terms we used in this Cochrane Review update.

Searching other resources

We also searched:

- Reference lists of all relevant papers to identify further studies;
- Conference proceedings likely to contain trials relevant to the review;
- We contacted investigators seeking information about unpublished or incomplete trials.

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

Data collection and analysis

Selection of studies

For the previous update of this review, two review authors (SV, RS) independently screened the titles and abstracts of all publications obtained through the search strategy. We obtained all potentially eligible studies as full text articles. Three review authors (SV, RS, SM) independently assessed these for inclusion. In doubtful or controversial cases, we discussed all identified discrepancies and reached consensus on all items.

For this update, two review authors (SM, FDC) independently screened the titles and abstracts and assessed the full text of potentially eligible studies. In doubtful or controversial cases, we discussed all identified discrepancies and reached consensus on all items.

Data extraction and management

Two review authors (LA, SM) assessed study quality according to the criteria indicated in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and extracted data.

Assessment of risk of bias in included studies

We performed 'Risk of bias' assessments for included RCTs and CCTs using the criteria recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The recommended approach for 'Risk of bias' assessment in studies included in a Cochrane Review is a two-part tool, addressing specific domains, namely sequence generation and allocation concealment (selection bias), blinding of participants and providers (performance bias), blinding of outcome assessor (detection bias), incomplete outcome data (attrition bias) and selective outcome reporting (reporting bias). The first part of the tool involves describing what was reported to have happened in the included study. The second part of the tool involves assigning a judgement relating to the risk of bias for that entry, in terms of 'low', 'high' or 'unclear' risk. We used the criteria indicated by Higgins 2011 and adapted to the addiction field (see Table 1 for details).

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

We considered blinding of participants and outcome assessor (avoidance of detection bias) separately for objective outcomes (e.g. dropout, abstinence measured by urine-analysis, subjects relapsed at the end of follow-up) and subjective outcomes (e.g. duration and severity of signs and symptoms of withdrawal, craving, patient self-reported use of substance, side effects, psychiatric symptoms, clinical global valuation).

Incomplete outcome data (avoidance of attrition bias) was considered for all outcomes except for dropout from the treatment, which is very often the primary outcome measure in trials on addiction (see Table 1 for a detailed description on how we assessed the risk of bias in this review).

Grading of evidence

We assessed the overall quality of the evidence for the primary outcome using the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) system. The GRADE Working Group developed a system for grading the quality of evidence (Atkins 2004; Schünemann 2006; Guyatt 2008; Guyatt 2011) which takes into account issues not only related to internal validity but also to external validity, such as directness of results. The 'Summary of findings' tables present the main findings of a review in a transparent and simple tabular format. In particular, they provide key information concerning the quality of evidence, the magnitude of effect of the interventions examined and the sum of available data on the main outcomes.

The GRADE system uses the following criteria for assigning grades of evidence:

- High: further research is very unlikely to change our confidence in the estimate of effect;
- Moderate: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate;
- Low: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate;
- Very low: any estimate of effect is very uncertain.

Quality of the evidence may be downgraded for the following reasons:

- Serious (-1) or very serious (-2) limitation to study quality;
- Important inconsistency (-1);
- Some (-1) or major (-2) uncertainty about directness;
- Imprecise or sparse data (-1);
- High probability of reporting bias (-1).

Quality of the evidence may be upgraded for the following reasons:

- Strong evidence of association - significant relative risk of > 2 (< 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1);
- Very strong evidence of association - significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2);
- Evidence of a dose response gradient (+1);
- All plausible confounders would have reduced the effect (+1).

Measures of treatment effect

We analysed dichotomous outcomes (dropouts, abstinence, abstinence at follow-up, side effects) by calculating the relative risk (RR) for each trial, with the uncertainty in each result being expressed by their confidence intervals (CIs). Continuous outcomes (craving, severity of dependence, clinical valuation, psychiatric symptoms) were analysed by calculating the standardised mean difference (SMD) with 95% CIs. We did not use 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. We made this decision because using the number of tests instead of the number of subjects as the unit of the analysis violates the hypothesis of independence among observations. In fact, the

results of test done for each participants are not independent. When studies reported number of missing urine stated that they were considered as positive, we included them in the analysis. All but adverse events were computed using intention-to-treat (ITT) principles.

Unit of analysis issues

If all arms in a multi-arm trial were included in the meta-analysis and one treatment arm was included more than once in some comparisons, then we divided the number of events and the number of participants in that arm by the number of treatment comparisons made. This method avoids the multiple use of participants in the pooled estimate of treatment effect while retaining information from each arm of the trial. It compromises the precision of the pooled estimate slightly.

Assessment of heterogeneity

We tested the presence of heterogeneity between trials using the I^2 statistic and with Chi^2 test. A P value < 0.1 and an I^2 statistic value > 50% indicated significant heterogeneity.

Assessment of reporting biases

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

Data synthesis

We combined the outcomes from the individual trials through meta-analysis where possible (comparability of intervention and outcomes between trials) using a random-effect models because we expected a certain degree of heterogeneity among trials. For the abstinence rate we used the number of randomised patients as the denominator, assuming that people who dropped out continued to use cocaine.

Sensitivity analysis

To incorporate the 'Risk of bias' assessment in the review process, we first plotted intervention effects estimates stratified for risk of bias for each relevant domain. If differences in results were present among studies at different risk of bias, we performed a sensitivity analysis excluding studies at high risk of bias from the analysis.

RESULTS

Description of studies

For substantive descriptions of studies see the 'Characteristics of included studies' and 'Characteristics of excluded studies' tables.

Results of the search

This is an update of a Cochrane Review first published in 2001 (Soares 2003). In the first edition of this review we identified 442 reports. We excluded 392 on basis of title and abstract. We retrieved50 articles for more detailed evaluation, 27 of which we excluded after reading the full text. The remaining 23 studies satisfied all the inclusion criteria (see Figure 1).

Figure 1. Study flow diagram present update.

In this update, we identified 220 records after bibliographic searches and removal of duplicates. We excluded 213 records on the basis of title and article. We retrieved the full text of seven articles for more detailed evaluation. We excluded five articles after full text evaluation. Two articles, related to one study, met the inclusion criteria (see Figure 2).

Included studies

Twenty-four studies, 2147 participants, met the inclusion criteria for this Cochrane Review (for details see the 'Characteristics of included studies' tables.

Trial duration

The mean duration of the trials was seven weeks (range 1.5 to 16 weeks).

Treatment regimes and setting

The included studies considered the dopamine agonists of amantadine, bromocriptine, cabergoline, hydergine, L dopa/carbidopa, pergolide and pramipexole:

- Amantadine: 10 studies compared amantadine with placebo (Giannini 1989; Weddington 1991; Alterman 1992; Kolar 1992; Kosten 1992; Handelsman 1995; Kampman 1996; Pérez de los Cobos 2001; Shoptaw 2002; Kampman 2006), four studies with the antidepressant desipramine (Weddington 1991; Kolar 1992; Kosten 1992; Oliveto 1995), one study with the antidepressant fluoxetine (Oliveto 1995), one with the beta-adrenergic antagonist propanolol (Kampman 2006). The mean dosage of amantadine was 267 mg/day (range 100 to 400 mg/day);
- Bromocriptine: bromocriptine was considered in five studies compared with placebo (Giannini 1989; Moscovitz 1993; Eiler 1995; Handelsman 1997; Gorelick 2006), the mean dosage of bromocriptine was 6.2 mg/day (range 2.5 to 10 mg/day);
- L-dopa/carbidopa: six studies compared L-dopa/Carbidopa with placebo (Shoptaw 2005; Mooney 2007a; Mooney 2007b; Schmitz 2008; Schmitz 2010; Schmitz 2014), the mean dosages of these drug were respectively 545 mg/183 mg/day (range 75 mg/100 mg to 800 mg/200 mg/day). Schmitz 2014 also compared L-dopa/carbidopa with naltrexone and modafinil;
- Pergolide: two studies (Malcolm 2000; Focchi 2005) compared pergolide with placebo and the mean dosage was 0.2 mg/day (range 0.1 to 0.5 mg/day);
- Single studies considered the other three dopamine agonists: cabergoline (0.5 mg/week) and hydergine (3 mg) were considered in Shoptaw 2005, a study with four arms that also compared L-dopa/carbidopa and placebo. Ciraulo 2005 considered pramipexole and compared it at a dosage of 1.5 mg with placebo and the antidepressant venlafaxine.

In 16 studies, psychosocial interventions were added to the pharmacological one: cognitive behavioural therapy (Handelsman 1997; Kampman 2006; Schmitz 2008; Schmitz 2014), counselling sessions (Kolar 1992; Kampman 1996; Shoptaw 2002; Shoptaw 2005; Mooney 2007a; Mooney 2007b), contingency management (Schmitz 2008; Schmitz 2010; Schmitz 2014), group relapse prevention therapy (Kosten 1992; Oliveto 1995) and interpersonal psychotherapy (Weddington 1991).

Twenty-one studies were conducted in outpatient settings and four were performed in inpatient settings.

Participants

All participants were addicted to cocaine according to DSM criteria (DSM IIIR; DSM IV; DSM-IV-R; five studies (Kosten 1992; Handelsman 1995; Oliveto 1995; Handelsman 1997; Pérez de los Cobos 2001) enrolled patients with also opioid dependence in methadone maintenance therapy. Most participants were male (82%), with a mean age of 37 years.

Trial location (country)

Twenty-two studies were conducted in the USA, one in Brazil and one in Spain.

Comparisons

1. Any dopamine agonist versus placebo;
2. Amantadine versus placebo;
3. Bromocriptine versus placebo;
4. L dopa/carbidopa versus placebo;
5. Amantadine versus antidepressants.

Excluded studies

We excluded 32 studies from this review for the following reasons: inappropriate outcome measures (13 studies); inappropriate study design (six studies); inappropriate type of intervention considered (nine studies), comparisons considered not in the inclusion criteria (two studies), study design and outcomes not in the inclusion criteria (two studies). See the 'Characteristics of excluded studies' table for further details.

Risk of bias in included studies

We have presented judgements for each 'Risk of bias' item for each included study (Figure 2) and as percentages across all included studies (Figure 3).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

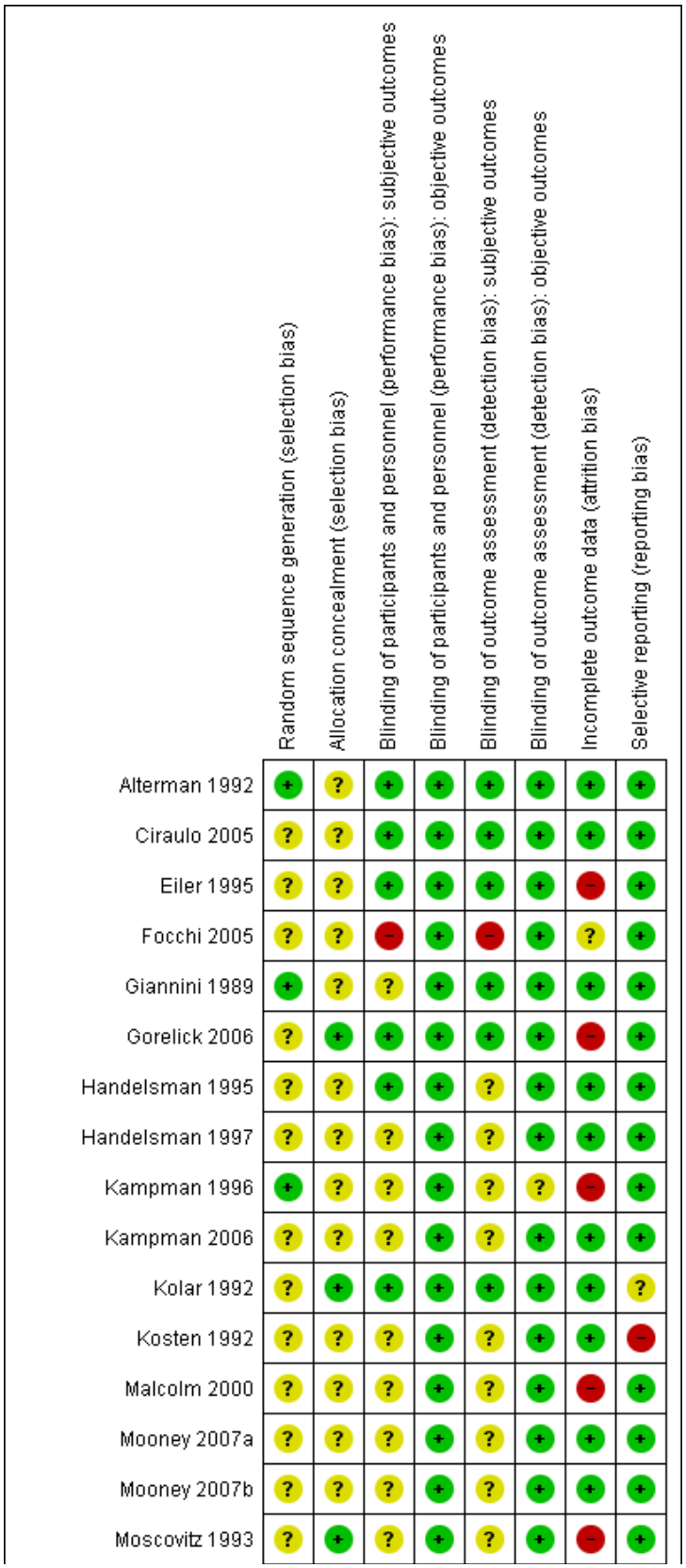
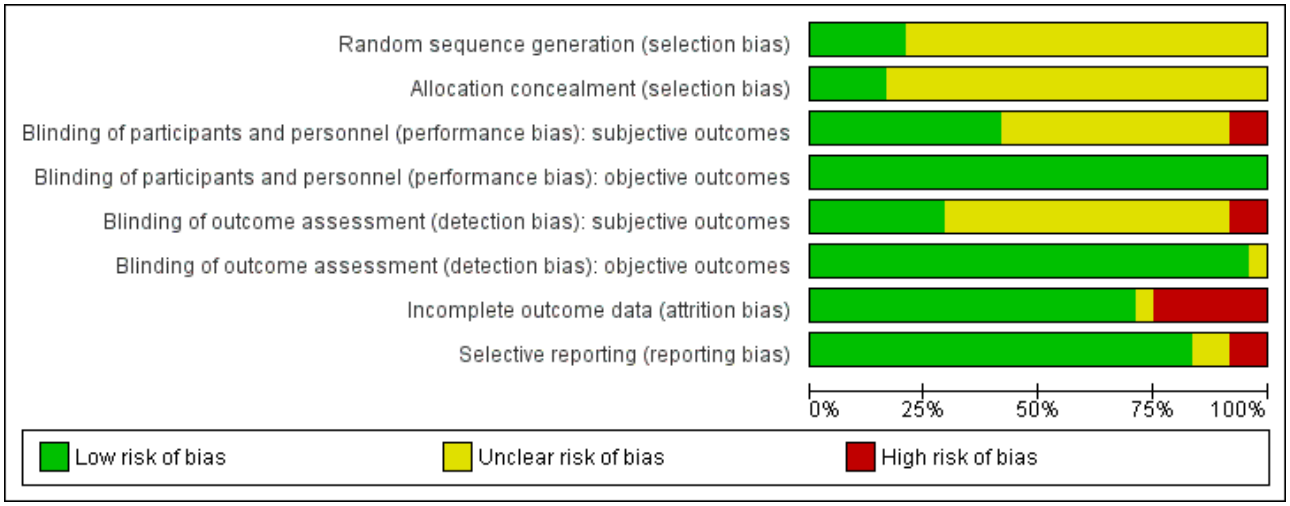


Figure 2. (Continued)

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Random sequence generation

Only five included studies (20.8%) used an adequate method of sequence generation. We classifed all other included studies at unclear risk of bias because the trial authors gave no information about the method used.

Allocation concealment

Only four included studies (16.6%) used an adequate method of allocation concealment. The remaining studies were classified at unclear risk of bias because no information was given about the method used.

Blinding

Performance bias

All but two trials adopted a double-blind design. Weddington 1991 and Focchi 2005 were both single-blinded and judged at high risk of bias for subjective outcomes. Ten trials (41.6%) gave detailed information about the way to maintain blinding and were judged at low risk of bias. We considered the remaining trials at unclear risk for subjective outcomes. We judged all included studies at low risk of performance bias for objective outcomes.

Detection bias

Two studies were single blinded and were judged at high risk of detection bias (Weddington 1991; Focchi 2005). Seven trials (29.1%) stated that outcome assessors were blinded. We judged all other included studies at unclear risk of detection bias.

Incomplete outcome data

Seventeen included studies (70.8%) were judged at low risk of attrition bias or because the ITT principle was used or because there were few lost at follow-up, balanced between groups and reason for dropout were reported. We judged six studies at high risk of attrition bias (Weddington 1991; Moscovitz 1993; Eiler 1995;

Kampman 1996; Malcolm 2000; Gorelick 2006) and one at unclear risk (Focchi 2005).

Selective reporting

We considered 20/24 (83.3%) of the included studies at low risk of reporting bias. Two were judged at high risk (Kosten 1992; Schmitz 2014) and two at unclear risk (Kolar 1992; Oliveto 1995).

Effects of interventions

See: **Summary of findings for the main comparison** Any dopamine agonist versus placebo for the treatment of cocaine dependence; **Summary of findings 2** Amantadine versus placebo for the treatment of cocaine dependence; **Summary of findings 3** Amantidine versus antidepressants for the treatment of cocaine dependence

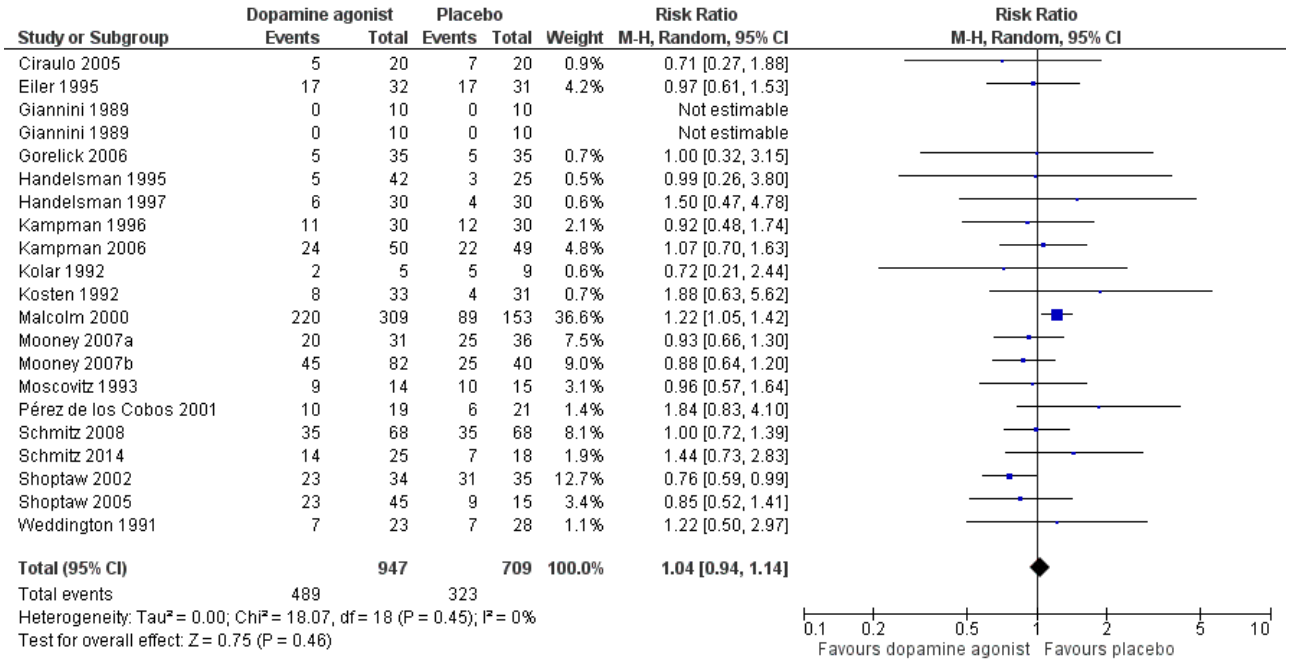
1. Dopamine agonist versus placebo

See Summary of findings for the main comparison

1.1 Dropouts

Twenty trials, 1656 participants, examined this outcome (Giannini 1989; Weddington 1991; Kolar 1992; Kosten 1992; Moscovitz 1993; Eiler 1995; Handelsman 1995; Kampman 1996; Handelsman 1997; Malcolm 2000; Pérez de los Cobos 2001; Shoptaw 2002; Ciraulo 2005; Shoptaw 2005; Gorelick 2006; Kampman 2006; Mooney 2007a; Mooney 2007b; Schmitz 2008; Schmitz 2014) showing no difference between the two treatments, RR 1.04, (95% CI 0.94 to 1.14); moderate quality of evidence. Analysis 1.1; Figure 4. Sensitivity analysis excluding studies at high risk of attrition bias did not change results.

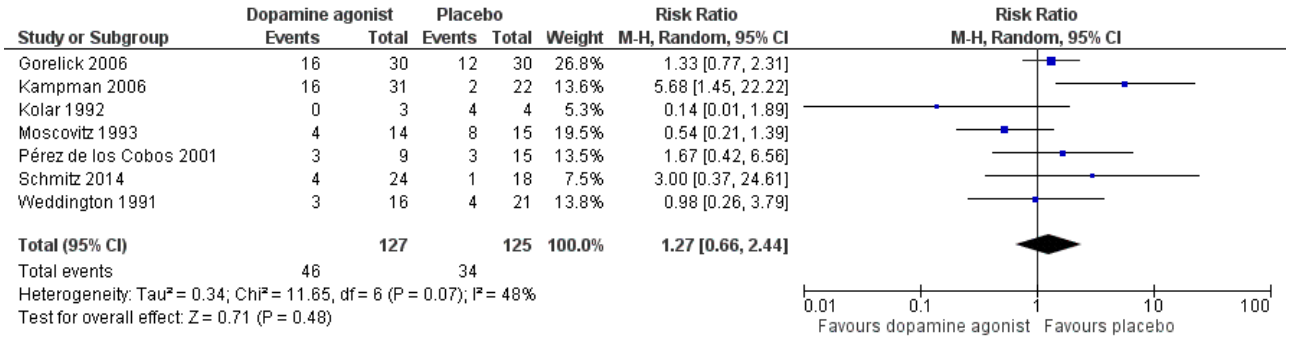
Figure 4. Forest plot of comparison: 1 Any dopamine agonist versus placebo, outcome: 1.1 Dropouts.



1.2 Adverse events as number of participants with at least one adverse event

Seven studies, 252 participants, reported on this outcome (Weddington 1991; Kolar 1992; Moscovitz 1993; Pérez de los Cobos 2001; Gorelick 2006; Kampman 2006; Schmitz 2014) we detected no difference between the two treatments, RR 1.27 (95% CI 0.66 to 2.44); moderate quality of evidence ; Analysis 1.2; Figure 5.

Figure 5. Forest plot of comparison: 1 Any dopamine agonist versus placebo, outcome: 1.2 Adverse events as number of participants with at least one adverse event.



1.3 Abstinence (objective)

Eleven trials, 731 participants, reported this outcome (Weddington 1991; Alterman 1992; Kosten 1992; Moscovitz 1993; Kampman 1996; Shoptaw 2002; Focchi 2005; Shoptaw 2005; Mooney 2007a; Mooney 2007b; Schmitz 2008;) and we detected no difference between the two treatments, RR 1.12 (95% CI 0.85 to 1.47); low quality of evidence; Analysis 1.3. Sensitivity analysis excluding studies at high risk of attrition bias did not affect the results.

1.4 Abstinence at follow-up (objective)

We detected no difference between the two treatments after analysis of the results of four included studies, 136 participants, that reported on this outcome (Alterman 1992; Kolar 1992; Shoptaw 2002; Shoptaw 2005): RR 1.10 (95% CI 0.61 to 1.98); low quality of evidence; Analysis 1.4.

1.5 Severity of dependence (measured as difference before and after treatment)

Based on four included studies, 202 participants, (Alterman 1992; Ciraulo 2005; Shoptaw 2005; Kampman 2006), there was a statistically significant result in favour of placebo treatment: SMD 1.69 (95% CI 0.17 to 3.20); low quality of evidence; Analysis 1.5.

1.6 Dropouts due to adverse effects

Based on the results of four studies, 368 participants (Mooney 2007a; Mooney 2007b; Schmitz 2008; Schmitz 2014), we did not detect no difference between the two treatments, RR 1.21 (95% CI 0.27 to 5.38); Analysis 1.6.

1.7 Craving at the end of treatment

Three studies, 151 participants, reported on this outcome (Shoptaw 2002; Ciraulo 2005; Focchi 2005). We detected no differences between treatments: SMD 0.20 (95% CI -0.35 to 0.74); Analysis 1.7.

1.8 Clinical global evaluation at the end of the treatment

Two studies, 70 participants, reported this outcome (Ciraulo 2005; Shoptaw 2005) and we detected no difference between treatments: SMD -0.04 (95% CI -0.50 to 0.43); Analysis 1.8.

1.9 Depression (measured as difference before and after treatment)

We included five studies, 292 participants in this analysis (Alterman 1992; Handelsman 1995; Kampman 1996; Focchi 2005; Shoptaw 2005) and detected no difference between treatments: SMD 0.47 (95% CI -0.35 to 1.28); Analysis 1.9.

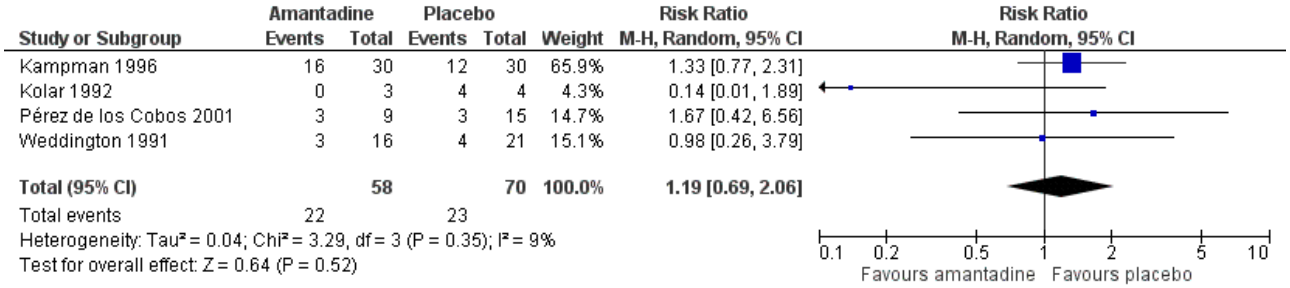
2. Amantadine versus placebo

See Summary of findings 2

2.1 Dropouts

Nine studies, 484 participants, reported on this outcome (Giannini 1989; Weddington 1991; Kolar 1992; Kosten 1992; Handelsman 1995; Kampman 1996; Pérez de los Cobos 2001; Shoptaw 2002; Kampman 2006). We detected no difference between treatments, RR 0.98 (95% CI 0.77 to 1.26); moderate quality of evidence; Analysis 2.1; Figure 6).

Figure 6. Forest plot of comparison: 2 Amantadine versus placebo, outcome: 2.2 Adverse events as number of participants with at least one adverse event.



2.2 Adverse events as number of participants with at least one adverse event

Four studies, 275 participants, were included in this analysis (Weddington 1991; Kolar 1992; Kampman 1996; Pérez de los Cobos 2001). We detected no difference between treatments, RR 1.19 (95% CI 0.69 to 2.06); moderate quality of evidence; Analysis 2.2.

2.3 Abstinence (objective)

Five studies, 275 participants, reported on this outcome (Weddington 1991; Alterman 1992; Kosten 1992; Kampman 1996; Shoptaw 2002) and we detected no difference between treatments,RR 1.13, (95% CI 0.59 to 2.13); low quality of evidence; Analysis 2.3.

2.4 Abstinence at follow-up (objective)

We included three studies , 76 participants, in this analysis (Alterman 1992; Kolar 1992; Shoptaw 2002) and detected no difference between treatments, RR 1.49 (95% CI 1.03 to 2.15); moderate quality of evidence; Analysis 2.4.

2.5 Severity of dependence (measured as difference before and after the treatment)

Two studies, 102 participants, reported on this outcome (Alterman 1992; Kampman 2006). No difference was detected between treatments, SMD 0.39 (95% CI -0.00 to 0.79); Analysis 2.5.

2.6 Depression (measured as difference before and after the treatment)

We included two studies, 109 participants, in this analysis (Alterman 1992; Handelsman 1995). There was no difference between treatments, SMD -0.30 (95% CI -1.33 to 0.74); Analysis 2.6.

3. Bromocriptine versus placebo

3.1 Dropouts

Five studies, 242 participants, (Giannini 1989; Moscovitz 1993; Eiler 1995; Handelsman 1997; Gorelick 2006) and there was no difference between treatments, RR 1.00 (95% CI 0.73 to 1.38); Analysis 3.1.

3.2 Adverse events as number of participants with at least one adverse event

We included two studies, 89 participants, in this analysis (Moscovitz 1993; Gorelick 2006) and detected no difference between treatments, RR 0.92 (95% CI 0.38 to 2.22); Analysis 3.2.

4. L dopa/carbidopa versus placebo

4.1 Dropouts

Four studies, 262 participants, reported this outcome (Mooney 2007a; Mooney 2007b; Shoptaw 2005; Schmitz 2014) and there was no difference between treatments, RR 0.95 (95% CI 0.78 to 1.17); Analysis 4.1.

4.2 Dropouts due to adverse effects

We included four studies, 368 participants, in this analysis (Mooney 2007a; Mooney 2007b; Schmitz 2008; Schmitz 2014). We did not detect any difference between treatments, RR 1.21 (95% CI 0.27 to 5.38); Analysis 4.2.

4.3 Abstinence (objective)

Four studies, 355 participants, reported on this outcome (Mooney 2007a; Mooney 2007b; Shoptaw 2005; Schmitz 2008) and we detected no difference between treatments, RR 1.11 (95% CI 0.80 to 1.52); Analysis 4.3.

5. Amantadine versus antidepressants

See Summary of findings 3.

The antidepressants considered in the studies were desipramine (four trials: Kolar 1992; Kosten 1992; Oliveto 1995; Weddington 1991) and fluoxetine (one trial: Oliveto 1995).

5.1 Dropouts

We included four studies, 153 participants, in this analysis (Weddington 1991; Kolar 1992; Kosten 1992; Oliveto 1995) and detected no difference between treatments, RR 0.86 (95% CI 0.48 to 1.53); moderate quality of evidence; Analysis 5.1.

5.2 Adverse events as number of participants with at least one adverse event

Two studies, 44 participants, reported this outcome (Weddington 1991; Kolar 1992) and we did not detect any difference between treatments, RR 0.56 (95% CI 0.18 to 1.77); low quality of evidence; Analysis 5.2.

5.3 Abstinence (objective)

Based on two studies, 68 participants, (Weddington 1991; Kolar 1992), the result was in favour of antidepressants, RR 0.25 (95% CI 0.12 to 0.53); low quality of evidence; Analysis 5.3.

6. L-dopa/carbidopa versus naltrexone or modafinil

One study (Schmitz 2014) reported that there were no difference in retention between L-dopa and modafinil (14/25 and 9/22 respectively) and between L-dopa and naltrexone (14/25 and 9/16 respectively).

DISCUSSION

Summary of main results

Twenty-four studies, including a total of 2147 participants, met the inclusion criteria for this review. However, the large variety of outcomes and rating scales considerably limited a quantitative synthesis of data. We could not synthesize a large amount of information.

Comparing any dopamine agonist versus placebo, we found moderate to low quality of evidence that there were no significant differences for any of the outcomes considered (dropout, abstinence, craving, severity of dependence depression adverse events). This also occurred when single dopamine agonists were compared against placebo.

Comparing amantadine versus antidepressants (desipramine in four comparisons and fluoxetine in one comparison), we found low quality of evidence that antidepressants performed better for abstinence, but results were from only two studies with 44 participants. The other two outcomes considered did not show statistically significant differences, although dropouts and adverse events tended to be more common in the antidepressant group.

Overall completeness and applicability of evidence

As seen for other treatments, the trials included in this review had important differences in psychiatric and substance use diagnoses, definitions of outcomes variables and varying amounts of psychotherapy provided in conjunction with medications. These discrepancies have two consequences: data are more generalizable, but there is a clear limitation for pooling data.

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 and the outcomes investigated (dropouts, abstinence, 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 trial location. Despite our systematic bibliographical search, only two out of 23 included studies were conducted outside of the USA. It should be considered that different social contexts can influence the severity of dependence and the availability to enter an experimental design. Also different clinical contests can differentially influence participant selection 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

Regarding risk of bias of the included trials, only 20.8% used an adequate method of sequence generation and the 17% an adequate method of allocation concealment. We judged the other studies were at unclear risk because the trial authors did not provide details. Only 41% of included trials described an adequate method to maintain blinding. Only 21% of included trials declared that outcome assessors were blinded. We judged all but two of the other at unclear risk of bias for subjective outcomes. We considered 83.3% of the included studies at low risk of reporting bias. We judged 70.8% at low risk of attrition bias or because the ITT principle was used or there were few participants lost at follow-up, balanced between groups and reason for dropout were reported.

Finally, the great heterogeneity of the scales used in the primary studies and the way in which results were reported meant it was not possible at times to undertake a cumulative analysis.

The quality of evidence using GRADE was judged from moderate to low, see Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3

AUTHORS' CONCLUSIONS

Implications for practice

In spite of theoretical foundations on which the use of dopamine agonists for the treatment of cocaine dependence is based on (Gardner 1999; Volkow 1999a; Volkow 1999b; Volkow 2003b; Gorelick 2004; Volkow 2006; Rush 2009; Rush 2010; Volkow 2010), current evidence from RCTs does not support the use of dopamine agonists for treating people with cocaine dependence.

Implications for research

This Cochrane Review shows that direct dopamine agonists alone do not appear to be efficacious. Nevertheless, their use in combination with indirect dopamine agonists, which have shown mixed results for the treatment of cocaine dependence, could be justifiable if laboratory studies demonstrate a reduction in cocaine craving or cocaine reinforcing effects.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Alterman 1992

Methods	RCT
Participants	N = 42 cocaine dependents (DSM-III-R); mean age: 35 years; sex: male 100%; Race: African-American 90%, less than 20% currently married. History: 15 days of cocaine use last month, cocaine regular use for ˜3 years. Recent use of alcohol and cannabis were also reported, but not a dependence on these drugs. Inclusion criteria: cocaine dependence according to the DSM III criteria. Exclusion criteria: patients with significant cardiovascular, hepatic, renal, neurological or endocrinological abnormalities; dependence on a substance other than cocaine or nicotine; inability to understand self-medication instructions; taking neuroleptic medications; not having used cocaine in the past week; unstable housing arrangements.
Interventions	1. Amantadine 200 mg, N = 21; 2. Placebo, N = 21. Setting: outpatient; Duration: 10 days, follow-up 1 month; country of origin: USA.
Outcomes	No retention in treatment; Positive urine for cocaine metabolites; BDI; Side effects (total number of side effects); ASI (related to follow-up period- 30 days); CSR - craving; HDRS: SCL-90
Notes	The subjects received 27 hours per week of day hospital treatment. Participants were paid for completing each assessments.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"random assignment was completed by a research technician using a constrained block randomisation procedure; the procedure ensured equal subjects numbers for each group within series of 10 subjects."

Alterman 1992 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) subjective outcomes	Low risk	"both research/clinical personnel and the subjects were unaware of drug group assignment".
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	"both research/clinical personnel and the subjects were unaware of drug group assignment".
Blinding of outcome assessment (detection bias) subjective outcomes	Low risk	"both research/clinical personnel and the subjects were unaware of drug group assignment".
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	"both research/clinical personnel and the subjects were unaware of drug group assignment".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout: 25%; no difference between groups.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section were reported.

Ciraulo 2005

Methods	RCT
Participants	60 subjects; age 43 on the average; males 43/60; black 55/60; married 29/60. Inclusion criteria: age between 18 and 60years; meet DSM-IV criteria for cocaine dependence and reported use of cocaine on at least six occasions or days within 28 days prior to screening and 3/6 urine positive. Exclusion criteria: current dependence on any psychoactive substance other than cocaine and nicotine or physiological dependence on alcohol requiring medical detoxification; neurological or psychiatric disorders that require treatment; serious medical illness; pregnancy or lactation; renal stone formation; asthma or actively using beta-adrenergic agonist medications.
Interventions	1. Pramipexole (dopamine agonist) 1.5 mg daily, N = 20; 2. Venlafaxine (antidepressant (150 mg daily), N = 20; 3. Placebo, N = 20. Setting: outpatient; duration: 8 weeks; country of origin: USA.
Outcomes	Retention in treatment; use of cocaine (urine BE); ASI; CGI-O; HAM-D; HAM-A; BSCS.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Ciraulo 2005 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) subjective outcomes	Low risk	"Medications and placebo were supplied by the manufacturer in identically appearing tablets; Participants, therapists and research staff were not told the specific medication that a participants was taking".
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	"Medications and placebo were supplied by the manufacturer in identically appearing tablets; Participants, therapists and research staff were not told the specific medication that a participants was taking".
Blinding of outcome assessment (detection bias) subjective outcomes	Low risk	"Participants, therapists and research staff were not told the specific medication that a participants was taking".
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	" Participants, therapists and research staff were not told the specific medication that a participants was taking".
Incomplete outcome data (attrition bias) All outcomes	Low risk	No significant differences in the attrition rate between groups; mean attrition rate: 20%.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section were reported.

Eiler 1995

Methods	RCT
Participants	N = 63 Mean 35.6 years; male 100%; black 86%, Caucasian 15%; unemployed 60%, married 24%; 55% intranasal use and 3% intravenously. Duration of use average 7.9 years, average amount of cocaine used in a typical week 9.2 g. Alcohol abuse could be present, but not alcohol dependence. Inclusion criteria: meet DSM-III-R criteria for cocaine dependence, last cocaine use was within 6 days. Exclusion criteria: other drug dependence,alcohol dependence, psychotropic medication other than Halcion for sleep prescribed.
Interventions	1. Bromocriptine 2.5 to 10 mg/day, N = 32; 2. Placebo, N = 31. Setting: inpatient; duration: 18 to 21 days; country of origin: USA.
Outcomes	Dropouts; dropouts due to adverse effects; BDI; craving; withdrawal symptoms
Notes	
Risk of bias	

Eiler 1995 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) subjective outcomes	Low risk	"the patients, ward staff, research assistant and physician prescribing the medication were blind to whether the patient was receiving the active drug or placebo".
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	"the patients, ward staff, research assistant and physician prescribing the medication were blind to whether the patient was receiving the active drug or placebo".
Blinding of outcome assessment (detection bias) subjective outcomes	Low risk	"the patients, ward staff, research assistant and physician prescribing the medication were blind to whether the patient was receiving the active drug or placebo".
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	""the patients, ward staff, research assistant and physician prescribing the medication were blind to whether the patient was receiving the active drug or placebo".
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 50% of patients completed the study; there was no significant difference in the attrition rate between groups.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section were reported.

Focchi 2005

Methods	RCT
Participants	N = 42 All male; average age 26.5 years; white 35/42; married 14/42; working 29/42; cocaine smoked 3/42, inhaled 20/42, smoked and inhaled 19/42. Inclusion criteria: male, between 18 and 50 years, cocaine dependents (DSM-IV), living in São Paulo, at least primary school education. Exclusion criteria: active psychiatric illness or psychosis, hypersensitivity to pergolide or other ergot derivatives, without permanent address or telephone number.
Interventions	1. Pergolide 0.05 mg/day in the first week and 0.1 mg/day in the second week, until 0.2 mg/day in the fourth week, N = 22; 2. Placebo, N = 20. Setting: outpatient; duration: 4 weeks, follow-up 3 months; country of origin: Brazil.
Outcomes	HAM-D; Minnesota Cocaine Craving Scale; adverse effects.

Focchi 2005 *(Continued)*

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	No details provided.
Blinding of participants and personnel (performance bias) subjective outcomes	High risk	Single blinded.
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	No blinding or incomplete blinding, but the outcome is unlikely to have been influenced by lack of blinding.
Blinding of outcome assessment (detection bias) subjective outcomes	High risk	Single blinded.
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	No blinding or incomplete blinding, but the outcome is unlikely to have been influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details provided.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section were reported.

Giannini 1989

Methods	RCT 3 parallel groups
Participants	N = 30 All male; age: range 24 to 32 years; Caucasians 100%. All subjects had abused cocaine intranasally on a daily basis for at least 4 weeks before study entry, confirmed by urine drug screen before and during the study; 2 subjects in the bromocriptine group and one each in the amantadine and placebo group met DSM-III-R criteria for antisocial personality disorder. Inclusion criteria: not reported. Exclusion criteria: not reported.
Interventions	1. Amantadine 400 mg/day, N = 10; 2. Bromocriptine 10 mg/day, N = 10; 3. Placebo, N = 10.

Giannini 1989 *(Continued)*

	Setting: outpatient; duration: 30 days; country of origin: USA.
Outcomes	Side effects; BPRS; craving
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using a "Texas Instrument Programable 68" random computer programme.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) subjective outcomes	Unclear risk	Stated as double blinded, but no details provided.
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	No information about blinding, but the outcome is unlikely to have been influenced by lack of blinding.
Blinding of outcome assessment (detection bias) subjective outcomes	Low risk	"subject response was measured by two experienced research psychologists without knowledge of the purpose of the study or the medications used".
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	"subject response was measured by two experienced research psychologists without knowledge of the purpose of the study or the medications used".
Incomplete outcome data (attrition bias) All outcomes	Low risk	None lost at follow-up.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section were reported.

Gorelick 2006

Methods	RCT
Participants	N = 70 All men; mean age 34 years; 86% African-American; mean 39 months of regular cocaine use (predominantly smoked). Inclusion criteria: met DSM IV criteria for current cocaine abuse or dependence; age 18 to 65 years, living within 25 miles of the hospital, no other current substance abuse or dependence except nicotine. Exclusion criteria: myocardial infarction within the past 6 months, current serious or unstable medical or psychiatric condition, allergy or hypersensitivity to bromocriptine or ergot alkaloids, current treatment with dopamine affecting medications (i.e. disulfiram, amantadine, anti-depressants, neuroleptics), inability to give informed consent or inability to cooperate with study procedures.

Gorelick 2006 *(Continued)*

Interventions	1. Bromocriptine max dose 2.5 mg, N = 35; 2. Placebo, N = 35. Setting: inpatient; duration: 4 weeks; country of origin: USA.
Outcomes	Compliance; retention; use of cocaine (urine samples); craving (0-5 Likert scale); BDI; HAM-D; adverse effects.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"subjects were randomly assigned". No other details provided.
Allocation concealment (selection bias)	Low risk	"treatment assignment was done by the pharmaceutical company which provided the medication".
Blinding of participants and personnel (performance bias) subjective outcomes	Low risk	"the study medication capsules or the matching placebo capsules were provided by Sandoz Pharmaceuticals CO. the medication was not known to either the investigators or clinical staff".
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	"the study medication capsules or the matching placebo capsules were provided by Sandoz Pharmaceuticals CO. the medication was not known to either the investigators or clinical staff".
Blinding of outcome assessment (detection bias) subjective outcomes	Low risk	"the medication was not known to either the investigators or clinical staff".
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	"the medication was not known to either the investigators or clinical staff".
Incomplete outcome data (attrition bias) All outcomes	High risk	71% of attrition in the bromocriptine group, 54% in the placebo group.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section were reported

Handelsman 1995

Methods	RCT
Participants	N = 67 methadone-maintained patients in treatment for heroine dependence (59 analysed). Age: ˜36 years; sex: male 100%; race: unclear. Inclusion criteria: male, age between 21 and 50, fulfil DSM-III criteria for cocaine dependence including active dependence in the 3-month period prior to research, reported cocaine use on 3 or more days per week during the prior 3 months.

Handelsman 1995 *(Continued)*

	Exclusion criteria: any serious medical illness, assuming a systematically active medication, abnormal electrocardiogram, fulfilled criteria for any psychoactive substance use disorder other than heroin, cocaine, nicotine or caffeine, fulfilled DSM III criteria for any current major psychiatric disorder including psychotic, affective or panic disorders.
Interventions	1. Amantadine 200 mg/day, N = 19; 2. Amantadine 400 mg/day, N = 23; 3. Placebo, N = 25. Setting: outpatient; duration: 9 weeks; country of origin: USA.
Outcomes	Retention in treatment; BDI; SCL-90; Positive urine sample for cocaine metabolites; craving; compliance; adverse effects.
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	"randomised after one week period of placebo use". No further details provided.
Blinding of participants and personnel (performance bias) subjective outcomes	Low risk	"medication was administered in a double blind fashion except during the first week of the nine week trial. In the first week placebo was administered under single blind condition".
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	"medication was administered in a double blind fashion except during the first week of the nine week trial. In the first week placebo was administered under single blind condition".
Blinding of outcome assessment (detection bias) subjective outcomes	Unclear risk	No details provided.
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	No information about blinding, but the outcome is unlikely to have been influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"67 completed enrolment, 8 dropped out after the clinical trial began, statistical analysis were restricted to 59 subjects".
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section were reported.

Handelsman 1997

Methods	RCT
Participants	N = 60.

Handelsman 1997 *(Continued)*

	Methadone-maintained patients with cocaine abuse or dependence (DSM-III-R). Age: ˜39 years; male 100%; 24% black. Inclusion criteria: older than 21 years of age, using cocaine in the last 30 days and at least one positive urine for cocaine metabolite. Exclusion criteria: serious medical illness, history of alcohol or sedative dependence that need medical detoxification, any psychotic disorder, female.
Interventions	1. Bromocriptine 5 mg, N = 30; 2. Placebo, N = 30. For both groups intensive cognitive behavioral therapy. Setting: outpatient; duration: 5 weeks; country of origin: USA.
Outcomes	Retention in treatment; use of cocaine (self report and urine based); craving, POMS; PANAS.
Notes	Patients were paid for participation.

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	No details provided.
Blinding of participants and personnel (performance bias) subjective outcomes	Unclear risk	Stated as double blinded, but no details provided.
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	No information about blinding, but the outcome is unlikely to have been influenced by lack of blinding.
Blinding of outcome assessment (detection bias) subjective outcomes	Unclear risk	Stated as double blinded, but no details provided.
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	No information about blinding, but the outcome is unlikely to have been influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	16.6% dropout from the study; no significant differences in the attrition rate between groups; reason for dropout reported.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section were reported.

Kampman 1996

Methods	RCT
Participants	N = 61 Cocaine use within 10 days of entering the stud. Age: ˜35 years; male in amantadine group 87%; in placebo group 77%; African-American in amantadine group 67%; in placebo group 71%. Inclusion criteria: not reported. Exclusion criteria: dependents on any drug except cocaine, marijuana and alcohol, pregnancy, breast feeding, psychosis, dementia, epilepsy, use of psychotropic medication. Alcohol and marijuana dependent were not excluded.
Interventions	1. Amantadine 300 mg, N = 30; 2. Placebo, N = 31. For all 50 minutes individual counselling sessions and twice weekly 90 minutes therapy sessions. Setting: outpatient; duration: 4 weeks, follow-up at 8 weeks; country of origin: USA.
Outcomes	Retention in treatment; abstinence; ASI; BDI; BAI; craving; adverse effects.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, utilizing a stratified block procedure.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) subjective outcomes	Unclear risk	Stated as double blinded, but no details were provided.
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	No information about blinding, but the outcome is unlikely to have been influenced by lack of blinding.
Blinding of outcome assessment (detection bias) subjective outcomes	Unclear risk	Stated as double blinded, but no details provided.
Blinding of outcome assessment (detection bias) objective outcomes	Unclear risk	No information about blinding, but the outcome is unlikely to have been influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	38% of patients dropped out from the study; no significant difference in the attrition rate.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section were reported.

Kampman 2006

Methods	RCT
Participants	N = 199 Mean age: 42.2 years, male: 65.5% African American: 85%, Caucasian: 17%, Hispanic: 2.5%. Days of cocaine use in past 30 days: 15.4. Year of cocaine use: 11.6. Inclusion criteria: aged between 18 and 60 years, cocaine dependents, patients addicted also to alcohol were also admitted. Exclusion criteria: other addictions, except nicotine, psychosis, dementia, use of psychotropic medications, pregnancy, breastfeeding, hyperthyroidism, bronchoplastic disease, heart disease, history of chest pain.
Interventions	1. Propanolol 20 mg twice daily for the first 3 days, then 40 mg twice daily, N = 50; 2. Amantadine 100 mg three times daily, N = 50; 3. Amantadine + Propanolol, N = 50; 4. Placebo, N = 49. For all twice-weekly individual cognitive behavioural therapy Setting: outpatient; Duration:10 weeks; Country of origin: USA
Outcomes	Retention; Use of cocaine based on urine test, CSSA, ASI, 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	No details provided.
Blinding of participants and personnel (performance bias) subjective outcomes	Unclear risk	Stated as double blinded, no details provided.
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	No information about blinding, but the outcome is unlikely to have been influenced by lack of blinding.
Blinding of outcome assessment (detection bias) subjective outcomes	Unclear risk	Stated as double blinded, but no details provided.
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	No information about blinding, but the outcome is unlikely to have been influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	Missing urine counted as positives.

Kampman 2006 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section were reported.

Kolar 1992

Methods	RCT
Participants	N = 24 Mean 34.8 years, 85% male, African-American 68% Patients had used cocaine on average for 10 years. Other diagnosis were found such as attention deficit disorder, affective and anxiety disorders. Patients were required to be stabilized on a daily methadone dose of 40 mg or greater for a minimum of six weeks. Inclusion criteria: DSM III criteria for cocaine dependence, stabilized on daily methadone dose of 40 mg or greater for a minimum of 6 weeks. Exclusion criteria: current use or dependence on any substance other than marijuana, nicotine, and caffeine or took prescribed medication; currently medically ill, psychotic, and/or pregnant.
Interventions	1. Desipramine 200 mg, N = 8; 2. Amantadine 200 mg followed by placebo, N = 5; 3. Placebo, N = 9. For all weekly group counselling sessions as well as weekly or more frequent individual counselling sessions. Setting: outpatient; duration:12 weeks; country of origin: USA.
Outcomes	No retention in treatment; use of cocaine; BDI; craving; adverse effects; participants presenting at least one adverse effect.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Low risk	"assignment done by study pharmacist who had no client contact".
Blinding of participants and personnel (performance bias) subjective outcomes	Low risk	"subjects, study nurse, research assistant were blind to treatment condition".
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	"subjects, study nurse, research assistant were blind to treatment condition".
Blinding of outcome assessment (detection bias)	Low risk	"subjects, study nurse, research assistant were blind to treatment condition".

Kolar 1992 *(Continued)*

subjective outcomes		
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	"subjects, study nurse, research assistant were blind to treatment condition".
Incomplete outcome data (attrition bias) All outcomes	Low risk	24 participants, data on 22 analysed.
Selective reporting (reporting bias)	Unclear risk	Not all the outcome measures were clearly reported.

Kosten 1992

Methods	RCT
Participants	N = 94 Opioid and cocaine dependents (DSM-III-R) Sex: male 52%, at least 3/6 urine positive for cocaine metabolites during the 3 months before the onset of the study; patients had been receiving methadone maintenance for a mean of 7.6 months before entering the study. Additional diagnosis: antisocial personality disorder (20%); major depression (5%), dysthymia (22%). Mean 32 years, 82% white. Inclusion criteria: meeting the DSM III criteria for a and opioid dependence, with at least three urine toxicology screening positive for cocaine metabolites during the 3 months before the study. Exclusion criteria: taking zidovudine for HIV syndrome, asthma, renal dysfunction, high blood pressure, diabetes, current alcoholism, refuse to use adequate birth control.
Interventions	1. Desipramine 150 mg, N = 30; 2. Amantadine 300 mg, N = 33; 3. Placebo, N = 31. For all weekly group relapse prevention therapy. Setting: outpatient; duration:12 weeks; country of origin: USA.
Outcomes	Retention in treatment; use of cocaine (urine based); dropout due to adverse effects; craving.
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	No details provided.
Blinding of participants and personnel (performance bias) subjective outcomes	Unclear risk	Stated as double blinded, but no details provided.

Kosten 1992 *(Continued)*

Blinding of participants and personnel (performance bias) objective outcomes	Low risk	No information about blinding, but the outcome is unlikely to have been influenced by lack of blinding.
Blinding of outcome assessment (detection bias) subjective outcomes	Unclear risk	Stated as double blinded, but no details provided.
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	No information about blinding, but the outcome is unlikely to have been influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing urine counted as positives. Dropout rate of 21%; no significant differences between groups. Principle of analysis: ITT.
Selective reporting (reporting bias)	High risk	Outcomes not pre-defined.

Malcolm 2000

Methods	RCT
Participants	N = 464 Age: range 18 to 52 years, male 79%, black 52%, mean years of cocaine use ˜8. Inclusion criteria: able to give informed consent, met DSM-III-R criteria for cocaine dependence with or without comorbid alcohol dependence, crack or cocaine as their primary drug of choice. Exclusion criteria: past or present major Axis I disorders, previous treatment with dopamine agonists, treatment with anxiolytics, antidepressants or antipsychotic within 30 days of entering the study, females of childbearing potential without reliable birth control measures, patients with unstable medical conditions.
Interventions	1. High dose pergolide 0.25 mg bid, N = 156; 2. Low dose pergolide 0.05 mg bid, N = 155; 3. Placebo (sucrose powder), N = 153. Setting: outpatient; duration: 12 weeks + 6 months follow-up; country of origin: USA.
Outcomes	Retention in treatment(12 weeks); positive urine samples; adverse effects.
Notes	Patients were paid USD 25 at weeks.

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	No details provided.

Malcolm 2000 *(Continued)*

Blinding of participants and personnel (performance bias) subjective outcomes	Unclear risk	Stated as double blinded, but no details provided.
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	No information about blinding, but the outcome is unlikely to have been influenced by lack of blinding.
Blinding of outcome assessment (detection bias) subjective outcomes	Unclear risk	Stated as double blinded, but no details provided.
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	No information about blinding, but the outcome is unlikely to have been influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	27% dropped out in the first week; 357 analysed.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section were reported.

Mooney 2007a

Methods	RCT
Participants	Two trials N = 67 Mean age: 35 years; male 67.5%; white 45.5%, black 47.5%, Hispanic 7%; mean years of cocaine use: 8.5. Inclusion criteria: age between 18 and 55 years, current users of cocaine. Exclusion criteria: pregnancy or nursing, current dependence on substances other than cannabis or nicotine, current psychotic, affective or anxiety disorder, serious medical conditions including movement disorder.
Interventions	1. 400/100mg L-dopa/Carbidopa, N = 31; 2. Placebo, N = 36. For all supportive behavioural counselling for 1 h each week. Setting: outpatient; duration: 1, 5 weeks; country of origin: USA.
Outcomes	Retention in treatment; adverse effects; cocaine use; craving; mood.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Mooney 2007a *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) subjective outcomes	Unclear risk	Stated as double blinded, but no details provided.
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	No information about blinding, but the outcome is unlikely to have been influenced by lack of blinding.
Blinding of outcome assessment (detection bias) subjective outcomes	Unclear risk	Stated as double blinded, but no details were provided.
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	No information about blinding, but the outcome is unlikely to have been influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section were reported.

Mooney 2007b

Methods	RCT
Participants	N = 122 Mean age: 39.7, male 67.5%; white 28.5%, black 65.4%, Hispanic 6%; mean years of cocaine use: 10.6. Inclusion criteria: age between 18 and 55 years, current users of cocaine. Exclusion criteria: pregnancy or nursing, current dependence on substances other than cannabis or nicotine, current psychotic, affective or anxiety disorder, serious medical conditions including movement disorder.
Interventions	1. 400/100 mg L-dopa/carbidopa, N = 43; 2. 800/200mg L-dopa/carbidopa, N = 39; 3. Placebo, N = 40. For all supportive behavioural counselling for 1 h each week. Setting: outpatient; duration: 2, 9 week; country of origin: USA.
Outcomes	Retention in treatment; adverse effects; cocaine use; craving; mood.
Notes	

Mooney 2007b *(Continued)*

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	No details provided.
Blinding of participants and personnel (performance bias) subjective outcomes	Unclear risk	Stated as double blinded, but no details provided.
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	No information about blinding, but the outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) subjective outcomes	Unclear risk	Stated as double blinded, but no details provided.
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	No information about blinding, but the outcome is unlikely to have been influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section were reported.

Moscovitz 1993

Methods	RCT
Participants	N = 29 Diagnosis: cocaine users, age: ˜37 years, male 100%. Participants used cocaine at least four times per week for the previous month. Inclusion criteria: frequent cocaine use defined as intranasal, inhalational (crack), or intravenous administration of cocaine more than three times per week for the previous four weeks. A positive urine test for benzoylecgonine, a cocaine metabolite, was also required for entry into the study. Exclusion criteria: use of narcotics, dependence on other substances, consumption more than the equivalent of a pint of hard liquor per day, use of neuroleptic or antidepressant medications; a history of schizophrenia, cardiovascular disease, or hypertension; and a prior adverse reaction to bromocriptine.
Interventions	1. Bromocriptine 3.75 mg/day, N = 14; 2. Placebo, N = 15. Setting: outpatient; duration: 2 weeks; country of origin: USA.

Moscovitz 1993 *(Continued)*

Outcomes	Retention in treatment, positive urine sample for cocaine metabolites, participants presenting at least one adverse effect.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Low risk	"A pharmacist who had no contact with the subjects or the test data, coded the study medications".
Blinding of participants and personnel (performance bias) subjective outcomes	Unclear risk	Stated as double blind, no details provided.
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	No information about blinding, but the outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) subjective outcomes	Unclear risk	Stated as double blind, no details provided.
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	No information about blinding, but the outcome is not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	65% dropped out from the study.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section were reported.

Oliveto 1995

Methods	RCT
Participants	N = 21 Opioid dependents on methadone maintenance and cocaine abusers, mean age: 33.1 years; 52.9% male; 94.1% white; education: mean 11.6 years; e mployed full-time: 35.3%; heroin use: mean 8.8 years, 22.9 days last month; cocaine use: 8.4 days last month. Inclusion criteria: opioid dependence, cocaine use, no current alcohol or sedative physical dependence, no current use of medications for psychiatric conditions, women who have negative pregnancy test and agree to effective birth control. Exclusion criteria: significant medical contra-indications (e.g. cerebral, renal, thyroid, hepatic or cardiac pathology), acute suicidality or severity of clinical conditions such that inpatient treatment is indi-

Oliveto 1995 *(Continued)*

	cated, illiteracy or inability to comprehend the consent for study procedure or both, concurrent treatment with AZT or other medications for the treatment of AIDS.
Interventions	Buprenorphine 8 mg/day and: 1. Amantadine 300 mg/day, N = 5; 2. Desipramine 150 mg/day, N = 8; 3. Fluoxetine 60 mg/day, N = 4. For all at least once-weekly group relapse prevention. Setting: outpatient; duration: 12 weeks; country of origin: USA.
Outcomes	Retention in treatment; positive urine sample; cocaine craving; BDI.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Low risk	"the pharmacist and the principal investigator held the code".
Blinding of participants and personnel (performance bias) subjective outcomes	Low risk	"To maintain the blind, the dosages of Amantidine, desipramine and fluoxitine were placed in seize 00 blue opaque capsules with lactose filter".
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	"To maintain the blind, the dosages of Amantidine, desipramine and fluoxitine were placed in seize 00 blue opaque capsules with lactose filter".
Blinding of outcome assessment (detection bias) subjective outcomes	Unclear risk	No details provided.
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	No information about blinding, but the outcome is not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/21 (19%) participants left the studies for administrative reasons.
Selective reporting (reporting bias)	Unclear risk	No details provided.

Pérez de los Cobos 2001

Methods	RCT
Participants	N = 42

Pérez de los Cobos 2001 *(Continued)*

	Heroin and cocaine dependents, mean age: ˜31 years; 77% male; race: unclear; education: mean ˜8 years; employment: unclear; heroin use: mean ˜10 years; cocaine use: mean 20 days last month. Inclusion criteria: 18 to 45 years old, meet DSM-III-R criteria for heroin dependence and for current cocaine abuse or dependence, urine toxicology test positive for BE on the first day of hospitalisation. Exclusion criteria: pregnancy, DSM-III-R diagnosis of dependence on alcohol, hypnotics or sedative, as well as schizophrenia or other psychotic disorders, presence of severe physical alterations that contraindicated participation in the trial (e.g. impaired renal function, peptic ulcere disease and seizures).
Interventions	Methadone maintenance, on the first or second day of hospitalisation never higher than 50 mg/day, tapered at a rate of 5 mg/day and: 1. Amantadine 200 to 300 mg/day, N = 19; 2. Placebo N = 21. Setting: inpatient; duration: 14 days; country of origin: Spain.
Outcomes	Retention in treatment; craving; BDI; STAI; adverse effects.
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	No details provided.
Blinding of participants and personnel (performance bias) subjective outcomes	Low risk	"to preserve the clinical trial double blind conditions...identical opaque capsules were used".
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	"to preserve the clinical trial double blind conditions...identical opaque capsules were used".
Blinding of outcome assessment (detection bias) subjective outcomes	Unclear risk	No details provided.
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	No information about blinding, but the outcome is unlikely to have been influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only two patients (4.76%) dropped out from the studies.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section were reported.

Schmitz 2008

Methods	RCT
Participants	N = 161 Mean age: 41.1 years, male: 83.2%; white: 24.1% black :67.7%, Hispanic: 7.4%; mean education years: 12.7, mean years of cocaine use: 11.7. Inclusion criteria: meet DSM-IV criteria for current cocaine dependence and self reporting recent use of cocaine (confirmed by BE positive urine). Exclusion criteria: dependence on drugs other than cannabis or nicotine, current non substance induced psychotic, depressive or anxiety disorder, presence of significant suicidal or homicidal ideation, major medical illness or condition (e.g. severe pulmonary or cardiovascular disease, renal function impairment), concomitant medications interacting with levodopa/carbidopa (e.g. MAO inhibitors, anticonvulsants), pregnancy, inability to read, write or speak English.
Interventions	1. Levodopa/carbidopa + Clinical Management, N = 25; 2. Levodopa/carbidopa + CBT, N = 28; 3. Levodopa/carbidopa + VBRT, N = 23; 4. Placebo + Clinical Management, N = 27; 5. Placebo + CBT, N = 31; 6. Placbo + VBRT, N = 27. Levodopa/carbidopa sustained release tablet, days 1.2, 50/12.5 BId; days 3 to 4 100/25 BID, days 5 to 6 200/50 BID, day 7 400/100 BID, followed by maintenance for 11 weeks and a 7-day dose reduction at week 12. For all brief clinical management and CBT or CBT plus VBRT. Setting: outpatient; duration: 12 weeks; country of origin: USA.
Outcomes	Cocaine use; craving; compliance; adverse effects.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"urn randomisation procedure to ensure even distribution of treatment groups".
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) subjective outcomes	Unclear risk	Stated as double blind, no details provided: "double blind for medical conditions".
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	No information about blinding, but the outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) subjective outcomes	Unclear risk	No details provided.

Schmitz 2008 *(Continued)*

Blinding of outcome assessment (detection bias) objective outcomes	Low risk	No information about blinding, but the outcome is not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Principle of analysis: ITT.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section were reported.

Schmitz 2010

Methods	RCT
Participants	N = 136 83% male, 71% African American, mean age 41 years, mean education of 12.8 years, 53% employed, 64% previous drug treatment, recent cocaine use 13.4 days in the past 30, lifetime cocaine use 12.0 years. Inclusion criteria: meet DSM-Iv criteria for current cocaine dependence and self reporting recent use of cocaine (confirmed by BE positive urine). Exclusion criteria: dependence on drugs other than cannabis or nicotine, current non substance induced psychotic, depressive or anxiety disorder, presence of significant suicidal or homicidal ideation, major medical illness or condition (e.g. severe pulmonary or cardiovascular disease, renal function impairment), concomitant medications interacting with levodopa/carbidopa (e.g. MAO inhibitors, anticonvulsants), pregnancy, inability to read, write or speak English.
Interventions	1. Levodopa/carbidopa+CM-Clinical attendance, N = 23; 2. Levodopa/carbidopa+CM-Urine, N = 23; 3. Levodopa/carbidopa+CM-Medication, N = 22; 4. Placebo+CM-Clinical Attendance, N = 21; 5. Placebo+CM-Urine, N = 27; 6. Placebo+CM-Medication, N = 20. • CM-Clinical Attendance: subjects received cash-valued vouchers contingent on attending thrice weekly clinic visits; • CM-Urine: subjects received cash-valued vouchers contingent on cocaine negative urine toxicology results; • CM-Medication: subjects received cash-valued vouchers contingent on medication event monitoring system and riboflavin based evidence of pill taking behavior. Levodopa/carbidopa sustained release tablet, days 1.2, 50/12.5 BId; days 3 to 4 100/25 BID, days 5 to 6 200/50 BID, day 7 400/100 BID, followed by maintenance for 11 weeks and a 7-day dose reduction at week 12. Setting: outpatient; duration: 12 weeks; country of origin: USA.
Outcomes	Retention in treatment, attendance, compliance, cocaine use.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Schmitz 2010 *(Continued)*

Random sequence generation (selection bias)	Low risk	"urn randomisation procedure to ensure even distribution of treatment groups".
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) subjective outcomes	Unclear risk	Stated as double blinded, but no details provided.
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	No information about blinding, but the outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) subjective outcomes	Unclear risk	Stated as double blind, no details provided.
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	No information about blinding, but the outcome is not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	136 randomised, 101 received initial dose of treatment; data on these 101 (74%) patients.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section were reported.

Schmitz 2014

Methods	RCT
Participants	N = 81. 82% male, 70% African American, mean age 42.1 years, with a 13-year history of cocaine use and recent use reported on 15.2 of the past 30 days. Inclusion criteria: meet DSM-Iv criteria for current cocaine dependence (Diagnostic and Statistical Manual, Fourth Edition (DSM-IV)) and submitting at least one cocaine-positive urine result during screening. Exclusion criteria: acutely unstable medical or psychiatric disorders or substance dependence aside from cocaine, cannabis, or nicotine; subjects currently enrolled in drug-abuse treatment and women who were pregnant, nursing, or of childbearing potential and unwilling to use acceptable birth control methods during study participation.
Interventions	1. Placebo, N = 18; 2. Modafinil, N = 22; 3. Levodopa, N = 25; 4. Naltrexone, N = 16. For all subjects cognitive behavioral therapy and contingency management targeting medication compliance.

Schmitz 2014 *(Continued)*

	Setting: outpatient; duration: 12 weeks; country of origin: USA.
Outcomes	Retention in treatment, adverse events, compliance, cocaine use.
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	No details provided.
Blinding of participants and personnel (performance bias) subjective outcomes	Low risk	All active and placebo capsules were identical in appearance, and each contained 50 mg riboflavin for subsequent evaluation of medication compliance. All investigators and staff, except the pharmacist, were blinded to medication assignment.
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	All active and placebo capsules were identical in appearance, and each contained 50 mg riboflavin for subsequent evaluation of medication compliance. All investigators and staff, except the pharmacist, were blinded to medication assignment.
Blinding of outcome assessment (detection bias) subjective outcomes	Low risk	All investigators and staff, except the pharmacist, were blinded to medication assignment.
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	All investigators and staff, except the pharmacist, were blinded to medication assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Principle of analysis: ITT.
Selective reporting (reporting bias)	High risk	Results for cocaine use in each group not reported.

Shoptaw 2002

Methods	RCT
Participants	N = 69 Cocaine dependence (SCID) - 85% smoking coca, mean age: 36.4 years, male 79%, 39.4% Latino; 33.3%, African American, mean education years: 12.6, mean years of cocaine use: 9. Inclusion criteria: not reported. Exclusion criteria: not reported.
Interventions	1. Amantadine 100 mg BID, N = 34; 2. Placebo, N = 35. Associated with 3 times/ week group counselling.

Shoptaw 2002 *(Continued)*

	Setting: outpatient; duration: 16 weeks + 9 months follow-up; country of origin: USA.
Outcomes	At 16 weeks: retention in treatment, non-abstinent for consecutive 3 weeks, adverse events, craving, clinical global impression rated by staff, compliance. At 9 months follow-up: positive urine sample.
Notes	Subjects paid US$ 25 for the 9 months follow-up.

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	No details provided.
Blinding of participants and personnel (performance bias) subjective outcomes	Unclear risk	Stated as double blinded, no details provided.
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	No information about blinding, but the outcome is unlikely to have been influenced by lack of blinding.
Blinding of outcome assessment (detection bias) subjective outcomes	Unclear risk	Stated as double blinded, no details provided.
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	No information about blinding, but the outcome is unlikely to have been influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Sixty-nine randomised, analysis on 68 who completed.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section were reported.

Shoptaw 2005

Methods	RCT
Participants	N = 60 Mean age: 38.1 years, male: 69.8%; African-American: 59.5%, Caucasian: 15%, Hispanic: 16.8%. Days used cocaine in last 30 days: 14.1, years of cocaine use: 9.1. Inclusion criteria: current cocaine dependence (DSM-IV-R), two substantiated episodes of cocaine use in a 2-week baseline period, seeking treatment for cocaine dependence, if female and of childbearing potential, used reliable birth control method, access to sufficient resources to attend clinic reliably (e.g. bus, car).

Shoptaw 2005 *(Continued)*

	Exclusion criteria: concurrent dependence upon substances other than cocaine, nicotine or caffeine, participation in a clinical trial in the past 30 days, medical conditions that would preclude safe study participation or that would alter metabolism or excretion of study medication, psychiatric condition that required medical or behavioural intervention, recent therapy (past 60 days) with any opiate substitution, suicide risk, known sensitivity to hydergine, levodopa/carbidopa or cabergoline, history of asthma or seizures.
Interventions	1. Hydergine 1 mg three times daily, N = 15; 2. Levodopa/carbidopa 25/100 mg three times daily, N = 15; 3. Cabergoline 0.5 mg per week, N = 15; 4. Placebo three times daily, N = 15. For all 1 hour per week of cognitive behavioural drug counselling. Setting: outpatient; duration: 8 weeks + 4 weeks follow-up; country of origin: USA.
Outcomes	Retention in treatment; use of cocaine; craving: Clinical Global Impression Scale (self and observer), HIV risk behaviours.
Notes	Participants received $5 in grocery vouchers each for six screening and 23 medication phase research visits and an additional USD 20 for completing visits for a maximum value of USD 165 in vouchers.

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	No details provided.
Blinding of participants and personnel (performance bias) subjective outcomes	Low risk	"in order to maximize protection of the modified blind in the clinic, personnel charged with administering and counting medications were kept isolated from clinical staff and research team during clinic hours".
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	"in order to maximize protection of the modified blind in the clinic, personnel charged with administering and counting medications were kept isolated from clinical staff and research team during clinic hours".
Blinding of outcome assessment (detection bias) subjective outcomes	Unclear risk	No details provided.
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	No information about blinding, but the outcome is unlikely to have been influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No details provided but data on all randomised.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section were reported.

Weddington 1991

Methods	RCT
Participants	N = 83 Age: ˜30 years; sex: male 76%; race: white 69%; diagnosis: cocaine dependence (DSM-III-R); history: cocaine use was 1 g or more per week for 12 weeks. Additional diagnosis: attention deficit disorder, affective and anxiety disorders. Inclusion criteria: cocaine addicts applied for treatment, minimum 1 g cocaine per week for 12 weeks prior to treatment. Exclusion criteria: current abuse/dependence on any substance other than nicotine, medical illness, pregnancy, psychosis, mandated treatment.
Interventions	1. Desipramine 200 mg/day, N = 32 per 12 weeks; 2. Amantadine 400 mg/day, N = 23, per 4 weeks followed placebo per 8 weeks; 3. Placebo, N = 28 per 12 weeks. For all individual interpersonal psychotherapy (both supportive and psychodynamic) twice per week. Setting: outpatient; duration: 12 weeks; country of origin: USA.
Outcomes	Retention in treatment, cocaine use, craving, depression, duration of treatment, participants presenting at least one side effect.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated as "random assignment", no further details provided.
Allocation concealment (selection bias)	Unclear risk	Stated as "random assignment", no further details provided.
Blinding of participants and personnel (performance bias) subjective outcomes	High risk	Only participants were blinded.
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	Only participants were blinded but the outcome is unlikely to have been influenced by lack of blinding.
Blinding of outcome assessment (detection bias) subjective outcomes	High risk	Only participants were blinded.
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	Only participants were blinded but the outcome is unlikely to have been influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	Results only on 54/83 subjects that continued in treatment for 14 days (dropout 35%).

Weddington 1991 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section were reported.

Abbreviations: ASI - Addiction Severity Index; BAI - Beck Anxiety Inventory; BE- benzoylecgonine; BDI - Beck Depression Inventory; BSCS- Brief Substance Craving Scale; BPRS- Brief Psychiatric Rating Scale; CBT- Cognitive Behavioral Therapy; CGI-O- Clinical Global Inventory-Observer; CM - Contingency Management; CSR - Cocaine Status Report; CSSA- Cocaine Selective Severity Assessment; DSM- Diagnostic and Statistic Manual (American Psychiatric Association); HAM-A -Hamilton Anxiety Scale; HAM-D -Hamilton Depression Scale; PANAS - Positive Affect Negative Affect Scale; POMS - Profile of Mood States; SCL-90 R - Symptom Checklist 90-Revised; STAI - State Anxiety Inventory; VBRT - voucher-based reinforcement therapy.

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

Study	Reason for exclusion
Collins 2003	Study design and outcomes measures not in the inclusion criteria.
Collins 2006	Study design and outcomes measures not in the inclusion criteria.
Cunningham 2010	Outcomes measures not in the inclusion criteria.
Dackis 1985	Study design not in the inclusion criteria.
Dackis 1986	Outcomes measures not in the inclusion criteria.
Elkashef 2003	Type of intervention not in the inclusion criteria.
Ersche 2011a	Types of intervention and outcome not in the inclusion criteria.
Ersche 2011b	Types of intervention and outcome not in the inclusion criteria.
Extein 1989	Study design not in the inclusion criteria.
Fairbairn 2008	Outcomes measures not in the inclusion criteria.
Gawin 1985	Study design not in the inclusion criteria.
Gawin 1989	Outcomes measures not in the inclusion criteria.
Haney 1999	Study design not in the inclusion criteria.
Johnson 2006	Type of intervention not in the inclusion criteria.
Kjome 2010	Outcome measures not in the inclusion criteria.
Kosten 2005	Type of intervention not in the inclusion criteria.
Kranzler 1992	Outcomes measures not in the inclusion criteria.
Kumor 1989	Outcomes measures not in the inclusion criteria.
Liu 2014	Outcome measures not in the inclusion criteria.
Malcolm 1994	Type of comparison not in the inclusion criteria.
McDougle 1992	Outcomes measures not in the inclusion criteria.

Study	Reason for exclusion
Montoya 2002	Type of intervention not in the inclusion criteria.
Morgan 1988	Study design not in the inclusion criteria.
Preston 1992	Outcomes measures not in the inclusion criteria.
Robbins 1992	Outcomes measures not in the inclusion criteria.
Rotheram-Fuller 2007	Outcomes measures not in the inclusion criteria.
Shoptaw 2008	Type of intervention not in the inclusion criteria.
Sule 2008	Study design not in the inclusion criteria.
Tennant 1987	Type of comparison not in the inclusion criteria.
Tennant 1990	Type of intervention and study design not in the inclusion criteria.
Winhusen 2007	Type of intervention not in the inclusion criteria.
Wolfsohn 1993	Outcomes measures not in the inclusion criteria.

DATA AND ANALYSES

Comparison 1. Any dopamine agonist versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dropouts	20	1656	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.94, 1.14]
2 Adverse events as N of participants with at least one adverse event	7	252	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.66, 2.44]
3 Abstinence (objective)	11	731	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.85, 1.47]
4 Abstinence at follow-up (objective)	4	136	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.61, 1.98]
5 Severity of dependence (difference before and after)	4	202	Std. Mean Difference (IV, Random, 95% CI)	1.69 [0.17, 3.20]
6 Dropouts due to adverse events	4	368	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.27, 5.38]
7 Craving at the end of treatment	3	151	Std. Mean Difference (IV, Random, 95% CI)	0.20 [-0.35, 0.74]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Clinical global evaluation (end of treatment)	2	70	Std. Mean Difference (IV, Random, 95% CI)	-0.04 [-0.50, 0.43]
9 Depression (difference before and after)	5	292	Std. Mean Difference (IV, Random, 95% CI)	0.47 [-0.35, 1.28]

Analysis 1.1. Comparison 1 Any dopamine agonist versus placebo, Outcome 1 Dropouts.

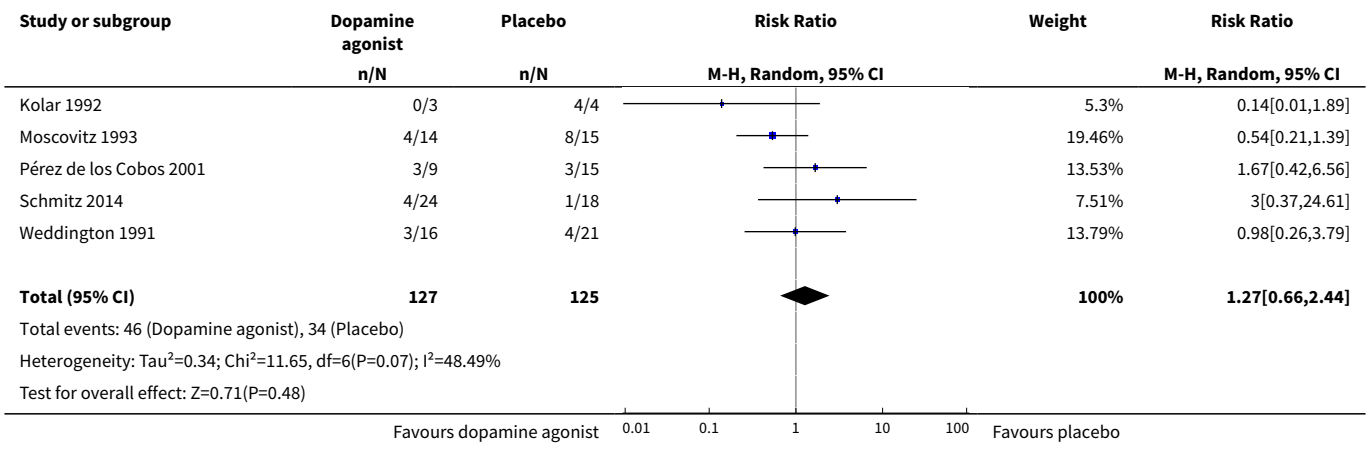
Study or subgroup	Dopamine agonist n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Ciraulo 2005	5/20	7/20		0.93%	0.71[0.27,1.88]
Eiler 1995	17/32	17/31		4.18%	0.97[0.61,1.53]
Giannini 1989	0/10	0/10			Not estimable
Giannini 1989	0/10	0/10			Not estimable
Gorelick 2006	5/35	5/35		0.66%	1[0.32,3.15]
Handelsman 1995	5/42	3/25		0.48%	0.99[0.26,3.8]
Handelsman 1997	6/30	4/30		0.65%	1.5[0.47,4.78]
Kampman 1996	11/30	12/30		2.11%	0.92[0.48,1.74]
Kampman 2006	24/50	22/49		4.84%	1.07[0.7,1.63]
Kolar 1992	2/5	5/9		0.58%	0.72[0.21,2.44]
Kosten 1992	8/33	4/31		0.73%	1.88[0.63,5.62]
Malcolm 2000	220/309	89/153		36.59%	1.22[1.05,1.42]
Mooney 2007a	20/31	25/36		7.53%	0.93[0.66,1.3]
Mooney 2007b	45/82	25/40		9%	0.88[0.64,1.2]
Moscovitz 1993	9/14	10/15		3.1%	0.96[0.57,1.64]
Pérez de los Cobos 2001	10/19	6/21		1.36%	1.84[0.83,4.1]
Schmitz 2008	35/68	35/68		8.13%	1[0.72,1.39]
Schmitz 2014	14/25	7/18		1.91%	1.44[0.73,2.83]
Shoptaw 2002	23/34	31/35		12.65%	0.76[0.59,0.99]
Shoptaw 2005	23/45	9/15		3.45%	0.85[0.52,1.41]
Weddington 1991	7/23	7/28		1.1%	1.22[0.5,2.97]
Total (95% CI)	**947**	**709**		**100%**	**1.04[0.94,1.14]**
Total events: 489 (Dopamine agonist), 323 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=18.07, df=18(P=0.45); I^2=0.4%					
Test for overall effect: Z=0.75(P=0.46)					

Favours dopamine agonist — Favours placebo

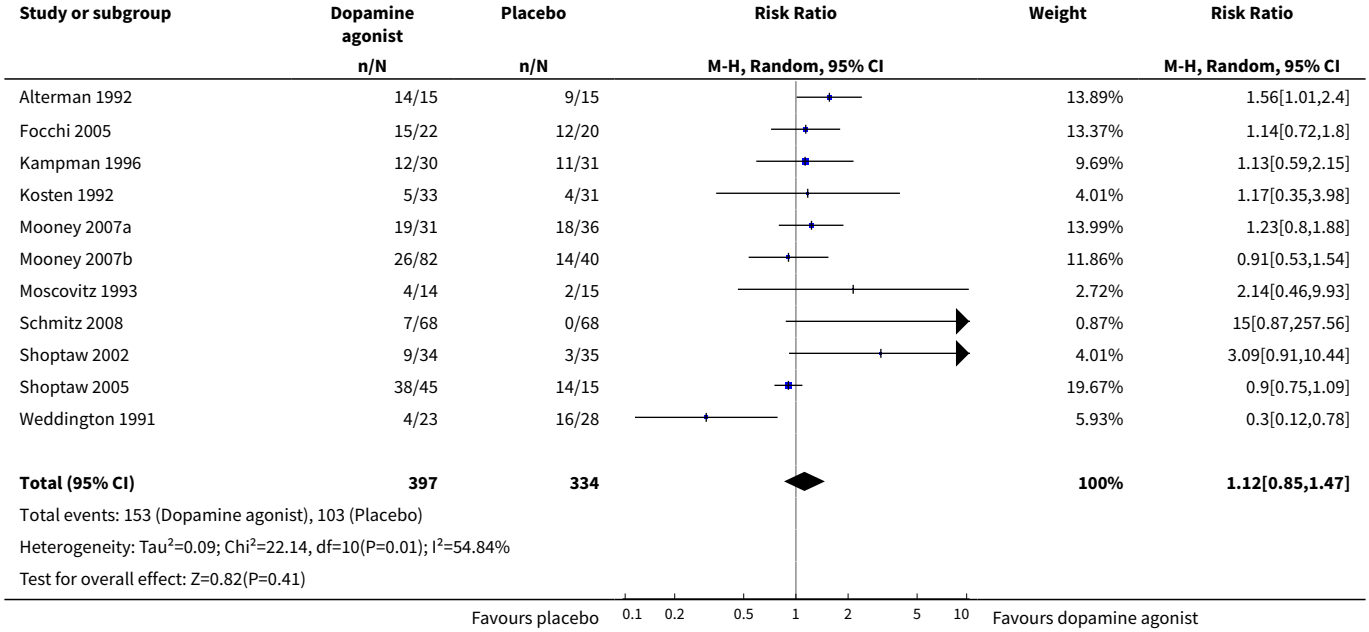
Analysis 1.2. Comparison 1 Any dopamine agonist versus placebo, Outcome 2 Adverse events as N of participants with at least one adverse event.

Study or subgroup	Dopamine agonist n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Gorelick 2006	16/30	12/30		26.81%	1.33[0.77,2.31]
Kampman 2006	16/31	2/22		13.6%	5.68[1.45,22.22]

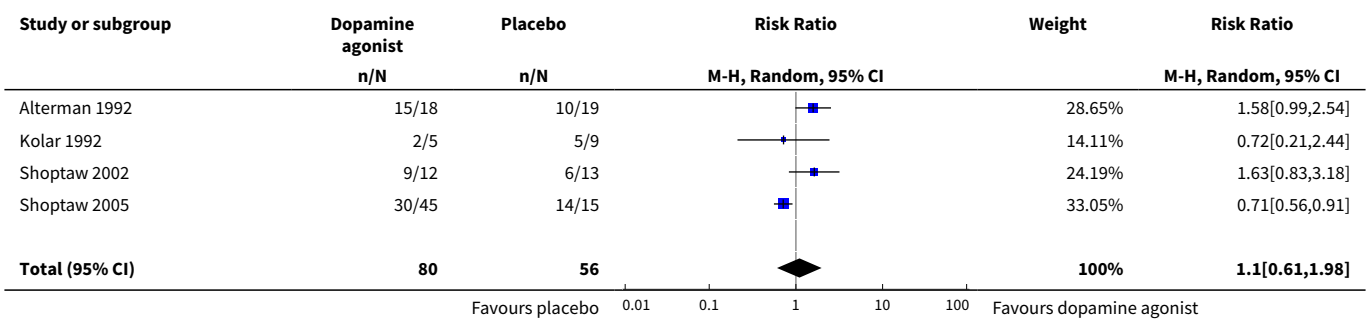
Favours dopamine agonist — Favours placebo

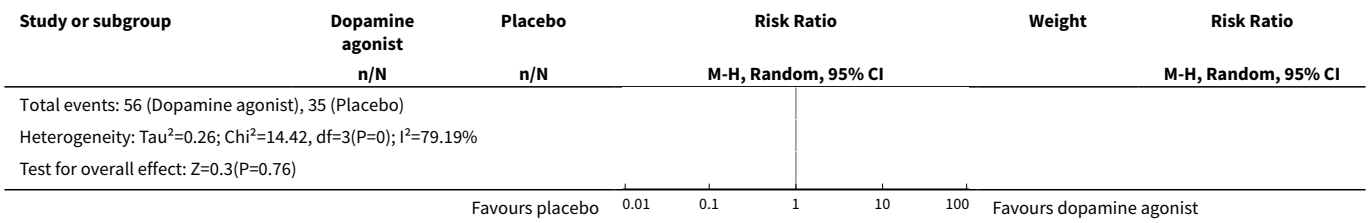


Analysis 1.3. Comparison 1 Any dopamine agonist versus placebo, Outcome 3 Abstinence (objective).

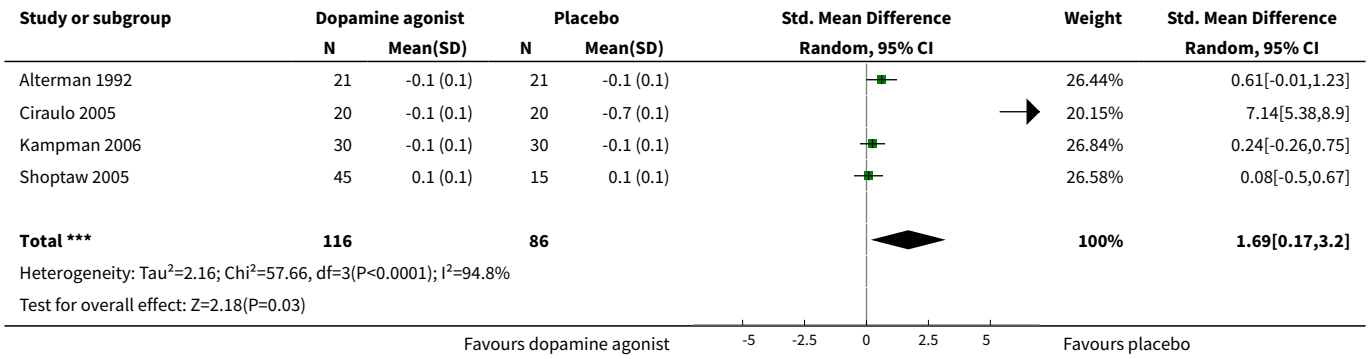


Analysis 1.4. Comparison 1 Any dopamine agonist versus placebo, Outcome 4 Abstinence at follow-up (objective).

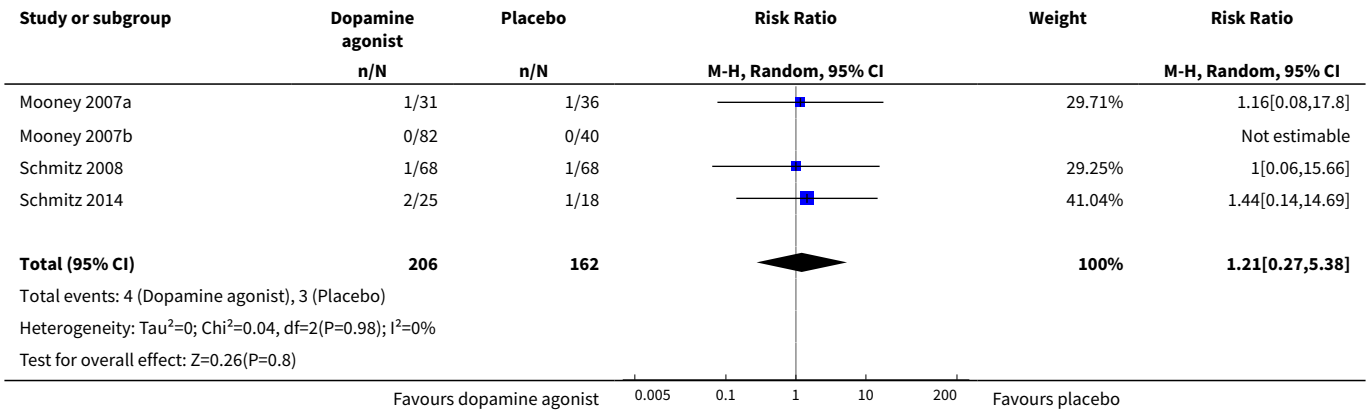




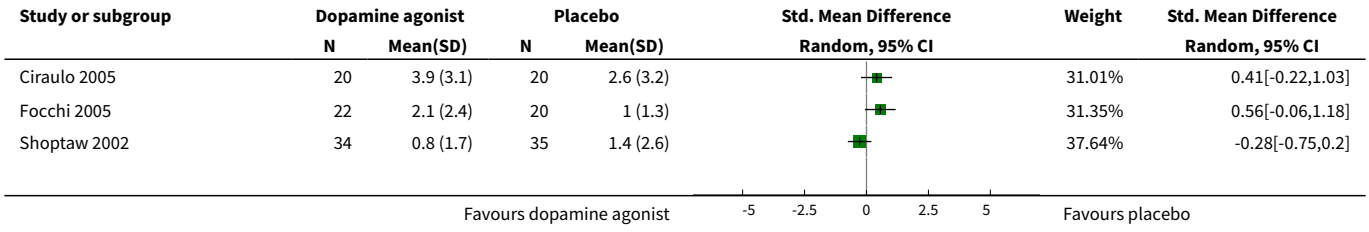
Analysis 1.5. Comparison 1 Any dopamine agonist versus placebo, Outcome 5 Severity of dependence (difference before and after).

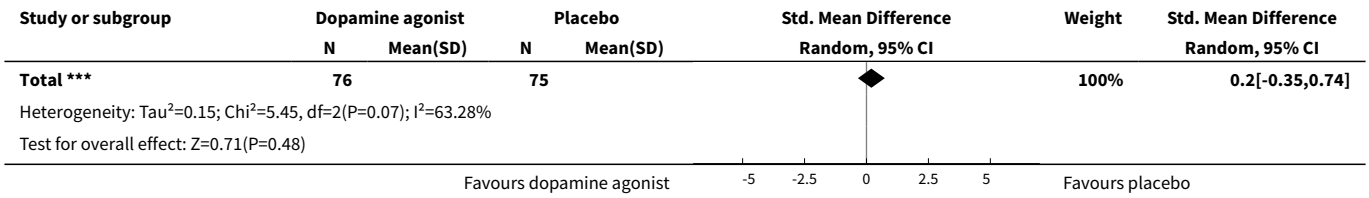


Analysis 1.6. Comparison 1 Any dopamine agonist versus placebo, Outcome 6 Dropouts due to adverse events.

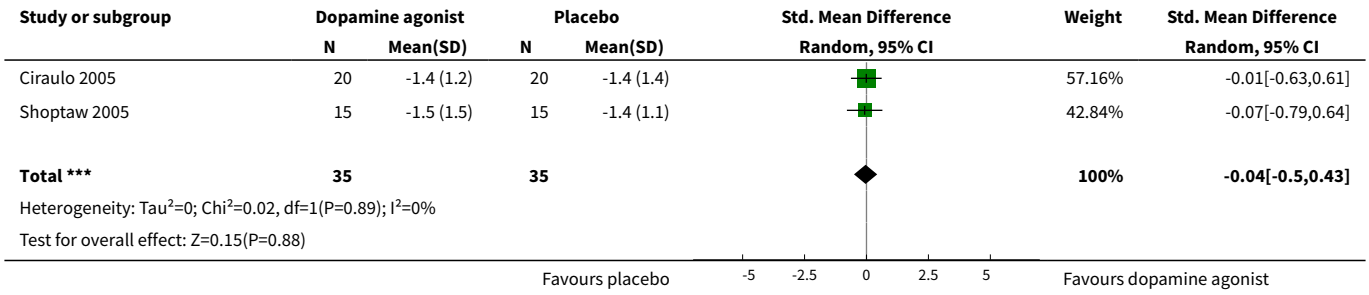


Analysis 1.7. Comparison 1 Any dopamine agonist versus placebo, Outcome 7 Craving at the end of treatment.

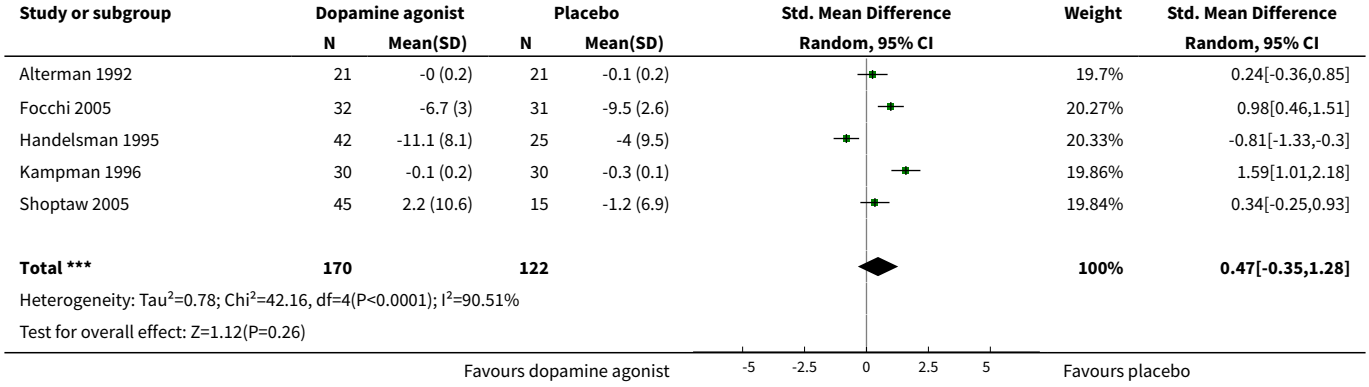




Analysis 1.8. Comparison 1 Any dopamine agonist versus placebo, Outcome 8 Clinical global evaluation (end of treatment).



Analysis 1.9. Comparison 1 Any dopamine agonist versus placebo, Outcome 9 Depression (difference before and after).



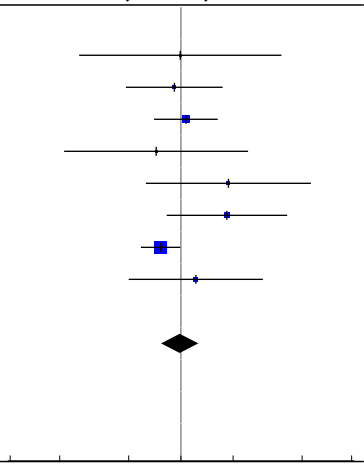
Comparison 2. Amantadine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dropouts	9	484	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.77, 1.26]
2 Adverse events as N of participants with at least one adverse event	4	128	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.69, 2.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Abstinence (objective)	5	275	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.59, 2.13]
4 Abstinence at follow-up (objective)	3	76	Risk Ratio (M-H, Random, 95% CI)	1.49 [1.03, 2.15]
5 Severity of dependence (difference before and after)	2	102	Std. Mean Difference (IV, Random, 95% CI)	0.39 [-0.00, 0.79]
6 Depression (difference before and after)	2	109	Std. Mean Difference (IV, Random, 95% CI)	-0.30 [-1.33, 0.74]

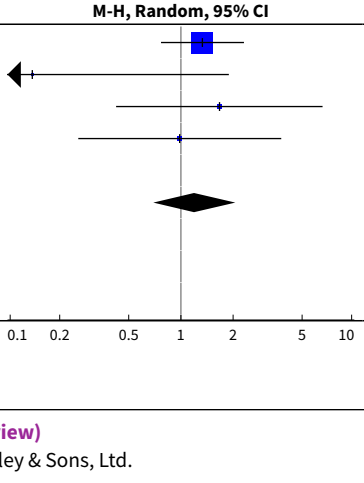
Analysis 2.1. Comparison 2 Amantadine versus placebo, Outcome 1 Dropouts.

Study or subgroup	Amantadine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Giannini 1989	0/10	0/10			Not estimable
Handelsman 1995	5/42	3/25		3.25%	0.99[0.26,3.8]
Kampman 1996	11/30	12/30		12.15%	0.92[0.48,1.74]
Kampman 2006	24/50	22/49		22.55%	1.07[0.7,1.63]
Kolar 1992	2/5	5/9		3.88%	0.72[0.21,2.44]
Kosten 1992	8/33	4/31		4.76%	1.88[0.63,5.62]
Pérez de los Cobos 2001	10/19	6/21		8.41%	1.84[0.83,4.1]
Shoptaw 2002	23/34	31/35		38.05%	0.76[0.59,0.99]
Weddington 1991	7/23	7/28		6.95%	1.22[0.5,2.97]
Total (95% CI)	**246**	**238**		**100%**	**0.98[0.77,1.26]**
Total events: 90 (Amantadine), 90 (Placebo)					
Heterogeneity: Tau^2=0.02; Chi^2=8.71, df=7(P=0.27); I^2=19.59%					
Test for overall effect: Z=0.13(P=0.9)					

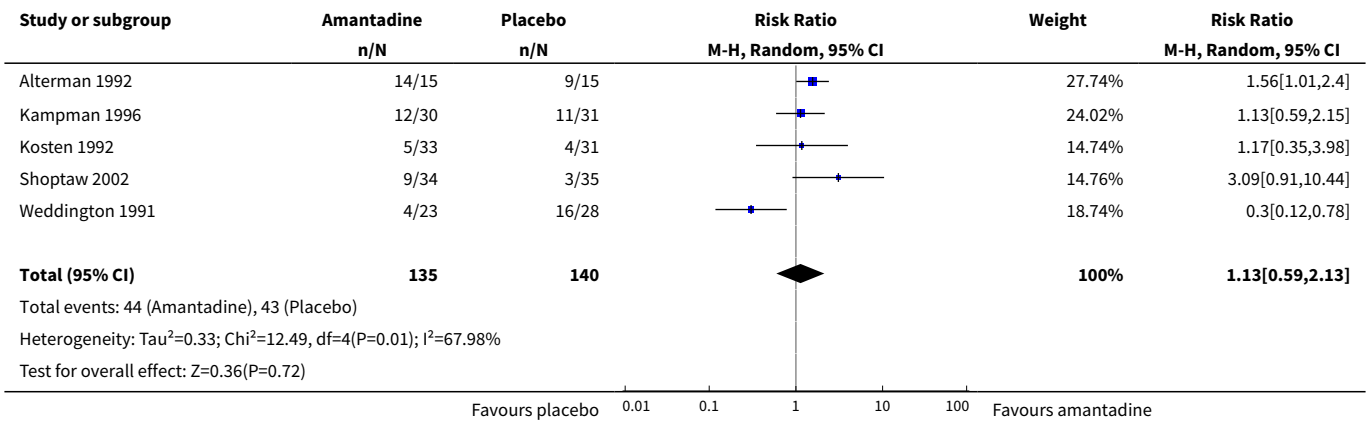


Analysis 2.2. Comparison 2 Amantadine versus placebo, Outcome 2 Adverse events as N of participants with at least one adverse event.

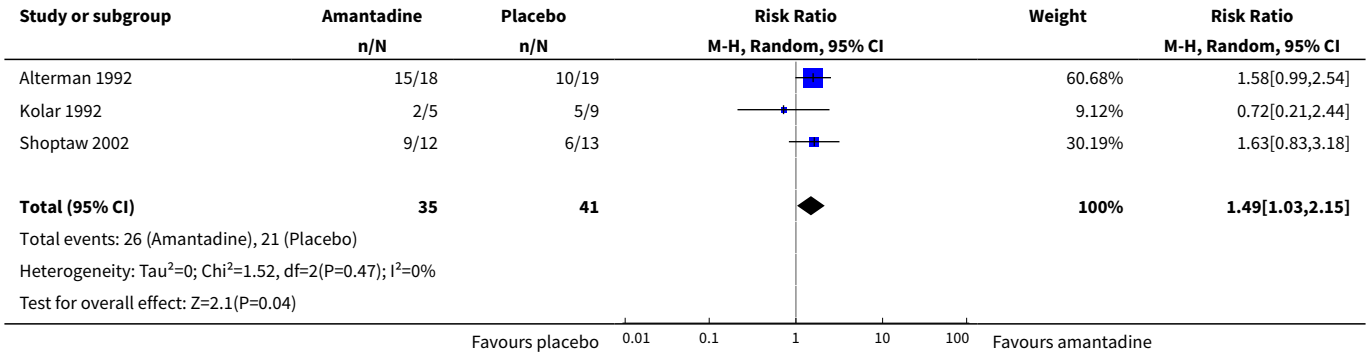
Study or subgroup	Amantadine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Kampman 1996	16/30	12/30		65.95%	1.33[0.77,2.31]
Kolar 1992	0/3	4/4		4.27%	0.14[0.01,1.89]
Pérez de los Cobos 2001	3/9	3/15		14.67%	1.67[0.42,6.56]
Weddington 1991	3/16	4/21		15.12%	0.98[0.26,3.79]
Total (95% CI)	**58**	**70**		**100%**	**1.19[0.69,2.06]**
Total events: 22 (Amantadine), 23 (Placebo)					
Heterogeneity: Tau^2=0.04; Chi^2=3.29, df=3(P=0.35); I^2=8.83%					
Test for overall effect: Z=0.64(P=0.52)					



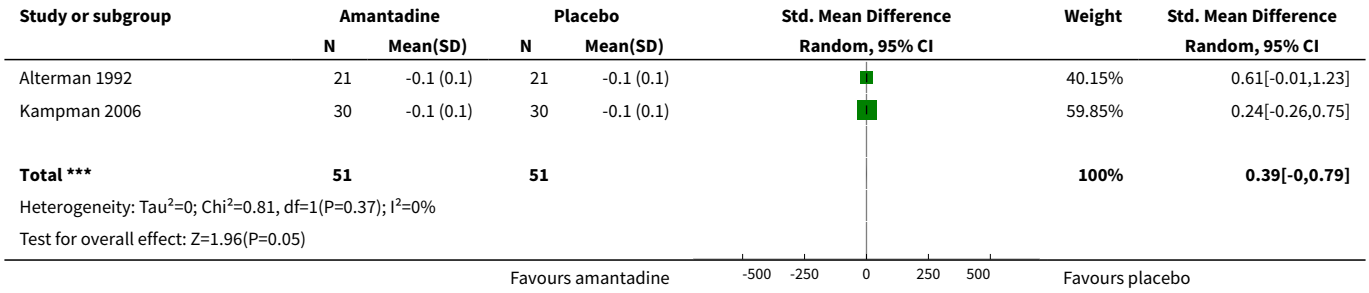
Analysis 2.3. Comparison 2 Amantadine versus placebo, Outcome 3 Abstinence (objective).



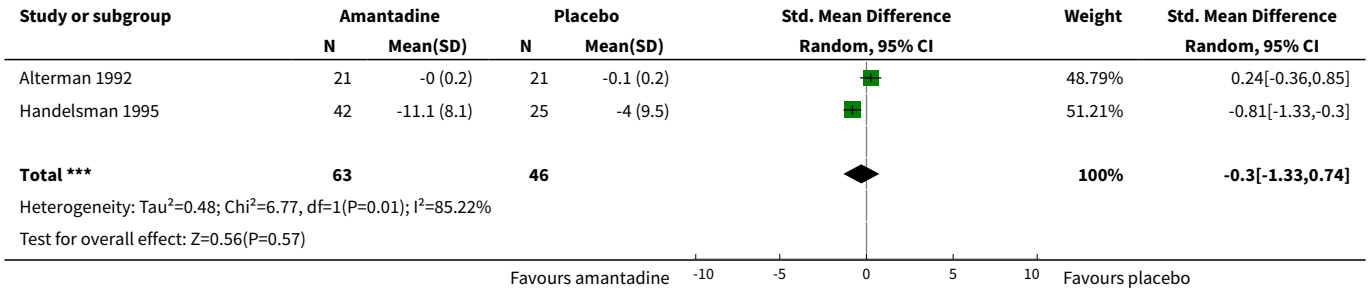
Analysis 2.4. Comparison 2 Amantadine versus placebo, Outcome 4 Abstinence at follow-up (objective).



Analysis 2.5. Comparison 2 Amantadine versus placebo, Outcome 5 Severity of dependence (difference before and after).



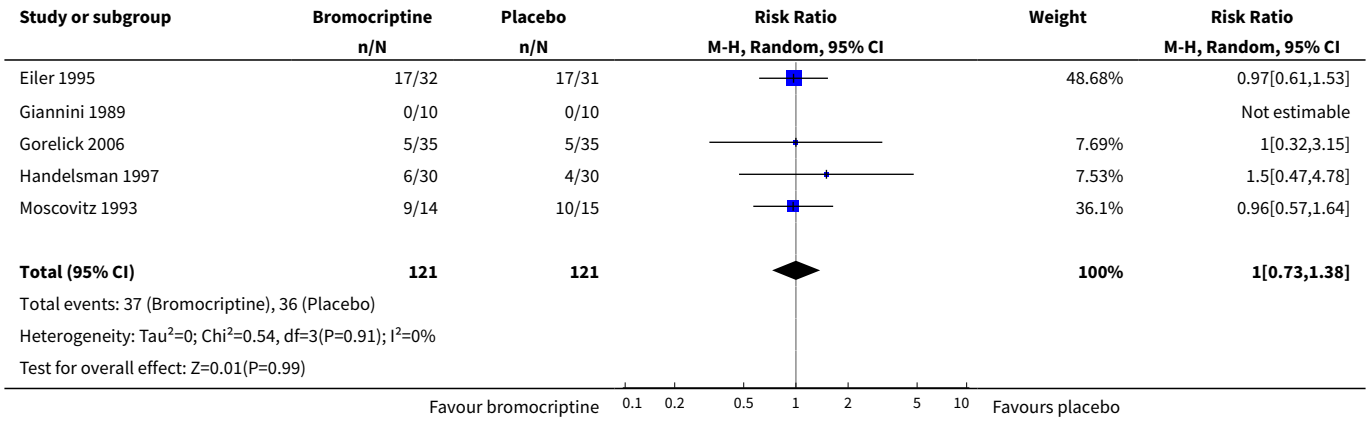
Analysis 2.6. Comparison 2 Amantadine versus placebo, Outcome 6 Depression (difference before and after).



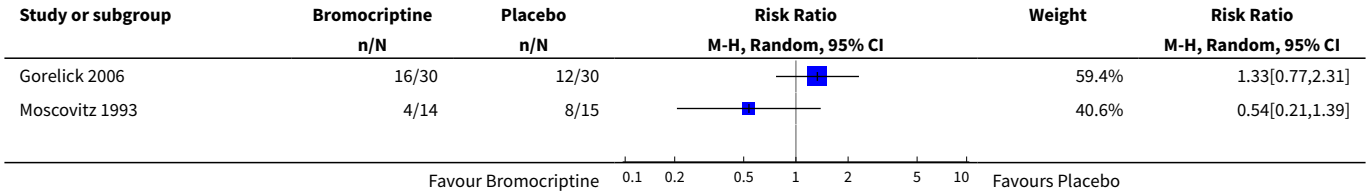
Comparison 3. Bromocriptine versus placebo

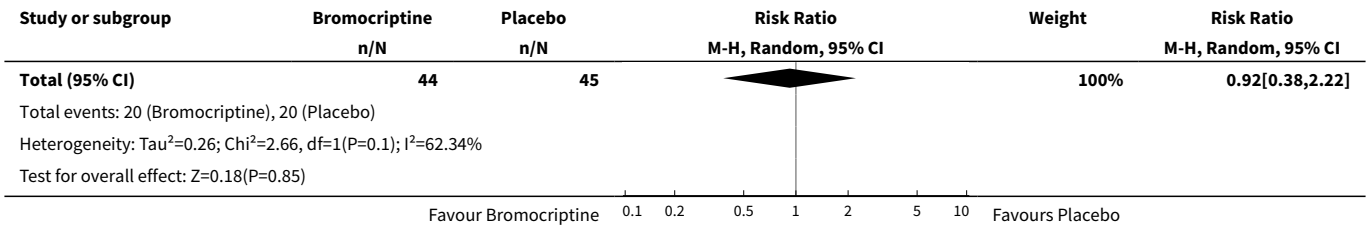
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dropouts	5	242	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.73, 1.38]
2 Adverse events as N of participants with at least one adverse event	2	89	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.38, 2.22]

Analysis 3.1. Comparison 3 Bromocriptine versus placebo, Outcome 1 Dropouts.



Analysis 3.2. Comparison 3 Bromocriptine versus placebo, Outcome 2 Adverse events as N of participants with at least one adverse event.

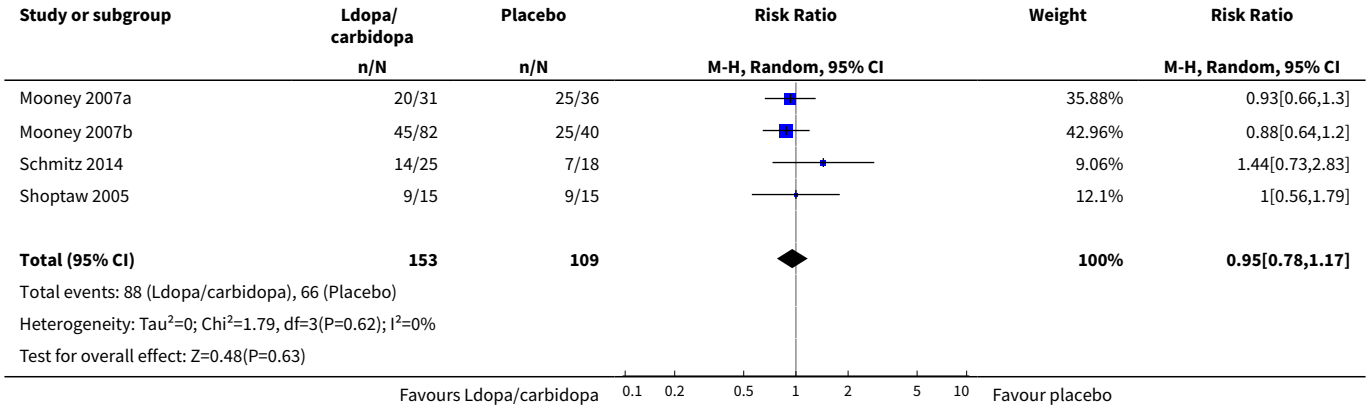




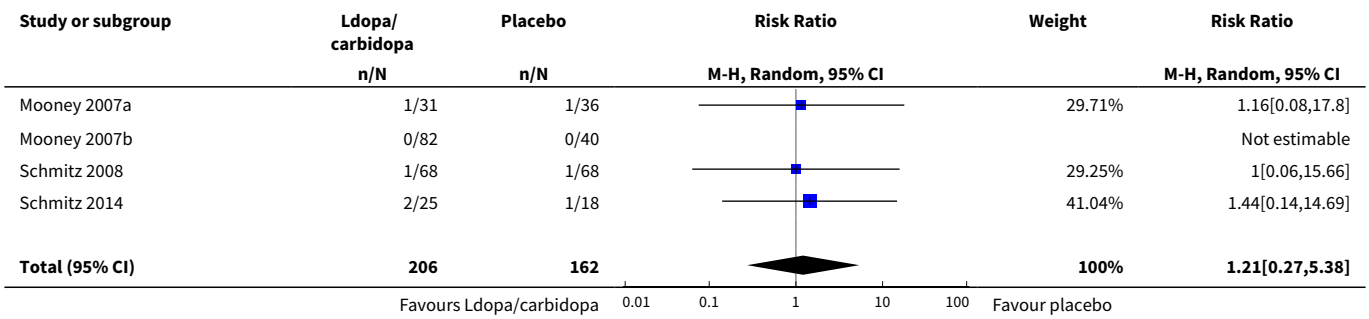
Comparison 4. L dopa/carbidopa versus placebo

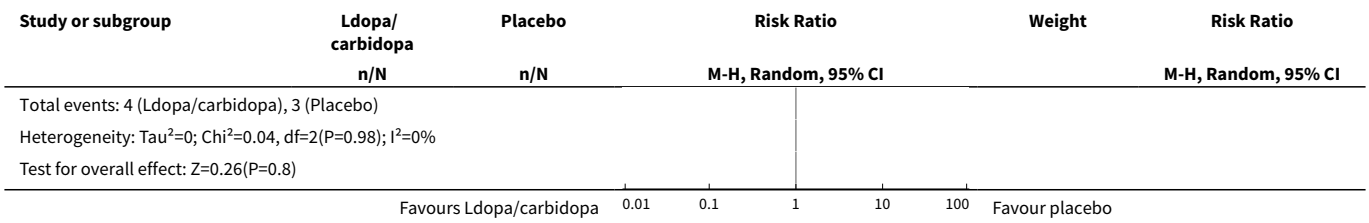
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dropouts	4	262	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.78, 1.17]
2 Dropouts due to adverse events	4	368	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.27, 5.38]
3 Abstinence (objective)	4	355	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.80, 1.52]

Analysis 4.1. Comparison 4 L dopa/carbidopa versus placebo, Outcome 1 Dropouts.

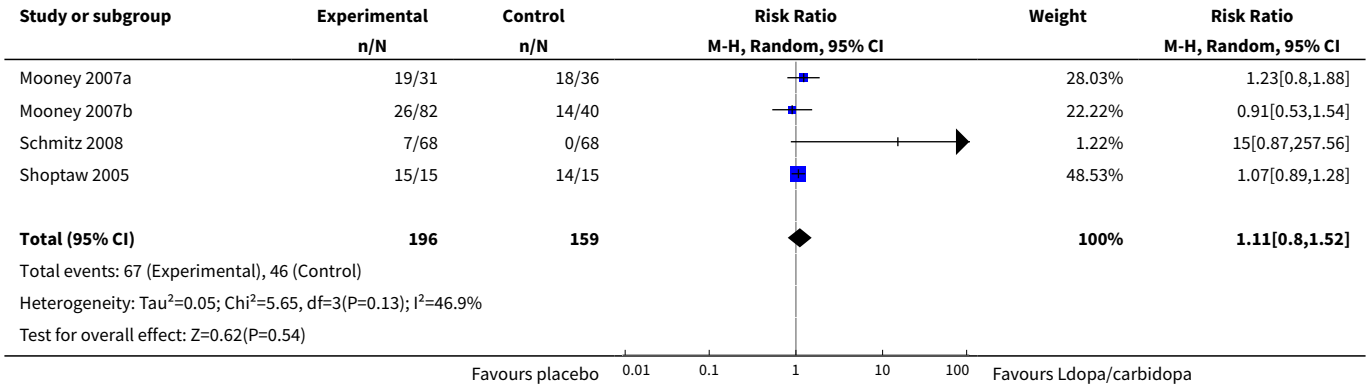


Analysis 4.2. Comparison 4 L dopa/carbidopa versus placebo, Outcome 2 Dropouts due to adverse events.





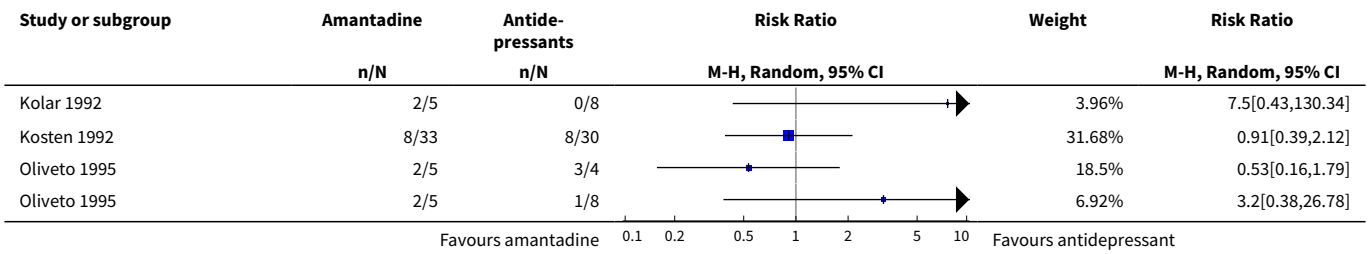
Analysis 4.3. Comparison 4 L dopa/carbidopa versus placebo, Outcome 3 Abstinence (objective).

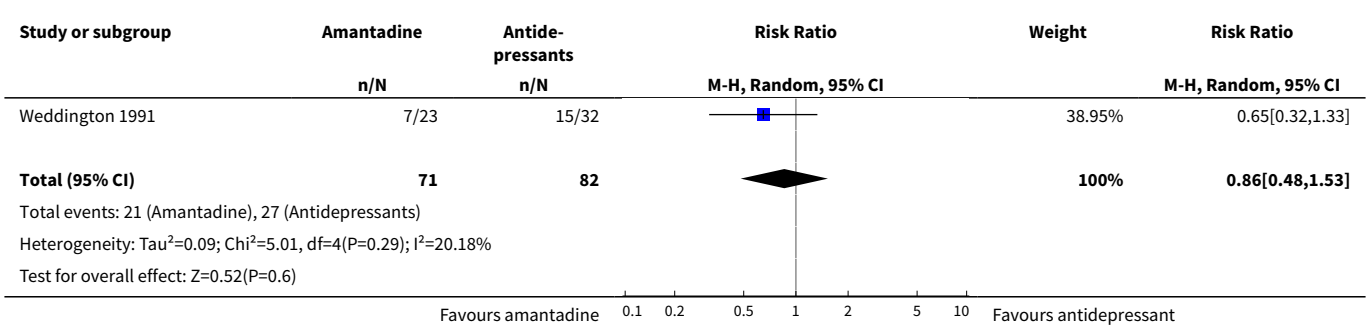


Comparison 5. Amantidine versus antidepressants

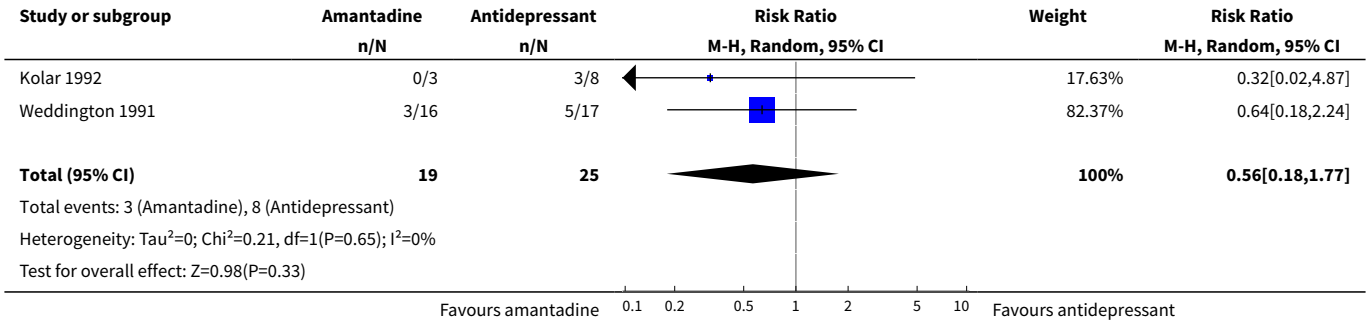
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dropouts	4	153	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.48, 1.53]
2 Adverse events as N of participants with at least one adverse event	2	44	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.18, 1.77]
3 Abstinence (objective)	2	68	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.12, 0.53]

Analysis 5.1. Comparison 5 Amantidine versus antidepressants, Outcome 1 Dropouts.

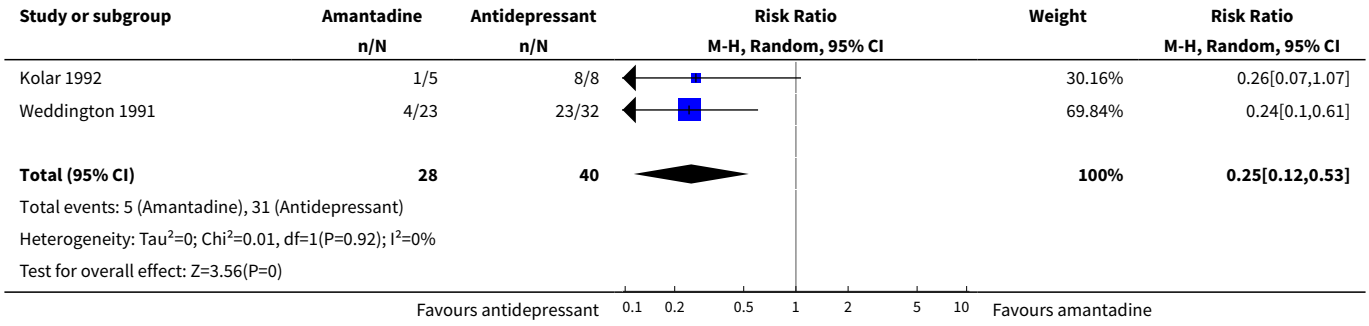




Analysis 5.2. Comparison 5 Amantidine versus antidepressants, Outcome 2 Adverse events as N of participants with at least one adverse event.



Analysis 5.3. Comparison 5 Amantidine versus antidepressants, Outcome 3 Abstinence (objective).



ADDITIONAL TABLES

Table 1. 'Risk of bias' assessment of included studies

Item	Judgment	Description
1. Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process such as: random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; or minimization.

Table 1. 'Risk of bias' assessment of included studies *(Continued)*

	High risk	The investigators describe a non-random component in the sequence generation process such as: odd or even date of birth; date (or day) of admission; hospital or clinic record number; alternation; judgement of the clinician; results of a laboratory test or a series of tests; or availability of the intervention.
	Unclear risk	Insufficient information about the sequence generation process to permit judgement of low or high risk.
2. Allocation concealment (selection bias)	Low risk	Investigators 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 nonopaque 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 low or high risk. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement.
3. Blinding of participants and providers (performance bias) subjective outcomes	Low risk	• No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; • Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk	• No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; • Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear risk	• Insufficient information to permit judgement of low or high risk.
4. Blinding of participants and providers (performance bias) objective outcomes	Low risk	• No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; • Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk	• No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; • Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear risk	• Insufficient information to permit judgement of low or high risk.
5. Blinding of outcome assessor (detection bias) Subjective outcomes	Low risk	• No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; • Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.

Table 1. 'Risk of bias' assessment of included studies *(Continued)*

	High risk	• No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; • Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear risk	• Insufficient information to permit judgement of low or high risk.
6. Blinding of outcome assessor (detection bias) objective outcomes	Low risk	• No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; • Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk	• No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; • Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear risk	• Insufficient information to permit judgement of low or high risk.
7. Incomplete outcome data (attrition bias) For all outcomes except retention in treatment or dropout	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 (ITT).
	High risk	• Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; • 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation.
	Unclear risk	• Insufficient information to permit judgement of low or high risk (e.g. number randomised not stated, no reasons for missing data provided; number of dropouts not reported for each group).
8. Selective reporting (reporting bias)	Low risk	• The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way;

Table 1. 'Risk of bias' assessment of included studies *(Continued)*

	• The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
High risk	• Not all of the study's pre-specified primary outcomes have been reported; • One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; • One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); • One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; • The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Unclear risk	• Insufficient information to permit judgement of low or high risk.

APPENDICES

Appendix 1. Search strategies June 2011

1. Cochrane Central Register of Controlled Trials (CENTRAL - the Cochrane Library, most recent);
2. PubMed (1966 to 1 June 2011);
3. EMBASE (1988 - to 1 June 2011);
4. CINAHL (1982 to 1 June 2011);
5. PsycINFO (1967 to 1 June 2011).

CENTRAL

1. MESH DESCRIPTOR¬ COCAINE-RELATED DISORDERS EXPLODE ALL TREES
2. ((DRUG OR SUBSTANCE) NEAR2 (ABUSE* OR¬ MISUSE* OR ADDICT* OR DEPENDEN*):TI,AB
3. #1 OR #2
4. MESH DESCRIPTOR¬ COCAINE EXPLODE ALL TREES
5. COCAINE :TI,AB
6. #4 OR #5
7. MESH DESCRIPTOR DOPAMINE AGONISTS EXPLODE ALL TREES
8. MeSH descriptor Levodopa explode all trees
9. DOPAMINE OR AMANTADINE OR BROMOCRIPTINE OR MAZINDOL OR PERGOLIDE OR LEVODOPA
10. #7 OR #8 OR #9
11. #3 AND #6 AND #10

EMBASE, PubMed on platform STN (Scientific & Technical Information Network)

1. COCAINE–RELATED DISORDER/CT
2. COCAINE DEPENDENCE/CT
3. (ADDICT? OR ABUSE? OR DEPENDEN? OR DISORDER?)/TI,AB¬
4. (COCAINE/CT OR COCAINE/TI,AB)
5. 1 OR 2 OR 3
6. 4 AND 5
7. DOPAMINE AGONIST/CT
8. DOPAMINE AGONIST#
9. LEVODOPA/CT
10. AMANTADINE*NT/CT OR AMANTADINE/TI,AB

11. BROMOCRIPTINE/CT OR BROMOCRIPTINE/TI,AB
12. PERGOLIDE/CT OR PERGOLIDE/TI,AB
13. LEVODOPA/TI,AB
14. DOPAMINE(S)AGONIST#/TI,AB
15. DOPAMINE RECEPTOR STIMULATING AGENT/CT
16. 6 AND (7-15)
17. RANDOMIZED CONTROLLED TRIAL/DT
18. RANDOMIZED CONTROLLED TRIAL/CT
19. CONTROLLED CLINICAL TRIAL/DT
20. PHASE 2 CLINICAL TRIAL/CT
21. PHASE 3 CLINICAL TRIAL/CT
22. DOUBLE BLIND PROCEDURE/CT
23. SINGLE BLIND PROCEDURE/CT
24. CROSSOVER PROCEDURE/CT
25. LATIN SQUARE DESIGN/CT
26. PLACEBO/CT
27. MULTICENTER STUDY/CT
28. DRUG THERAPY+NT/CT
29. RANDOM?/TI,AB
30. PLACEBO/TI,AB OR PLACEBOS/TI,AB
31. CROSSOVER?/TI,AB
32. TRIAL# OR GROUP#)/TI,AB
33. (SINGL? OR DOUBL? OR TREBL? OR TRIPL?)/TI,AB(S)(BLIND? OR MASK?)/TI,AB
34. 16 AND (17-33)
35. 34/HUMAN

PsycINFO

1. COCAINE-DEPENDENCE.KW.
2. COCAINE-RELATED-DISORDERS.KW
3. (ADDICT$4 OR DISORDER$1 OR DEPENDEN$3 OR ABUSE$1).TI,AB.
4. COCAINE.KW,TI,AB.
5. 4 AND (1 OR 2 OR 3)
6. MENTAL-HEALTH-PROGRAMME-EVALUATION.KW.
7. TREATMENT-EFFECTIVENESS-EVALUATION
8. PLACEBO.KW.
9. PLACEBO$1.TI,AB.
10. RANDOM$6.KW,TI,AB.
11. ((SINGL$2 OR DOUBL$3 OR TREVL$3 OR TRIPL$4) NEAR (BLIND$4 OR MASK$4 OR DUMMY)).TI,AB.
12. (FACTORIAL$1 OR ALLOCAT$5 OR ASSIGN$5 OR VOLUNTEER$1).TI,AB.
13. (CROSSOVER$).TI,AB.¬ OR (CROSS ADJ OVER$1).TI,AB.
14. (QUASI ADJ EXPERIMENTAL).TI,AB.
15. ((CONTROL$5 NEAR (TRIAL$1 OR STUDY OR STUDIES OR GROUP$1))).TI,AB.
16. 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15
17. 5 AND 16
18. (DOPAMINE-AGONIST.KW.)
19. (DOPAMINE ADJ AGONIST$1).TI,AB.
20. (DOPAMINE ADJ RECEPTOR$1 ADJ STIMULATING ADJ AGENT$1).TI,AB.
21. AMANTADINE.KW,TI,AB.
22. BROMOCRIPTINE.KW,TI,AB.
23. PERGOLIDE.KW,TI,AB.
24. LEVODOPA.KW,TI,AB.
25. 17 AND (18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24)

CINAHL (EBSCO)

1. MH SUBSTANCE ABUSE
2. ((DRUG OR SUBSTANCE OR COCAINE) AND (ABUSE* OR DEPENDEN* OR ADDICT* OR DISORDER*))
3. S1 OR S2
4. TX COCAINE OR MH COCAINE
5. S3 AND S4
6. (MH “DOPAMINE AGONISTS”)
7. TX DOPAMINE OR TX AMANTADINE OR TX BROMOCRIPTINE OR TX MAZINDOL OR TX PERGOLIDE OR TX LEVODOPA
8. S6 OR S7
9. TX RANDOM*
10. TX (CLINICAL AND TRIAL*)
11. TX ((SINGL* OR DOUBL* OR TRIPL* OR TREBL*) AND (MASK* OR BLIND*))
12. TX (CROSSOVER* OR ALLOCAT* OR¬ ASSIGN*)
13. MH RANDOM ASSIGNMENT/
14. MH CLINICAL TRIALS/
15. S9 OR S10 OR S11 OR S12 OR S13 OR S14
16. S5 AND S8 AND S15

Appendix 2. Search strategies 2015

CDAG Specialized Register (via CRS)

1. ((dopamine OR amantadine OR bromocriptine OR mazindol OR pergolide OR levodopa)ti,ab,kw) AND (INREGISTER)
2. (cocaine :ti,ab,ky,xdi) AND (INREGISTER)
3. #1 AND #2

CENTRAL

1. MeSH descriptor: [Cocaine-Related Disorders] explode all trees
2. ((drug* or substance) near/2 (abus* or misus* or addict* or dependen*)):ti,ab
3. #1 or #2
4. cocaine:ti,ab,kw (Word variations have been searched)
5. #3 and #4
6. (DOPAMINE or AMANTADINE or BROMOCRIPTINE or MAZINDOL or PERGOLIDE or LEVODOPA):ti,ab,kw (Word variations have been searched)
7. #5 and #6

MEDLINE (via PubMed)

1. "Cocaine-Related Disorders"[Mesh]
2. ((cocaine*[tiab]) AND (abuse*[tiab] OR addict*[tiab] OR dependen*[tiab]))
3. #1 OR #2
4. "Dopamine Agonists"[Mesh]
5. dopamine OR amantadine OR bromocriptine OR mazindol OR pergolide OR levodopa
6. #4 OR #5
7. randomized controlled trial [pt]
8. controlled clinical trial [pt]
9. randomized [tiab]
10. placebo [tiab]
11. clinical trials as topic [mesh: noexp]
12. randomly [tiab]
13. trial [ti]
14. #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
15. animals [mh] NOT humans [mh]
16. #14 NOT #15
17. #3 AND #6 AND #16

EMBASE (via embase.com)

'cocaine dependence'/exp OR (cocaine:ab,ti AND (abus*:ab,ti OR dependen*:ab,ti OR disorder*:ab,ti OR addict*:ab,ti)) AND ('dopamine receptor stimulating agent'/exp OR 'dopamine' OR 'amantadine' OR 'mazindol' OR pergolide OR 'levodopa') AND ('randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'controlled clinical trial'/exp OR 'clinical trial'/exp OR placebo:ab,ti OR 'double blind':ab,ti OR 'single blind':ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR random*:ab,ti OR factorial*:ab,ti OR crossover:ab,ti OR (cross:ab,ti AND over:ab,ti))

CINAHL (via EBSCOHOST)

1. (MH "Substance Abuse+")
2. TX((drug* or substance or cocaine) N3 (abus* or depend* or addict* or disorder*))
3. S1 OR S2
4. TI cocaine OR AB cocaine OR MH cocaine
5. S3 AND S4
6. (MH "Dopamine Agonists+")
7. TX DOPAMINE OR TX AMANTADINE OR TX BROMOCRIPTINE OR TX MAZINDOL OR TX PERGOLIDE OR TX LEVODOPA
8. S6 OR S7
9. S5 AND S8
10. MH "Clinical Trials+"
11. PT Clinical trial
12. TI clinic* N1 trial* or AB clinic* N1 trial*
13. TI (singl* or doubl* or trebl* or tripl*) and TI (blind* or mask*)
14. AB (singl* or doubl* or trebl* or tripl*) and AB (blind* or mask*)
15. TI randomi?ed control* trial* or AB randomi?ed control* trial*
16. MH "Random Assignment"
17. TI random* allocat* or AB random* allocat*
18. MH "Placebos"
19. TI placebo* or AB placebo*
20. MH "Quantitative Studies"
21. S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20
22. S9 AND S21

Web of Science

Indexes=SCI-EXPANDED, SSCI, A&HCI Timespan=All years

1. TS=(((cocaine* OR crack) AND (abuse* OR depend* OR addict* OR disorder* OR detox* OR withdraw* OR abstinen* OR abstain*)))
2. TS=(dopamine OR amantadine OR bromocriptine OR mazindol OR pergolide OR levodopa)
3. TS= clinical trial* OR TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=controlled trial* OR TS=follow-up stud* OR TS=prospective stud* OR TS=random* OR TS=placebo* OR TS=(single blind*) OR TS=(double blind*)
4. #1 AND #2 AND #3

WHAT'S NEW

Date	Event	Description
27 May 2015	Amended	typo correction

HISTORY

Protocol first published: Issue 1, 2001
Review first published: Issue 4, 2001

Date	Event	Description
3 April 2015	New citation required but conclusions have not changed	We included one new trial, and conclusions were not changed.
3 April 2015	New search has been performed	We performed a new search up to 12 January 2015.
12 October 2011	New citation required and conclusions have changed	New authors, new searches, new studies
12 October 2011	New search has been performed	New authors, new searches, new studies
21 April 2008	Amended	Converted to new review format.
25 February 2003	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

For the 2011 update,two review authors (SV, RS) developed the literature search strategy. Two review authors (SV, RS) inspected the search hits by reading titles and abstracts. We obtained each potentially relevant study located in the search in full text. Two review authors (LA, SM) independently assessed each article for inclusion. We resolved any disagreements by discussion between all review authors. Two review authors (SM, LA) assessed quality of the included trials. Two review authors (LA, SM) extracted data independently . Any disagreement was resolved by discussion between all review authors. PPP wrote the Background section and participated to results's discussion. MD and PGZ commented on and amended the review text.

For this review update, SM and FDC inspected the search hits by reading titles and abstracts. We obtained each potentially relevant study in full text and two review authors (SM, FDC) independently assessed articles for inclusion or exclusion.

DECLARATIONS OF INTEREST

Silvia Minozzi have no interests to declare relating to this work.

Laura Amato have no interests to declare relating to this work.

Pier Paolo Pani have no interests to declare relating to this work.

Roberta Solimini have no interests to declare relating to this work.

Simona Vecchi have no interests to declare relating to this work.

Franco De Crescenzo have no interests to declare relating to this work.

Pier Giorgio Zuccaro have no interests to declare relating to this work.

Marina davoli have no interests to declare relating to this work.

SOURCES OF SUPPORT

Internal sources

- Department of Epidemiology, Lazio Regional Health Service, ASL RM E, Italy.

External sources

- Italian Drug Agency, Italy.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This Cochrane Review is a substantial update, which has been performed by a new review author team several years after the first published version of the review (Soares 2003). We changed the Methods section substantially in accordance with developments within Cochrane.

NOTES

The review authors of the first published version of this review (Soares 2003) did not update this review and did not respond to our reminders to update it. The topic is considered relevant and therefore we decided to withdraw the review and make it available to a new author team.

INDEX TERMS

Medical Subject Headings (MeSH)

Amantadine [therapeutic use]; Antidepressive Agents [therapeutic use]; Bromocriptine [therapeutic use]; Cocaine-Related Disorders [*drug therapy]; Depression [drug therapy]; Dopamine Agonists [*therapeutic use]; Levodopa [therapeutic use]; Randomized Controlled Trials as Topic; Selection Bias

MeSH check words

Humans