Dopamine agonists for the treatment of cocaine dependence (Review)

Amato L, Minozzi S, Pani PP, Solimini R, Vecchi S, Zuccaro P, Davoli M

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[Intervention Review]

Dopamine agonists for the treatment of cocaine dependence

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ABSTRACT

Background

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

Objectives

To investigate the efficacy and acceptability of dopamine agonists alone or in combination with any psychosocial intervention for the treatment of cocaine abuse and dependence

Search methods

We searched the Cochrane Drugs and Alcohol Group (CDAG) Specialized Register, PubMed, EMBASE and CINAHL, PsycINFO in June 2011 and researchers for unpublished trials

Selection criteria

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

Data collection and analysis

Two authors independently assessed trial quality and extracted data

Main results

Twenty three studies, 2066 participants, met the inclusion criteria. Comparing any dopamine agonist versus placebo, placebo performed better for severity of dependence, four studies, 232 participants, SMD 0.43 (95% CI 0.15 to 0.71), depression, five studies, 322 participants, SMD 0.42 (95% CI 0.19 to 0.65) and abstinent at follow up RR 0.57 (95% CI 0.35 to 0.93). No statistically significant different for the other outcomes considered. Comparing amantadine versus placebo, results never gain the statistical significance, but there is a trend in favour of amantadine for dropouts and depression. Results on adverse events and depression, were in favour of placebo although the difference do not reach the statistical significance. Comparing bromocriptine and Ldopa/Carbidopa versus placebo, results never reached statistical significance. Comparing amantadine versus antidepressants, antidepressants performed better for abstinence.

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.

The quality of evidence, assessed according to GRADE method, may be judged as moderate for the efficacy of any dopamine agonist versus placebo and as moderate to high for amantadine versus placebo and versus antidepressants.

Authors' conclusions

Current evidence from randomised controlled trials does not support the use of dopamine agonists for treating cocaine dependence. 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 updated review.

PLAIN LANGUAGE SUMMARY

Dopamine agonists for the treatment of cocaine dependence

A pharmacological agent with proven efficacy does not exist for treatment of cocaine dependence. Cocaine is an alkaloid derived from the erythroxylon coca leaf that is used as powder for intranasal or intravenous use or as crack, a free-base form which is smoked. Cocaine dependence is a major public health problem because its use can be associated with medical and psychosocial complications including the spread of infectious diseases (such as AIDS, hepatitis and tuberculosis), crime, violence and neonatal drug exposure. This review looked at the evidence on the efficacy and acceptability of dopamine agonists as a treatment, alone or in combination with any psychosocial intervention.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Any dopamine agonist versus placebo for the treatment of cocaine dependence

Patient or population: patients with the treatment of cocaine dependence
Settings:
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 objective Follow-up: mean 6 years	**Study population**		**RR 1.05** (0.95 to 1.15)	1643 (19 studies)	⊕⊕⊕◯ **moderate**[1]	
	463 per 1000	**486 per 1000** (440 to 532)				
	Medium risk population					
	482 per 1000	**506 per 1000** (458 to 554)				
Adverse events as N of participants with at least one adverse event subjective and objective Follow-up: mean 6 weeks	**Study population**		**RR 1.29** (0.88 to 1.91)	210 (6 studies)	⊕⊕⊕◯ **moderate**[1]	
	308 per 1000	**397 per 1000** (271 to 588)				
	Medium risk population					
	300 per 1000	**387 per 1000** (264 to 573)				

Abstinence (objective) objective Follow-up: mean 6 weeks	**Study population**		**RR 1.09** (0.93 to 1.28)	761 (11 studies)	⊕⊕◯◯ **low**[1,2]	
	360 per 1000	**392 per 1000** (335 to 461)				
	Medium risk population					
	500 per 1000	**545 per 1000** (465 to 640)				
Abstinents at follow-up (objective) objective Follow-up: mean 6 weeks	**Study population**		**OR 0.81** (0.41 to 1.57)	166 (4 studies)	⊕⊕◯◯ **low**[1,2]	
	733 per 1000	**690 per 1000** (530 to 812)				
	Medium risk population					
	744 per 1000	**702 per 1000** (544 to 820)				
Severity of dependence (difference before and after) ASI Follow-up: mean 6 weeks		The mean Severity of dependence (difference before and after) in the intervention groups was **0.43 standard deviations higher** (0.15 to 0.71 higher)		232 (4 studies)	⊕⊕⊕◯ **moderate**[1]	SMD 0.43 (0.15 to 0.71)
Depression (difference before and after) Beck Depression Inventory Follow-up: mean 6 weeks		The mean Depression (difference before and after) in the intervention groups was **0.42 standard deviations higher** (0.19 to 0.65 higher)		322 (5 studies)	⊕⊕⊕◯ **moderate**[1]	SMD 0.42 (0.19 to 0.65)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds 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] The majority of studies were classified as at unclear risk of bias for sequence generation and method of allocation concealment;
[2] Overlap of confidence interval

BACKGROUND

Description of the condition

Cocaine is an alkaloid derived from the leaf of erythroxylon coca, being commonly used as powder, for intranasal or intravenous use, or as crack, a free-base form which is smoked. Cocaine dependence is a major public health problem that is characterized by recidivism and a host of medical and psychosocial complications (EMCDDA 2009).

There is a wide and well documented range of consequences associated 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. According to recent population surveys, between 0.1% and 16% of the adult population report having tried cocaine at least once (i.e. lifetime prevalence), with USA (16.2%), Colombia, Mexico, New Zealand, United Kingdom, Italy, and Spain (4.0% to 7.7%) being at the upper end of this range (EMCDDA 2009; Degenhardt 2008; SAMSHA 2007). Recent cocaine use (last 12 months) is, in general, reported by less than 1% of adults. In most countries, the range is between 0.3% and 1%. In Spain, United Kingdom, Italy and USA recent prevalence rates are higher than 2% (SAMSHA 2007; EMCDDA 2009). Although cocaine prevalence figures are much lower than comparable figures for cannabis, the prevalence of use among younger adults can be higher than the population average. In Europe, lifetime experience among 15- to 34-year-olds ranges from 0.7% to 12.7%, with the highest levels being found in Spain (9.6%) and the United Kingdom (12.7%); recent use ranges between 0.2% and 5.4%, with Spain and the United Kingdom having rates over 5% (EMCDDA 2009). In the USA, lifetime experience among 26- to 34-year-olds ranges from 21% to 24%, while recent use ranges from 4.2% to 5.2% (SAMSHA 2007). Recently an increase of cocaine use among addicts seeking treatment has been observed in USA (Craddok 1997; Karch 2006), Australia (Topp 2003), Italy (Davoli 2007; Siliquini 2005) and Spain (Suelves 2001).

Description of the intervention

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

Cocaine effect seems to rely on its ability to increase the availability of monoamines (dopamine, serotonin and noradrenaline) in the brain. The dopamine increase in specific areas of the meso-limbic system, such as the nucleus accumbens, which is shared by cocaine with other drugs, like heroin, alcohol, cannabis and nicotine, has been involved in rewarding effect of drugs and self-administration behaviour in animal and human (Di Chiara 1988; Drevets 1999; Drevets 2001; Volkow 2003a). Specifically, the speed with which addictive drugs enter the brain and elevate nucleus accumbens dopamine 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). Post-cocaine use depression 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 on. 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.

The use of dopamine agonists lays 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, therefore 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 heroin (Faggiano 2003; Mattick 2008; Mattick 2009) and alcohol dependence (Amato 2010; Rösner 2010a; Rösner 2010b) none exists currently for cocaine dependence despite three decades of clinical trials on the efficacy of pharmacological and psychosocial interventions to treat this syndrome.

Four Cochrane reviews have been published on the efficacy of antipsychotics (Amato 2007), anticonvulsants (Minozzi 2008), antidepressants (Pani 2011) and psychostimulants (Castells 2010) for cocaine dependence but none of them found support for the

efficacy of these treatments. Moreover, a Cochrane review assessing the efficacy and safety of disulphiram (Pani 2010) has shown low evidence supporting the clinical use of it for the treatment of cocaine dependence.

One Cochrane review has been published on the efficacy of psychosocial treatments for psychostimulants dependence (Knapp 2007) showing that existing treatments have shown modest outcomes at best, leading to the conclusion that there is still a need to develop and test different formats of existing treatment models and newer psychosocial interventions should be undertaken.

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

The former Cochrane review on dopamine agonists for cocaine dependence was published in 2003 (Soares 2003) and never updated. Moreover, the recent review on psychostimulants, which actually are dopamine agonists (Castells 2010), did not considered medications devoid of psychostimulant effect. Therefore for these dopamine agonists devoid of psychostimulant effects, which have been further explored in clinical trials, there is a need of an update. Furthermore, there are several studies that have investigated the ability of DA agonists to reduce cocaine reinforcing effects, cocaine self-administration and cocaine cue reactivity (Collins 2011).

OBJECTIVES

To evaluate the efficacy and the acceptability of dopamine agonists for the treatment of cocaine dependence.

METHODS

Criteria for considering studies for this review

Types of studies

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

Types of participants

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

Types of interventions

Experimental intervention

- Any dopamine agonist alone or in combination with any psychosocial intervention. Psychostimulants were excluded.

Control Intervention

- Placebo
- Other pharmacological interventions;
- Any psychosocial intervention

Furthermore we considered different factors as confounders and take them into account in the analysis whenever possible:
-setting (inpatient or outpatient treatment);
-starting dose/rate and pattern of dose reduction;
-scheduled duration of treatment;
-severity of dependence (duration of use, route of administration, frequency of 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 and/or number of participants with urine samples negative for cocaine.
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), 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), 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), Positive and Negative Syndrome Scale (PANSS).

Search methods for identification of studies

Electronic searches

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

We also searched ongoing trials via the following web sites:

- Current Controlled Trials (http://www.controlled-trials.com/);
- Clinical Trials.gov;
- Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali (https://oss-sperclin.
- agenziafarmaco.it/);
- Trialsjournal.com

Searching other resources

We also searched:

1. the reference lists of all relevant papers to identify further studies;.
2. conference proceedings likely to contain trials relevant to the review.

We contacted investigators seeking

1. information about unpublished or incomplete trials;
2. some of the main electronic sources of ongoing trials

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

Data collection and analysis

Selection of studies

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

Data extraction and management

Two authors (Amato, Minozzi) assessed study quality according to the criteria indicated in Cochrane Reviews Handbook (Higgins 2011) and extracted data.

Assessment of risk of bias in included studies

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

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

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

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

Grading of evidence

The quality of evidence was assessed according to GRADE method (Guyatt 2008), a method systematic and explicit. In order to indicate the extent to which one can be confident that an estimate of effect is correct, judgments about the quality of evidence are made for each comparison and outcome. These judgments consider study design (RCT, quasi RCT or observational study), study quality (detailed study design and execution), consistency of results (similarity of estimates of effect across studies), precision of estimates, and directness (the extent to which people, interventions and outcome measures are similar to those of interest). The following definitions in grading the quality of evidence for each outcome are used: High: further research is very unlikely to change

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

Measures of treatment effect

Dichotomous outcomes (dropouts, abstinence, abstinence at follow up, side effects) have been analysed calculating the Relative Risk (RR) for each trial with the uncertainty in each result being expressed by their confidence intervals (CI). Continuous outcomes (craving, severity of dependence, clinical valuation, psychiatric symptoms) have been analysed calculating the Standardised Mean Difference (SMD) with 95% CI. We have not used data presented as number of positive urine tests over the total number of tests in the experimental and control group as measure of substance use. This decision was made because using number of tests instead of number of subjects as unit of the analysis violates the hypothesis of independence among observations. In fact, the results of test done for each participants are not independent. 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 the Intention To Treat (ITT) principles.

Unit of analysis issues

If all arms in a multi-arm trial are to be included in the meta-analysis and one treatment arm is to be 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 avoid 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

The presence of heterogeneity between the trials was tested using the I-squared (I2) statistic and with Chisquared (Q) test. A P-value of the test lower than 0.05 indicates a significant heterogeneity.

Assessment of reporting biases

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

Data synthesis

The outcomes from the individual trials were combined through meta-analysis where possible (comparability of intervention and outcomes between trials) using a fixed effect model unless there was significant heterogeneity, in which a random effect model was used. For the abstinence rate we used the number of randomised patients as the denominator assuming that dropouts continued to use cocaine.

Sensitivity analysis

To incorporate 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 from the analysis studies with high risk of bias. We also performed subgroup analysis for studies with no and unclear risk of bias.

RESULTS

Description of studies

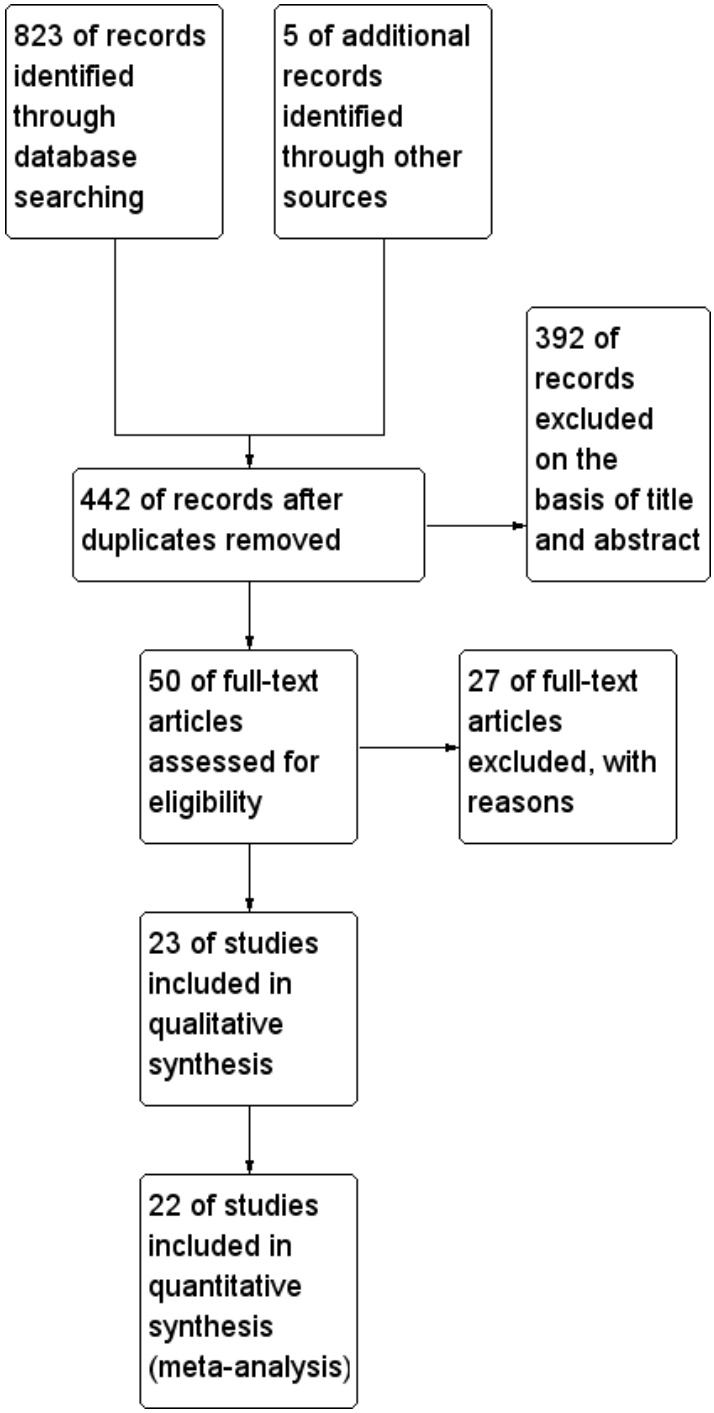
See: Characteristics of included studies; Characteristics of excluded studies.

For substantive descriptions of studies see Characteristics of included studies; Characteristics of excluded studies tables

Results of the search

We identified 442 reports, 392 were excluded on basis of title and abstract; 50 articles were retrieved for more detailed evaluation, 27 of which were excluded after reading the full text; the remaining 23 studies satisfied all the criteria to be included in the review, *see* Figure 1.

Figure 1. Study flow diagram.



Included studies

Twenty three studies, 2066 participants, met the inclusion criteria for this review, for details *see* Characteristics of included studies

Duration of trials:

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

Treatment regimes and setting

The dopamine agonists considered in the included studies were amantadine, bromocriptine, cabergoline, hydergine, L dopa/Carbidopa, pergolide and pramipexole

- Amantadine: Ten studies compared amantadine with placebo (Alterman 1992; Giannini 1989; Handelsman 1995; Kampman 1996; Kampman 2006; Kolar 1992; Kosten 1992; Pérez de los Cobos 2001; Shoptaw 2002; Weddington 1991), four studies with the antidepressant desipramine (Kolar 1992; Kosten 1992; Oliveto 1995; Weddington 1991), 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 (range100 to 400 mg/day).
- Bromocriptine: Bromocriptine was considered in other five studies compared with placebo (Eiler 1995; Giannini 1989; Gorelick 2006; Handelsman 1997; Moscovitz 1993), the mean dosage of bromocriptine was 6.2 mg/day (range 2.5 to 10 mg/day).
- L dopa/Carbidopa: Five studies compared L dopa/Carbidopa with placebo (Mooney 2007 a; Mooney 2007 b; Schmitz 2008; Schmitz 2010; Shoptaw 2005), the mean dosages of these drug were was 545/183 mg/day (range 75/100 to 800/200 mg/day)
- Pergolide: Two studies (Focchi 2005; Malcolm 2000) compared pergolide with placebo, the mean dosage was 0.2 mg/day (range 0.1 to 0.5 mg/day).
- The other three dopamine agonists were considered in single studies: Cabergoline 0,5 mg/week and Hydergine 3 mg were considered in Shoptaw 2005, a study with four arms that compare besides these two drugs, L dopa/Carbidopa and placebo. Pramipexole was considered in Ciraulo 2005 that compare it at dosage of 1.5 mg with placebo and the antidepressant venlafaxine.

In 13 studies, psychosocial interventions were added to the pharmacological one: Cognitive behavioural therapy (Handelsman 1997; Kampman 2006; Schmitz 2008), counselling sessions (Kampman 1996; Kolar 1992; Mooney 2007 a; Mooney 2007 b; Shoptaw 2002; Shoptaw 2005), contingency management (Schmitz 2008; Schmitz 2010), group relapse prevention therapy (Kosten 1992; Oliveto 1995), interpersonal psychotherapy (Weddington 1991).

Twenty studies were conducted in outpatient setting and four in inpatient

Participants

All the participants were cocaine addicted cocaine addicts according to DSM criteria ((DSM IIIR; DSM IV; DSM-IV-R), five studies (Handelsman 1995; Handelsman 1997; Kosten 1992; Oliveto 1995; Pérez de los Cobos 2001) enrolled patients with also opioid dependence in methadone maintenance therapy.

Countries in which the studies were conducted

Twenty one studies were conducted in 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

Twenty seven studies did not meet the criteria for inclusion in this review. The grounds for exclusion were: outcomes measures not in the inclusion criteria: 11 studies, study design not in the inclusion criteria: six studies; type of interventions considered not in the inclusion criteria: six studies, comparisons considered not in the inclusion criteria: two studies, study design and outcomes not in the inclusion criteria: two studies. *See* Characteristics of excluded studies

Risk of bias in included studies

See Figure 2; Figure 3 for review authors' judgements about each risk of bias item for each included study and authors' judgements about each risk of bias item presented as percentages across all included studies.

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

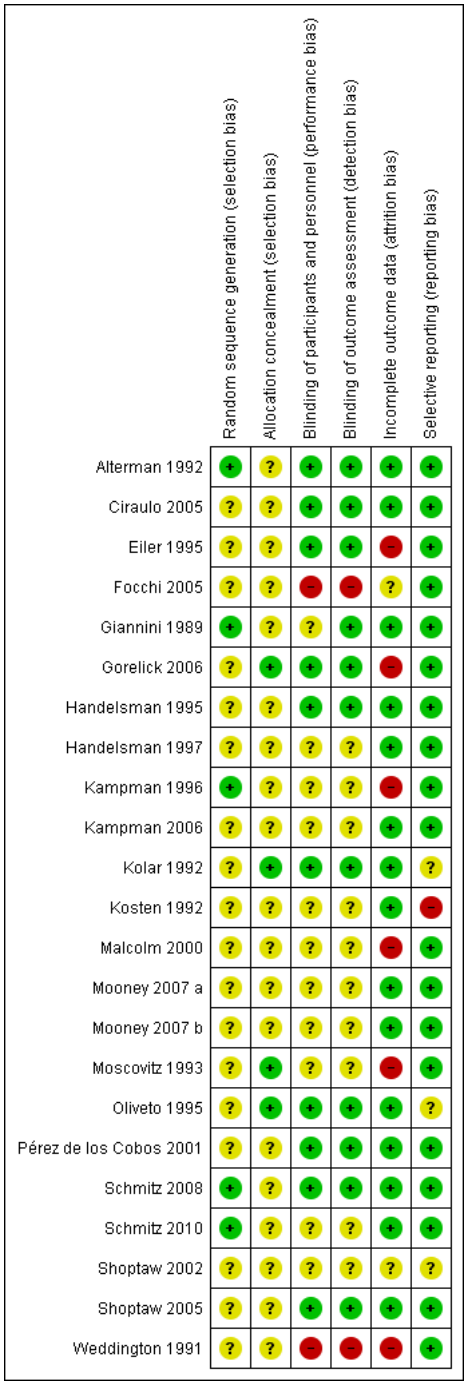
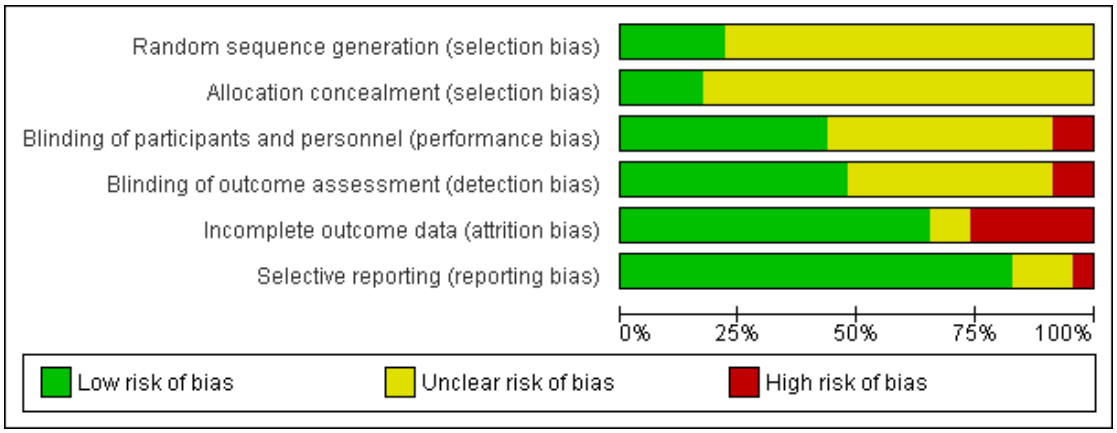


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Random sequence generation

Only 5/23 (22%) of the included studies used an adequate method of sequence generation**;** all the other studies were classified as at unclear risk of bias because no information was given about the method used.

Allocation concealment

Only 4/23 (17%) of the included studies used an adequate method of allocation concealment; all the other studies were classified as at unclear risk of bias because no information was given about the method used.

Blinding

Double-blind design was adopted in all but two studies (Focchi 2005 and Weddington 1991) both single-blind and judged at high risk of bias for performance and detection bias of subjective outcomes

Incomplete outcome data

16/23 (70%) of the included studies were judged at low risk of attrition bias or because the intention to treat principle was used or because there were few lost at follow up, balanced between groups and reason for drop out were reported. The remaining studies (Eiler 1995;Gorelick 2006;Kampman 1996; Malcolm 2000;Moscovitz 1993 and Weddington 1991) were judged at high risk of detection bias

Selective reporting

19/23 (87%) of the included studies were considered at low risk of reporting bias. One was judged at high risk (Kosten 1992) and two at unclear risk (Kolar 1992;Oliveto 1995

Effects of interventions

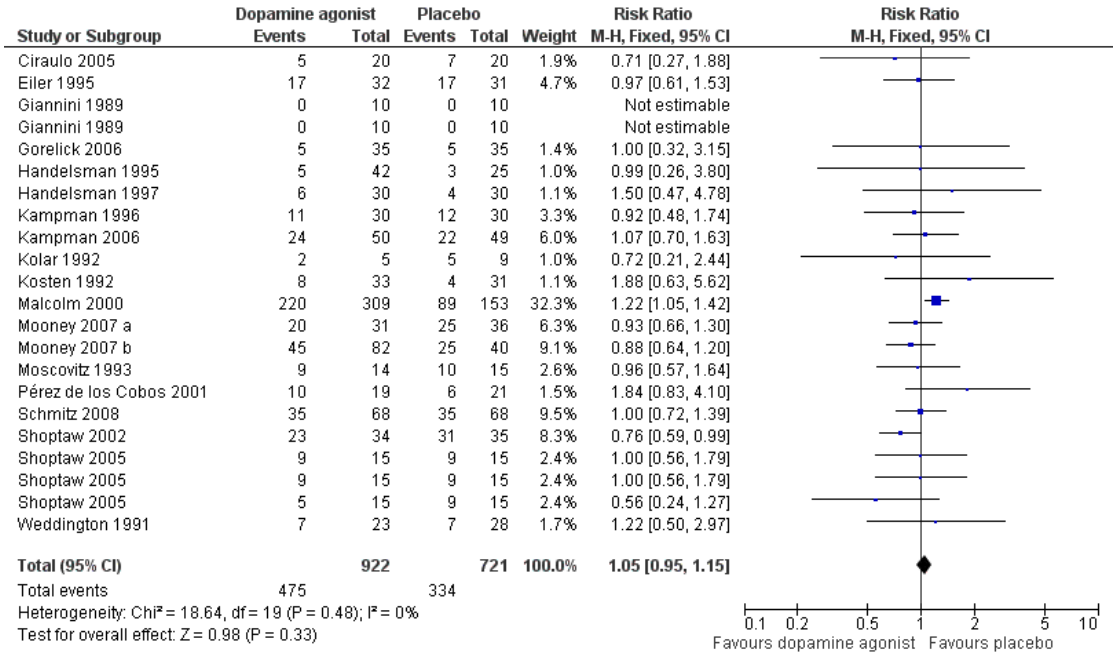
See: **Summary of findings for the main comparison** Any dopamine agonist versus placebo for the treatment of cocaine dependence; **Summary of findings 2** Amantadine versus placebo for the treatment of cocaine dependence; **Summary of findings 3** Amantidine versus antidepressants for the treatment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

1 Dopamine agonist versus placebo

1.1 Dropouts

19 studies (Ciraulo 2005; Eiler 1995; Giannini 1989; Gorelick 2006; Handelsman 1995; Handelsman 1997; Kampman 1996; Kampman 2006; Kolar 1992; Kosten 1992; Malcolm 2000; Mooney 2007 a; Mooney 2007 b; Moscovitz 1993; Pérez de los Cobos 2001; Schmitz 2008; Shoptaw 2002; Shoptaw 2005; Weddington 1991), 1643 participants, RR 1.05 (95% CI 0.95 to 1.15), the result is not statistically significant. *see* Analysis 1.1 or Figure 4

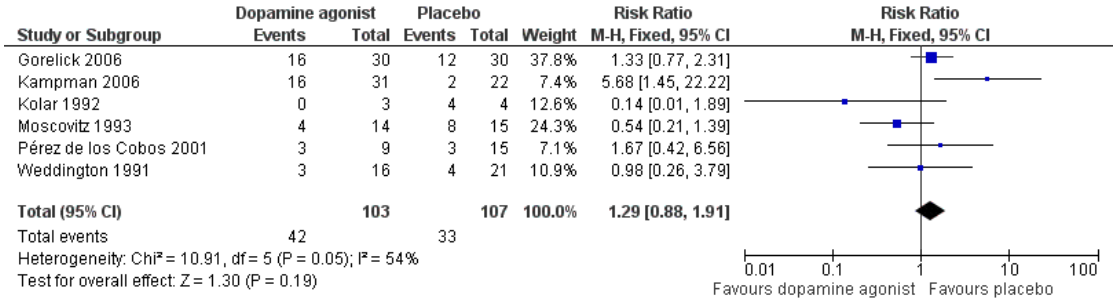
Figure 4. Forest plot of comparison: 1 Any dopamine agonist versus placebo, outcome: 1.1 Dropouts.



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

Six studies (Gorelick 2006; Kampman 2006; Kolar 1992; Moscovitz 1993; Pérez de los Cobos 2001; Weddington 1991), 210 participants, RR 1.29 (95% CI 0.88 to 1.91), the result is not statistically significant. *see* Analysis 1.2 or Figure 5

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



1.3 Dropouts due to adverse effects

Three studies (Mooney 2007 a; Mooney 2007 b; Schmitz 2008), 325 participants, RR 1.08 (95% CI 0.16 to 7.47), the result is not statistically significant *see* Analysis 1.3

1.4 Abstinence (objective)

11 studies (Alterman 1992; Focchi 2005; Kampman 1996; Kosten 1992; Mooney 2007 a; Mooney 2007 b; Moscovitz 1993; Schmitz 2008; Shoptaw 2002; Shoptaw 2005; Weddington 1991), 761 participants, RR 1.09 (95% CI 0.93 to1.28), the result is not statistically significant *see* Analysis 1.4

1.5 Abstinents at follow up (objective)

Four studies (Alterman 1992; Kolar 1992; Shoptaw 2002; Shoptaw 2005), 166 participants, RR 0.57 (95% CI 0.35 to 0.93), the result is statistically in favour of dopamine agonists *see* Analysis 1.5

1.6 Craving at the end of treatment

Three studies, Ciraulo 2005; Focchi 2005; Shoptaw 2002), 151 participants, SMD 0.13 (95% CI -0.19 to 0.54), the result is not statistically significant *see* Analysis 1.6

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

Four studies (Alterman 1992; Ciraulo 2005; Kampman 2006; Shoptaw 2005), 232 participants, SMD 0.43 (95% CI 0.15 to 0.71), the result is statistically in favour of placebo *see* Analysis 1.7

1.8 Clinical global evaluation at the end of the treatment

Two studies (Ciraulo 2005; Shoptaw 2005), 130 participants, SMD -0.12 (95% CI -0.47 to 0.22), the result is not statistically significant *see* Analysis 1.8

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

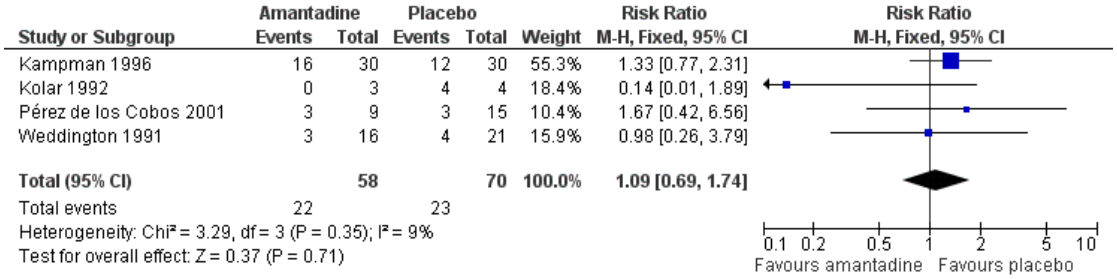
Five studies (Alterman 1992; Focchi 2005; Handelsman 1995; Kampman 1996; Shoptaw 2005), 322 participants, SMD 0.42 (95% CI 0.19 to 0.65), the result is statistically in favour of placebo *see* Analysis 1.9

2 Amantadine versus placebo

2.1 Dropouts

Nine studies (Giannini 1989; Handelsman 1995; Kampman 1996; Kampman 2006; Kolar 1992; Kosten 1992; Pérez de los Cobos 2001; Shoptaw 2002; Weddington 1991), 484 participants, RR 0.98 (95% CI 0.77 to 1.26), the result is not statistically significant *see* Analysis 2.1 or Figure 6

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



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

Four studies (Kampman 1996; Kolar 1992; Pérez de los Cobos 2001; Weddington 1991), 128 participants, RR 1.09 (95% CI 0.69 to 1.74), the result is not statistically significant *see* Analysis 2.2

2.3 Abstinence (objective)

Five studies (Alterman 1992; Kampman 1996; Kosten 1992; Shoptaw 2002; Weddington 1991), 275 participants, RR 1.08 (95% CI 0.77 to1.51), the result is not statistically significant *see* Analysis 2.3

2.4 Abstinents at follow up (objective)

Three studies (Alterman 1992; Kolar 1992; Shoptaw 2002), 76 participants, RR 1.43 (95% CI 0.99 to 2.08), the result is not statistically significant *see* Analysis 2.4

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

Two studies (Alterman 1992; Kampman 2006), 102 participants, SMD 0.39 (95% CI -0.00 to 0.79), the result is not statistically significant *see* Analysis 2.5

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

Two studies (Alterman 1992; Handelsman 1995), 109 participants, SMD -0.37 (95% CI -0.76 to 0.02), the result is not statistically significant but there is a trend in favour of amantadine *see* Analysis 2.6

3 Bromocriptine versus placebo

3.1 Dropouts

Five studies (Eiler 1995; Giannini 1989; Gorelick 2006; Handelsman 1997; Moscovitz 1993), 242 participants, RR 1.03 (95% CI 0.74 to 1.44), the result is not statistically significant *see*

Analysis 3.1

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

Two studies (Gorelick 2006; Moscovitz 1993), 89 participants, RR 0.92 (95% CI 0.38 to 2.22), the result is not statistically significant *see* Analysis 3.2

4 Ldopa/Carbidopa versus placebo

4.1 Dropouts

Three studies (Mooney 2007 a; Mooney 2007 b; Shoptaw 2005), 219 participants, RR 0.91 (95% CI 0.74 to 1.13), the result is not statistically significant *see* Analysis 4.1

4.2 Dropouts due to adverse effects

Three studies (Mooney 2007 a; Mooney 2007 b; Schmitz 2008), 325 participants, RR 1.08 (95% CI 0.16 to 7.47), the result is not statistically significant *see* Analysis 4.2

4.3 Abstinence (objective)

Four studies (Mooney 2007 a; Mooney 2007 b; Schmitz 2008; Shoptaw 2005), 355 participants, RR 1.49 (95% CI 0.85 to 2.63), the result is not statistically significant *see* Analysis 4.3

5 Amantadine versus antidepressants

The antidepressants considered in the studies were desipramine, four comparisons (Kolar 1992; Kosten 1992; Oliveto 1995; Weddington 1991) and fluoxetine, one comparison (Oliveto 1995)

5.1 Dropouts

Four studies (Kolar 1992; Kosten 1992; Oliveto 1995; Weddington 1991), 153 participants, RR 0.90 (95% CI 0.57 to 1.44), the result is not statistically significant *see* Analysis 5.1

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

Two studies (Kolar 1992; Weddington 1991), 44 participants, RR 0.54 (95% CI 0.17 to 1.70), the result is not statistically significant *see* Analysis 5.2

5.3 Abstinence (objective)

Two studies (Kolar 1992; Weddington 1991), 68 participants, RR 0.25 (95% CI 0.12 to 0.53), the result is statistically in favour of antidepressants *see* Analysis 5.3

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Amantadine versus placebo for the treatment of cocaine dependence

Patient or population: patients with the treatment of cocaine dependence
Settings:
Intervention: Amantadine 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	Amantadine versus placebo				
Dropouts objective Follow-up: mean 6 weeks	**Study population**		**RR 0.98** (0.77 to 1.26)	484 (9 studies)	⊕⊕⊕◯ **moderate**[1]	
	378 per 1000	**370 per 1000** (291 to 476)				
	Medium risk population					
	286 per 1000	**280 per 1000** (220 to 360)				
Adverse events as N of participants with at least one adverse event objective Follow-up: mean 6 weeks	**Study population**		**RR 1.09** (0.69 to 1.74)	128 (4 studies)	⊕⊕⊕⊕ **high**	
	329 per 1000	**359 per 1000** (227 to 572)				
	Medium risk population					
	300 per 1000	**327 per 1000** (207 to 522)				

Abstinence (objective) objective Follow-up: mean 6 weeks	**Study population**		**RR 1.08** (0.77 to 1.51)	275 (5 studies)	⊕⊕⊕○ **moderate**[1]
	307 per 1000	**332 per 1000** (236 to 464)			
	Medium risk population				
	355 per 1000	**383 per 1000** (273 to 536)			
Abstinence at follow up (objective) objective Follow-up: mean 6 weeks	**Study population**		**RR 1.43** (0.99 to 2.08)	76 (3 studies)	⊕⊕⊕○ **moderate**[1]
	512 per 1000	**732 per 1000** (507 to 1000)			
	Medium risk population				
	526 per 1000	**752 per 1000** (521 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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

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

[1] The majority of studies were classified as at unclear risk of bias for sequence generation and method of allocation concealment;

Amantidine versus antidepressants for the treatment of cocaine dependence

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

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	Amantidine versus antidepressants				
Dropouts objective Follow-up: mean 6 weeks	**Study population**		**RR 0.9** (0.57 to 1.44)	153 (4 studies)	⊕⊕⊕◯ **moderate**[1]	
	329 per 1000	**296 per 1000** (188 to 474)				
	Medium risk population					
	267 per 1000	**240 per 1000** (152 to 384)				
Adverse events as N of participants with at least one adverse event objective Follow-up: mean 6 weeks	**Study population**		**RR 0.54** (0.17 to 1.7)	44 (2 studies)	⊕⊕⊕⊕ **high**	
	320 per 1000	**173 per 1000** (54 to 544)				
	Medium risk population					
	335 per 1000	**181 per 1000** (57 to 570)				
Abstinence (objective) objective Follow-up: mean 6 weeks	**Study population**		**RR 0.25** (0.12 to 0.53)	68 (2 studies)	⊕⊕⊕⊕ **high**	

	775 per 1000	**194 per 1000** (93 to 411)
	Medium risk population	
	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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

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

[1] The majority of studies were classified as at unclear risk of bias for sequence generation and method of allocation concealment;

DISCUSSION

Methodological considerations

A decrease in DA activity in the brain of cocaine dependent patients may be related to cocaine craving and possibly relapse (Gold 1997). This is the rationale for using dopamine agonists in the treatment of cocaine dependence.

Summary of main results

Twenty three studies, with a total of 2066 participants, met the inclusion criteria for this review. However, the large variety of outcomes and rating scales considerably limited a quantitative synthesis of data. A large chunk of information could not be synthesized.
Comparing any dopamine agonist versus placebo, eight outcomes, placebo performed better for severity of dependence, four studies, for depression, five studies, both measured as difference before and after the treatment and for participants abstinent at follow up. No statistically significant different for the other outcomes considered but dopamine agonist showed a potentially protective benefit for the number of participants abstinent measured as number of participants with negative urine during the treatment and for an improvement of the clinical global evaluation at the end of the treatment. Dropouts, adverse events, and discontinuations due to adverse events tended to be more common in the dopamine agonist group but, however, none of these trends, reached statistical significance.
Comparing amantadine versus placebo, six outcomes considered, results never gain the statistical significance, but there is a trend in favour of amantadine for dropouts and depression. This trend in favour of amantadine is present also for number of participants abstinent during the treatment and at follow up controls. Results on adverse events and depression, were in favour of placebo although the difference do not reach the statistical significance.
Comparing bromocriptine versus placebo, two outcomes considered, results never reached statistical significance but bromocriptine performed better for adverse events and placebo for dropouts.
Comparing Ldopa/Carbidopa versus placebo, three outcomes considered, results never reached statistical significance but Ldopa/Carbidopa performed better for dropouts and abstinence and placebo for dropouts due to adverse events.
Comparing amantadine versus antidepressants (desipramine in four comparisons and fluoxetine in one comparison), three outcomes considered, antidepressants performed better for abstinence. 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, 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 the location of the study. Despite the systematic bibliographic search, only two out of 23 included studies was conducted out of the USA. In regard to this it should be considered that different social contests can influence differently the severity of dependence and the availability to enter an experimental design and different clinical contests can influence differently the selection of participants to the trials and the results of the treatment, acting as an effect modifier in the estimation of efficacy of treatment.

Quality of the evidence

The quality of evidence, assessed according to GRADE method, may be judged as moderate for the efficacy of any dopamine agonist versus placebo , see Summary of findings for the main comparison and as moderate to high for amantadine versus placebo and versus antidepressants, see Summary of findings 2; Summary of findings 3 respectively.
In respect to risk of bias, the quality of evidence, is quite good, 91% of included studies were were double blind, 87% were considered at low risk of reporting bias and 70% were judged at low risk of attrition bias or because the intention to treat principle was used or because there were few lost at follow up, balanced between groups and reason for drop out were reported. The more frequent bias detected in the studies was selection bias because only 22% of included studies used an adequate method of sequence generation, and 17% used an adequate method of allocation concealment.
Finally, the great heterogeneity of the scales used in the primary studies and the way in which results were reported made sometimes not possible to undertake a cumulative analysis.

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 (Gorelick 2004; Rush 2009; Rush 2010; Volkow 1999b;Volkow 2003b; Gardner 1999; Volkow 1999a; Volkow 2006; Volkow

2010), current evidence from randomised controlled trials does not support the use of dopamine agonists for treating cocaine dependence. 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 updated review.

Implications for research

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

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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 *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. "
Allocation concealment (selection bias)	Unclear risk	no details provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"both research/clinical personnel and the subjects were unaware of drug group assignment"
Blinding of outcome assessment (detection bias) All 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	drop out: 25%; no difference between groups

Alterman 1992 (*Continued*)

Selective reporting (reporting bias)	Low risk	all outcomes stated in the methods section are 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**
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) All 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) All 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"
Incomplete outcome data (attrition bias) All outcomes	Low risk	no significant differences in the attrition rate between groups; mean attrition rate: 20%

Ciraulo 2005 (*Continued*)

Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section are 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 grams. . 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
Interventions	1. Bromocriptine 2.5-10 mg/day, N=32 2. Placebo, N=31 Setting: inpatient; Duration: 18-21 days; Country of origin: USA
Outcomes	Dropouts; Dropouts due to adverse effects; BDI; Craving; Withdrawal symptoms
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) All 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) All 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 are 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:* males, between 18 and 50 years, cocaine dependents (DSM-IV), living in Sao 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 0.2mg/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;
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) All outcomes	High risk	Single blind
Blinding of outcome assessment (detection bias) All outcomes	High risk	Single blind
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 are reported

Giannini 1989

Methods	RCT 3 parallel groups
Participants	N= 30 All male; Age: range 24-32 years; Caucasians 100% All subjects had abused cocaine intranasally on a daily basis for at least 4 weeks before

Giannini 1989 (*Continued*)

	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
Interventions	1. Amantadine 400 mg/day, N=10 2. Bromocriptine 10 mg/day, N= 10 3. Placebo, N=10 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 program
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated as double blind, no details provided
Blinding of outcome assessment (detection bias) All 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	No lost at follow up.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section are 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 18-65 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. Disulfi-

Gorelick 2006 (*Continued*)

	ram, amantadine, anti-depressants, neuroleptics), inability to give informed consent or inability to cooperate with study procedures
Interventions	1. Bromocriptine max dose 2.5mg, 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) All 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) All 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 are 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 *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

Handelsman 1995 (*Continued*)

	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) All outcomes	Low risk	"medication was assigned randomly at the completion of enrolment week and 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) All outcomes	Low risk	"medication was assigned randomly at the completion of enrolment week and 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"
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 are reported

Handelsman 1997

Methods	RCT
Participants	N= 60; Methadone maintained patients with cocaine abuse or dependence (DSM-III-R), Age: ~39 years; male 100%; 24% black *Inclusion criteria:* older than 21, 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,

Handelsman 1997 (*Continued*)

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) All outcomes	Unclear risk	Stated as double blind, no details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated as double blind, no details provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	16.6% drop out from the study; no significant differences in the attrition rate between groups; reason for drop out reported
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section are reported

Kampman 1996

Methods	RCT
Participants	N= 61 Cocaine use within 10 days of entering the studAge: ~35 years; Male in amantadine group 87%; in placebo group 77%; Afro-American in amantadine group 67%; in placebo group 71% *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

Kampman 1996 (*Continued*)

	Setting: outpatient; Duration: 4 weeks, follow up at 8 weeks; Country of origin: USA	
Outcomes	Retention in treatment; Abstinents; 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) All outcomes	Unclear risk	Stated as double blind, no details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated as double blind, no details provided
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 are reported

Kampman 2006

Methods	RCT
Participants	N= 199 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

Kampman 2006 (*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) All outcomes	Unclear risk	Stated as double blind, no details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated as double blind, no details provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing urine counted as positives
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section are 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
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	

Kolar 1992 (*Continued*)

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) All outcomes	Low risk	"subjects, study nurse, research assistant were blind to treatment condition"
Blinding of outcome assessment (detection bias) All 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 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 *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 300mg, 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

Kosten 1992 (*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) All outcomes	Unclear risk	Stated as double blind, no details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated as double blind, no details provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing urine counted as positives. Drop out 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 18-52 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 US$25 at weeks

Risk of bias

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

Malcolm 2000 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated as double blind, no details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated as double blind, no details provided
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 are reported

Mooney 2007 a

Methods	RCT
Participants	Two trials N=67 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**
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) All outcomes	Unclear risk	Stated as double blind, no details provided

Mooney 2007 a (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated as double blind, no details provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	intention to treat analysis
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section are reported

Mooney 2007 b

Methods	RCT
Participants	N=122 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=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	

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) All outcomes	Unclear risk	Stated as double blind, no details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated as double blind, no details provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	intention to treat analysis

Mooney 2007 b (*Continued*)

Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section are 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
Interventions	1. Bromocriptine 3.75 mg/day, N= 14 2. Placebo, N=15 Setting: outpatient; Duration: 2 weeks; Country of origin: USA
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) All outcomes	Unclear risk	Stated as double blind, no details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated as double blind, no details provided
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 are 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; Employed 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 indicated, illiteracy and/or inability to comprehend the consent for study procedure, concurrent treatment with AZT or other medications for the treatment of AIDS
Interventions	Buprenorphine 8mg/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) All 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) All 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"
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 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:* 18-45 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 200-300 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) All outcomes	Low risk	"to preserve the clinical trial double blind conditions .., identical opaque capsules were used"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"to preserve the clinical trial double blind conditions .., identical opaque capsules were used"
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 are reported

Schmitz 2008

Methods	RCT
Participants	N=161 27/161 female, 39, white, 109 black, 12 Hispanic, 78 employed, 103 previous drug treatment, recent cocaine use 14.0 days in the past 30, lifetime cocaine use 11.8 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, inhability 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 3-4 100/25 BID, days 5-6 200/50 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 Voucher-Based reinforcement therapy (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) All outcomes	Low risk	"double blind for medical conditions"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double blind for medical conditions"

Schmitz 2008 (*Continued*)

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 are 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, inhability 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 3-4 100/25 BID, days 5-6 200/50 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) All outcomes	Unclear risk	Stated as double blind, no details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated as double blind, no details provided
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 are 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
Interventions	1. Amantadine 100 mg BID, N=34 2. Placebo, N=35 Associated with 3 times/ week group counselling 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

Shoptaw 2002 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated as double blind, no details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated as double blind, no details provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	69 randomised, analysis on 68 who completed
Selective reporting (reporting bias)	Unclear risk	All outcomes stated in the methods section are reported

Shoptaw 2005

Methods	RCT
Participants	N=60 *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) *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 $20 for completing visits for a maximum value of $165 in vouchers

Risk of bias

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

Shoptaw 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) All 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) All 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"
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 are 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 one gram or more per week for 12 weeks. Additional diagnosis: attention deficit disorder, affective and anxiety disorders *Inclusion criteria:* cocaine addicts applied for treatment, minimum one gram 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) 2 times 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

Weddington 1991 (*Continued*)

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) All outcomes	High risk	Only participants were blind
Blinding of outcome assessment (detection bias) All outcomes	High risk	Only participants were blind
Incomplete outcome data (attrition bias) All outcomes	High risk	Results only on 54/83 subjects that continued in treatment for 14 days (drop out 35%)
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section are reported

- 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
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
Kosten 2005	Type of intervention not in the inclusion criteria
Kranzler 1992	Outcomes measures not in the inclusion criteria
Kumor 1988	Outcomes measures not in the inclusion criteria
Malcolm 1994	Type of comparison not in the inclusion criteria
Mc Dougle 1992	Outcomes measures not in the inclusion criteria
Montoya 2002	Type of intervention not in the inclusion criteria
Morgan 1988	Study design not in the inclusion criteria
Preston 1991	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

(*Continued*)

Sule 2008	Study design not in the inclusion criteria
Tennant 1987	Type of comparison 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	19	1643	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.95, 1.15]
2 Adverse events as N of participants with at least one adverse event	6	210	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.88, 1.91]
3 Dropouts due to adverse events	3	325	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.16, 7.47]
4 Abstinence (objective)	11	761	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.93, 1.28]
5 Abstinents at follow-up (objective)	4	166	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.77, 1.14]
6 Craving at the end of treatment	3	151	Std. Mean Difference (IV, Fixed, 95% CI)	0.13 [-0.19, 0.45]
7 Severity of dependence (difference before and after)	4	232	Std. Mean Difference (IV, Fixed, 95% CI)	0.43 [0.15, 0.71]
8 Clinical global evaluation (end of treatment)	2	130	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.47, 0.22]
9 Depression (difference before and after)	5	322	Std. Mean Difference (IV, Fixed, 95% CI)	0.42 [0.19, 0.65]

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, Fixed, 95% CI)	1.09 [0.69, 1.74]
3 Abstinence (objective)	5	275	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.77, 1.51]
4 Abstinence at follow up (objective)	3	76	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.99, 2.08]
5 Severity of dependence (difference before and after)	2	102	Std. Mean Difference (IV, Fixed, 95% CI)	0.39 [-3.31, 0.79]
6 Depression (difference before and after)	2	109	Std. Mean Difference (IV, Fixed, 95% CI)	-0.37 [-0.76, 0.02]

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, Fixed, 95% CI)	1.03 [0.74, 1.44]
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]

Comparison 4. L dopa/Carbidopa versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dropouts	3	219	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.74, 1.13]
2 Dropouts due to adverse events	3	325	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.16, 7.47]
3 Abstinence (objective)	4	355	Odds Ratio (M-H, Fixed, 95% CI)	1.49 [0.85, 2.63]

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, Fixed, 95% CI)	0.90 [0.57, 1.44]
2 Adverse events as N of participants with at least one adverse event	2	44	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.17, 1.70]
3 Abstinence (objective)	2	68	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.12, 0.53]

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

Review: Dopamine agonists for the treatment of cocaine dependence

Comparison: 1 Any dopamine agonist versus placebo

Outcome: 1 Dropouts

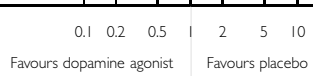
Study or subgroup	Dopamine agonist n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Ciraulo 2005	5/20	7/20		0.71 [0.27, 1.88]
Eiler 1995	17/32	17/31		0.97 [0.61, 1.53]
Giannini 1989	0/10	0/10		0.0 [0.0, 0.0]
Giannini 1989	0/10	0/10		0.0 [0.0, 0.0]
Gorelick 2006	5/35	5/35		1.00 [0.32, 3.15]
Handelsman 1995	5/42	3/25		0.99 [0.26, 3.80]
Handelsman 1997	6/30	4/30		1.50 [0.47, 4.78]
Kampman 1996	11/30	12/30		0.92 [0.48, 1.74]
Kampman 2006	24/50	22/49		1.07 [0.70, 1.63]
Kolar 1992	2/5	5/9		0.72 [0.21, 2.44]
Kosten 1992	8/33	4/31		1.88 [0.63, 5.62]
Malcolm 2000	220/309	89/153		1.22 [1.05, 1.42]
Mooney 2007 a	20/31	25/36		0.93 [0.66, 1.30]
Mooney 2007 b	45/82	25/40		0.88 [0.64, 1.20]
Moscovitz 1993	9/14	10/15		0.96 [0.57, 1.64]
Prez de los Cobos 2001	10/19	6/21		1.84 [0.83, 4.10]
Schmitz 2008	35/68	35/68		1.00 [0.72, 1.39]
Shoptaw 2002	23/34	31/35		0.76 [0.59, 0.99]
Shoptaw 2005	9/15	9/15		1.00 [0.56, 1.79]
Shoptaw 2005	9/15	9/15		1.00 [0.56, 1.79]
Shoptaw 2005	5/15	9/15		0.56 [0.24, 1.27]
Weddington 1991	7/23	7/28		1.22 [0.50, 2.97]
Total (95% CI)	**922**	**721**		**1.05 [0.95, 1.15]**

Total events: 475 (Dopamine agonist), 334 (Placebo)

Heterogeneity: Chi^2 = 18.64, df = 19 (P = 0.48); I^2 =0.0%

Test for overall effect: Z = 0.98 (P = 0.33)

Test for subgroup differences: Not applicable



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

Review: Dopamine agonists for the treatment of cocaine dependence

Comparison: 1 Any dopamine agonist versus placebo

Outcome: 2 Adverse events as N of participants with at least one adverse event

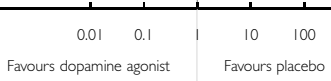
Study or subgroup	Dopamine agonist n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gorelick 2006	16/30	12/30		37.8 %	1.33 [0.77, 2.31]
Kampman 2006	16/31	2/22		7.4 %	5.68 [1.45, 22.22]
Kolar 1992	0/3	4/4		12.6 %	0.14 [0.01, 1.89]
Moscovitz 1993	4/14	8/15		24.3 %	0.54 [0.21, 1.39]
Prez de los Cobos 2001	3/9	3/15		7.1 %	1.67 [0.42, 6.56]
Weddington 1991	3/16	4/21		10.9 %	0.98 [0.26, 3.79]
Total (95% CI)	**103**	**107**		**100.0 %**	**1.29 [0.88, 1.91]**

Total events: 42 (Dopamine agonist), 33 (Placebo)

Heterogeneity: Chi^2 = 10.91, df = 5 (P = 0.05); I^2 =54%

Test for overall effect: Z = 1.30 (P = 0.19)

Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 Any dopamine agonist versus placebo, Outcome 3 Dropouts due to adverse events.

Review: Dopamine agonists for the treatment of cocaine dependence

Comparison: 1 Any dopamine agonist versus placebo

Outcome: 3 Dropouts due to adverse events

Study or subgroup	Dopamine agonist n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Mooney 2007 a	1/31	1/36		1.16 [0.08, 17.80]
Mooney 2007 b	0/82	0/40		0.0 [0.0, 0.0]
Schmitz 2008	1/68	1/68		1.00 [0.06, 15.66]
Total (95% CI)	**181**	**144**		**1.08 [0.16, 7.47]**

Total events: 2 (Dopamine agonist), 2 (Placebo)

Heterogeneity: $Chi^2 = 0.01$, df = 1 (P = 0.94); $I^2 = 0.0\%$

Test for overall effect: Z = 0.08 (P = 0.94)

Test for subgroup differences: Not applicable

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

Review: Dopamine agonists for the treatment of cocaine dependence

Comparison: 1 Any dopamine agonist versus placebo

Outcome: 4 Abstinence (objective)

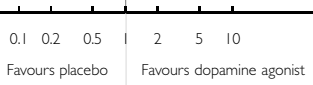
Study or subgroup	Dopamine agonist n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Alterman 1992	14/15	9/15		6.7 %	1.56 [1.01, 2.40]
Focchi 2005	15/22	12/20		9.4 %	1.14 [0.72, 1.80]
Kampman 1996	12/30	11/31		8.1 %	1.13 [0.59, 2.15]
Kosten 1992	5/33	4/31		3.1 %	1.17 [0.35, 3.98]
Mooney 2007 a	19/31	18/36		12.4 %	1.23 [0.80, 1.88]
Mooney 2007 b	26/82	14/40		14.0 %	0.91 [0.53, 1.54]
Moscovitz 1993	4/14	2/15		1.4 %	2.14 [0.46, 9.93]
Schmitz 2008	7/68	0/68		0.4 %	15.00 [0.87, 257.56]
Shoptaw 2002	9/34	3/35		2.2 %	3.09 [0.91, 10.44]
Shoptaw 2005	15/15	14/15		10.8 %	1.07 [0.89, 1.28]
Shoptaw 2005	10/15	14/15		10.4 %	0.71 [0.49, 1.05]
Shoptaw 2005	13/15	14/15		10.4 %	0.93 [0.73, 1.18]
Weddington 1991	4/23	16/28		10.7 %	0.30 [0.12, 0.78]
Total (95% CI)	**397**	**364**		**100.0 %**	**1.09 [0.93, 1.28]**

Total events: 153 (Dopamine agonist), 131 (Placebo)

Heterogeneity: Chi^2 = 23.64, df = 12 (P = 0.02); I^2 =49%

Test for overall effect: Z = 1.08 (P = 0.28)

Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1 Any dopamine agonist versus placebo, Outcome 5 Abstinents at follow-up (objective).

Review: Dopamine agonists for the treatment of cocaine dependence

Comparison: 1 Any dopamine agonist versus placebo

Outcome: 5 Abstinents at follow-up (objective)

Study or subgroup	Dopamine agonist n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Alterman 1992	15/18	10/19		15.9 %	1.58 [0.99, 2.54]
Kolar 1992	2/5	5/9		5.8 %	0.72 [0.21, 2.44]
Shoptaw 2002	9/12	6/13		9.4 %	1.63 [0.83, 3.18]
Shoptaw 2005	12/15	14/15		22.9 %	0.86 [0.64, 1.14]
Shoptaw 2005	10/15	14/15		22.9 %	0.71 [0.49, 1.05]
Shoptaw 2005	8/15	14/15		22.9 %	0.57 [0.35, 0.93]
Total (95% CI)	**80**	**86**		**100.0 %**	**0.94 [0.77, 1.14]**

Total events: 56 (Dopamine agonist), 63 (Placebo)

Heterogeneity: Chi^2 = 13.67, df = 5 (P = 0.02); I^2 =63%

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

Test for subgroup differences: Not applicable

Analysis 1.6. Comparison 1 Any dopamine agonist versus placebo, Outcome 6 Craving at the end of treatment.

Review: Dopamine agonists for the treatment of cocaine dependence

Comparison: 1 Any dopamine agonist versus placebo

Outcome: 6 Craving at the end of treatment

Study or subgroup	Dopamine agonist		Placebo		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Ciraulo 2005	20	3.85 (3.05)	20	2.55 (3.2)		26.5 %	0.41 [-0.22, 1.03]
Focchi 2005	22	2.06 (2.37)	20	0.96 (1.28)		27.2 %	0.56 [-0.06, 1.18]
Shoptaw 2002	34	0.77 (1.7)	35	1.39 (2.6)		46.3 %	-0.28 [-0.75, 0.20]
Total (95% CI)	**76**		**75**			**100.0 %**	**0.13 [-0.19, 0.45]**

Heterogeneity: Chi^2 = 5.45, df = 2 (P = 0.07); I^2 =63%

Test for overall effect: Z = 0.80 (P = 0.42)

Test for subgroup differences: Not applicable

Analysis 1.7. Comparison 1 Any dopamine agonist versus placebo, Outcome 7 Severity of dependence (difference before and after).

Review: Dopamine agonists for the treatment of cocaine dependence

Comparison: 1 Any dopamine agonist versus placebo

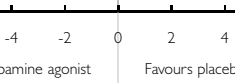
Outcome: 7 Severity of dependence (difference before and after)

Study or subgroup	Dopamine agonist N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Alterman 1992	21	-0.08 (0.08)	21	-0.13 (0.08)		20.6 %	0.61 [-0.01, 1.23]
Ciraulo 2005	20	-0.08 (0.08)	20	-0.7 (0.09)		2.6 %	7.14 [5.38, 8.90]
Kampman 2006	30	-0.08 (0.07)	30	-0.1 (0.09)		30.7 %	0.24 [-0.26, 0.75]
Shoptaw 2005	15	0.08 (0.1)	15	0.08 (0.07)		15.4 %	0.0 [-0.72, 0.72]
Shoptaw 2005	15	0.09 (0.13)	15	0.08 (0.07)		15.4 %	0.09 [-0.62, 0.81]
Shoptaw 2005	15	0.1 (0.11)	15	0.08 (0.07)		15.4 %	0.21 [-0.51, 0.93]
Total (95% CI)	**116**		**116**			**100.0 %**	**0.43 [0.15, 0.71]**

Heterogeneity: Chi^2 = 59.23, df = 5 (P<0.00001); I^2 =92%

Test for overall effect: Z = 3.00 (P = 0.0027)

Test for subgroup differences: Not applicable



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

Review: Dopamine agonists for the treatment of cocaine dependence

Comparison: 1 Any dopamine agonist versus placebo

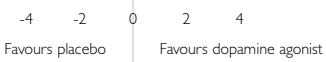
Outcome: 8 Clinical global evaluation (end of treatment)

Study or subgroup	Dopamine agonist N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Ciraulo 2005	20	-1.42 (1.23)	20	-1.41 (1.35)		31.0 %	-0.01 [-0.63, 0.61]
Shoptaw 2005	15	-1.4 (1.1)	15	-1.4 (1.1)		23.3 %	0.0 [-0.72, 0.72]
Shoptaw 2005	15	-2 (1.1)	15	-1.4 (1.1)		22.4 %	-0.53 [-1.26, 0.20]
Shoptaw 2005	15	-1.4 (1.5)	15	-1.4 (1.1)		23.3 %	0.0 [-0.72, 0.72]
Total (95% CI)	**65**		**65**			**100.0 %**	**-0.12 [-0.47, 0.22]**

Heterogeneity: Chi² = 1.56, df = 3 (P = 0.67); I² =0.0%

Test for overall effect: Z = 0.69 (P = 0.49)

Test for subgroup differences: Not applicable



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

Review: Dopamine agonists for the treatment of cocaine dependence

Comparison: 1 Any dopamine agonist versus placebo

Outcome: 9 Depression (difference before and after)

Study or subgroup	Dopamine agonist N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Alterman 1992	21	-0.04 (0.17)	21	-0.08 (0.15)		14.5 %	0.24 [-0.36, 0.85]
Focchi 2005	32	-6.7 (3)	31	-9.5 (2.61)		19.4 %	0.98 [0.46, 1.51]
Handelsman 1995	42	-11.1 (8.1)	25	-4 (9.5)		20.2 %	-0.81 [-1.33, -0.30]
Kampman 1996	30	-0.06 (0.18)	30	-0.32 (0.14)		15.6 %	1.59 [1.01, 2.18]
Shoptaw 2005	15	0.8 (10.8)	15	-1.2 (6.9)		10.4 %	0.21 [-0.50, 0.93]
Shoptaw 2005	15	-1.1 (6.9)	15	-1.2 (6.9)		10.5 %	0.01 [-0.70, 0.73]
Shoptaw 2005	15	6.9 (10.6)	15	-1.2 (6.9)		9.4 %	0.88 [0.13, 1.64]
Total (95% CI)	**170**		**152**			**100.0 %**	**0.42 [0.19, 0.65]**

Heterogeneity: Chi^2 = 45.08, df = 6 (P<0.00001); I^2 =87%

Test for overall effect: Z = 3.54 (P = 0.00040)

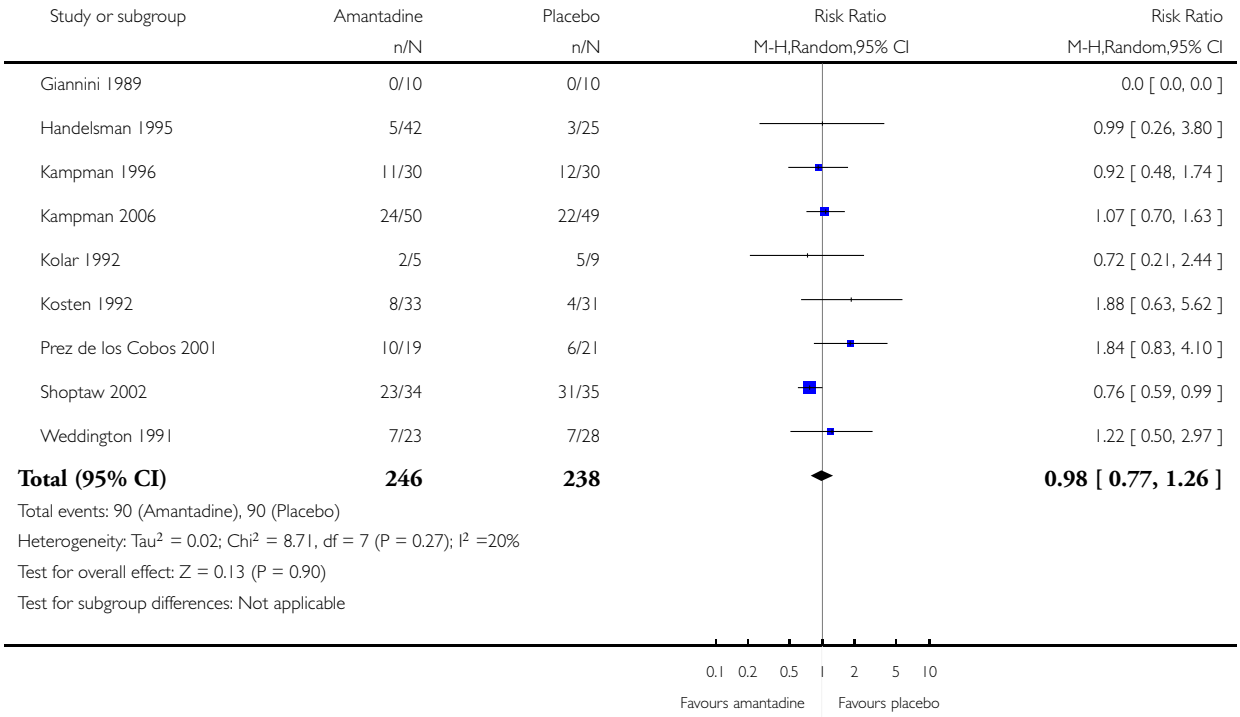
Test for subgroup differences: Not applicable

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

Review: Dopamine agonists for the treatment of cocaine dependence

Comparison: 2 Amantadine versus placebo

Outcome: 1 Dropouts



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

Review: Dopamine agonists for the treatment of cocaine dependence

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,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kampman 1996	16/30	12/30		55.3 %	1.33 [0.77, 2.31]
Kolar 1992	0/3	4/4		18.4 %	0.14 [0.01, 1.89]
Prez de los Cobos 2001	3/9	3/15		10.4 %	1.67 [0.42, 6.56]
Weddington 1991	3/16	4/21		15.9 %	0.98 [0.26, 3.79]
Total (95% CI)	**58**	**70**		**100.0 %**	**1.09 [0.69, 1.74]**
Total events: 22 (Amantadine), 23 (Placebo)					
Heterogeneity: Chi^2 = 3.29, df = 3 (P = 0.35); I^2 =9%					
Test for overall effect: Z = 0.37 (P = 0.71)					
Test for subgroup differences: Not applicable					

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

Review: Dopamine agonists for the treatment of cocaine dependence

Comparison: 2 Amantadine versus placebo

Outcome: 3 Abstinence (objective)

Study or subgroup	Amantadine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Alterman 1992	14/15	9/15		21.8 %	1.56 [1.01, 2.40]
Kampman 1996	12/30	11/31		26.2 %	1.13 [0.59, 2.15]
Kosten 1992	5/33	4/31		10.0 %	1.17 [0.35, 3.98]
Shoptaw 2002	9/34	3/35		7.2 %	3.09 [0.91, 10.44]
Weddington 1991	4/23	16/28		34.9 %	0.30 [0.12, 0.78]
Total (95% CI)	**135**	**140**		**100.0 %**	**1.08 [0.77, 1.51]**

Total events: 44 (Amantadine), 43 (Placebo)

Heterogeneity: Chi^2 = 12.49, df = 4 (P = 0.01); I^2 =68%

Test for overall effect: Z = 0.44 (P = 0.66)

Test for subgroup differences: Not applicable

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

Review: Dopamine agonists for the treatment of cocaine dependence

Comparison: 2 Amantadine versus placebo

Outcome: 4 Abstinence at follow up (objective)

Study or subgroup	Amantadine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Alterman 1992	15/18	10/19		51.0 %	1.58 [0.99, 2.54]
Kolar 1992	2/5	5/9		18.7 %	0.72 [0.21, 2.44]
Shoptaw 2002	9/12	6/13		30.2 %	1.63 [0.83, 3.18]
Total (95% CI)	**35**	**41**		**100.0 %**	**1.43 [0.99, 2.08]**

Total events: 26 (Amantadine), 21 (Placebo)

Heterogeneity: Chi^2 = 1.52, df = 2 (P = 0.47); I^2 =0.0%

Test for overall effect: Z = 1.90 (P = 0.057)

Test for subgroup differences: Not applicable

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

Review: Dopamine agonists for the treatment of cocaine dependence

Comparison: 2 Amantadine versus placebo

Outcome: 5 Severity of dependence (difference before and after)

Study or subgroup	Amantadine N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Alterman 1992	21	-0.08 (0.08)	21	-0.13 (0.08)		40.1 %	0.61 [-0.01, 1.23]
Kampman 2006	30	-0.08 (0.07)	30	-0.1 (0.09)		59.9 %	0.24 [-0.26, 0.75]
Total (95% CI)	**51**		**51**			**100.0 %**	**0.39 [0.00, 0.79]**

Heterogeneity: Chi² = 0.81, df = 1 (P = 0.37); I² =0.0%

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

Test for subgroup differences: Not applicable

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

Review: Dopamine agonists for the treatment of cocaine dependence

Comparison: 2 Amantadine versus placebo

Outcome: 6 Depression (difference before and after)

Study or subgroup	Amantadine N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Alterman 1992	21	-0.04 (0.17)	21	-0.08 (0.15)		41.8 %	0.24 [-0.36, 0.85]
Handelsman 1995	42	-11.1 (8.1)	25	-4 (9.5)		58.2 %	-0.81 [-1.33, -0.30]
Total (95% CI)	**63**		**46**			**100.0 %**	**-0.37 [-0.76, 0.02]**

Heterogeneity: Chi² = 6.77, df = 1 (P = 0.01); I² =85%

Test for overall effect: Z = 1.85 (P = 0.065)

Test for subgroup differences: Not applicable

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

Review: Dopamine agonists for the treatment of cocaine dependence

Comparison: 3 Bromocriptine versus placebo

Outcome: 1 Dropouts

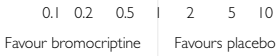
Study or subgroup	Bromocriptine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Eiler 1995	17/32	17/31		0.97 [0.61, 1.53]
Giannini 1989	0/10	0/10		0.0 [0.0, 0.0]
Gorelick 2006	5/35	5/35		1.00 [0.32, 3.15]
Handelsman 1997	6/30	4/30		1.50 [0.47, 4.78]
Moscovitz 1993	9/14	10/15		0.96 [0.57, 1.64]
Total (95% CI)	**121**	**121**		**1.03 [0.74, 1.44]**

Total events: 37 (Bromocriptine), 36 (Placebo)

Heterogeneity: $Chi^2 = 0.54$, df = 3 (P = 0.91); $I^2 = 0.0\%$

Test for overall effect: Z = 0.18 (P = 0.86)

Test for subgroup differences: Not applicable

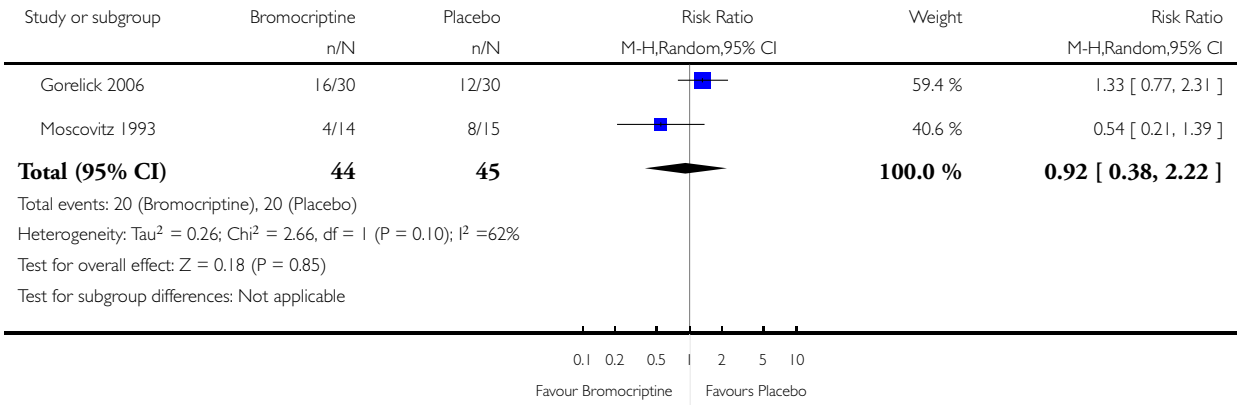


Analysis 3.2. Comparison 3 Bromocriptine versus placebo, Outcome 2 Adverse events as N of participants with at least one adverse event.

Review: Dopamine agonists for the treatment of cocaine dependence

Comparison: 3 Bromocriptine versus placebo

Outcome: 2 Adverse events as N of participants with at least one adverse event

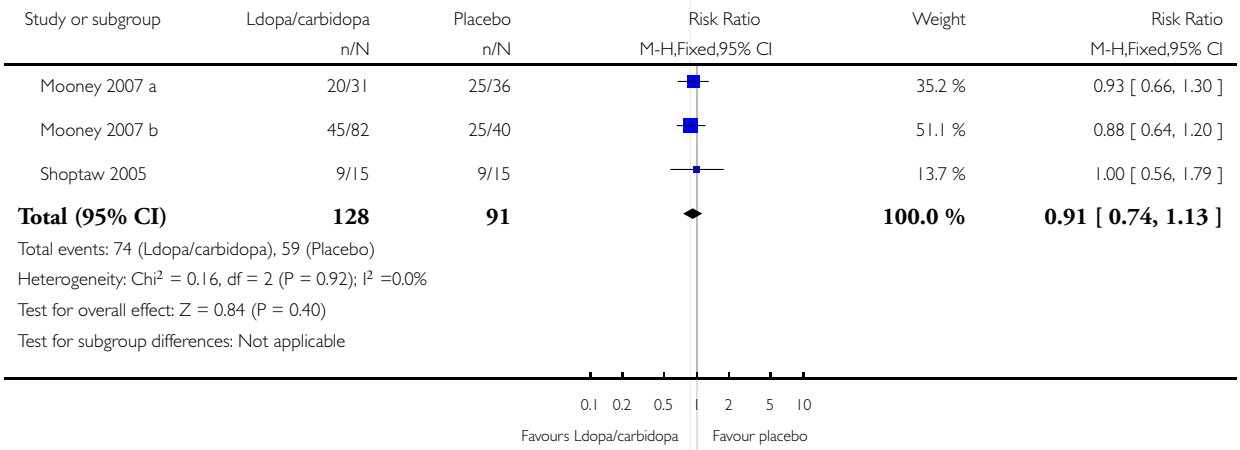


Analysis 4.1. Comparison 4 L dopa/Carbidopa versus placebo, Outcome 1 Dropouts.

Review: Dopamine agonists for the treatment of cocaine dependence

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.

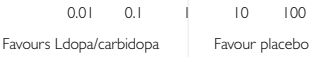
Review: Dopamine agonists for the treatment of cocaine dependence

Comparison: 4 L dopa/Carbidopa versus placebo

Outcome: 2 Dropouts due to adverse events

Study or subgroup	Ldopa/carbidopa n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Mooney 2007 a	1/31	1/36		1.16 [0.08, 17.80]
Mooney 2007 b	0/82	0/40		0.0 [0.0, 0.0]
Schmitz 2008	1/68	1/68		1.00 [0.06, 15.66]
Total (95% CI)	**181**	**144**		**1.08 [0.16, 7.47]**

Total events: 2 (Ldopa/carbidopa), 2 (Placebo)
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² =0.0%
Test for overall effect: Z = 0.08 (P = 0.94)
Test for subgroup differences: Not applicable



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

Review: Dopamine agonists for the treatment of cocaine dependence

Comparison: 4 L dopa/Carbidopa versus placebo

Outcome: 3 Abstinence (objective)

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Mooney 2007 a	19/31	18/36		31.9 %	1.58 [0.60, 4.19]
Mooney 2007 b	26/82	14/40		63.6 %	0.86 [0.39, 1.92]
Schmitz 2008	7/68	0/68		2.2 %	16.71 [0.93, 298.62]
Shoptaw 2005	15/15	14/15		2.2 %	3.21 [0.12, 85.20]
Total (95% CI)	**196**	**159**		**100.0 %**	**1.49 [0.85, 2.63]**

Total events: 67 (Experimental), 46 (Control)
Heterogeneity: Chi² = 4.73, df = 3 (P = 0.19); I² =37%
Test for overall effect: Z = 1.39 (P = 0.16)
Test for subgroup differences: Not applicable

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

Review: Dopamine agonists for the treatment of cocaine dependence

Comparison: 5 Amantidine versus antidepressants

Outcome: 1 Dropouts

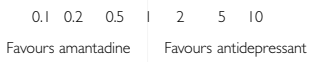
Study or subgroup	Amantadine n/N	Antidepressants n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kolar 1992	2/5	0/8		1.6 %	7.50 [0.43, 130.34]
Kosten 1992	8/33	8/30		33.0 %	0.91 [0.39, 2.12]
Oliveto 1995	2/5	1/8		3.0 %	3.20 [0.38, 26.78]
Oliveto 1995	2/5	3/4		13.1 %	0.53 [0.16, 1.79]
Weddington 1991	7/23	15/32		49.3 %	0.65 [0.32, 1.33]
Total (95% CI)	**71**	**82**		**100.0 %**	**0.90 [0.57, 1.44]**

Total events: 21 (Amantadine), 27 (Antidepressants)

Heterogeneity: Chi^2 = 5.01, df = 4 (P = 0.29); I^2 =20%

Test for overall effect: Z = 0.42 (P = 0.67)

Test for subgroup differences: Not applicable



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

Review: Dopamine agonists for the treatment of cocaine dependence

Comparison: 5 Amantidine versus antidepressants

Outcome: 2 Adverse events as N of participants with at least one adverse event

Study or subgroup	Amantadine n/N	Antidepressant n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kolar 1992	0/3	3/8		30.8 %	0.32 [0.02, 4.87]
Weddington 1991	3/16	5/17		69.2 %	0.64 [0.18, 2.24]
Total (95% CI)	**19**	**25**		**100.0 %**	**0.54 [0.17, 1.70]**

Total events: 3 (Amantadine), 8 (Antidepressant)

Heterogeneity: Chi^2 = 0.21, df = 1 (P = 0.65); I^2 =0.0%

Test for overall effect: Z = 1.05 (P = 0.29)

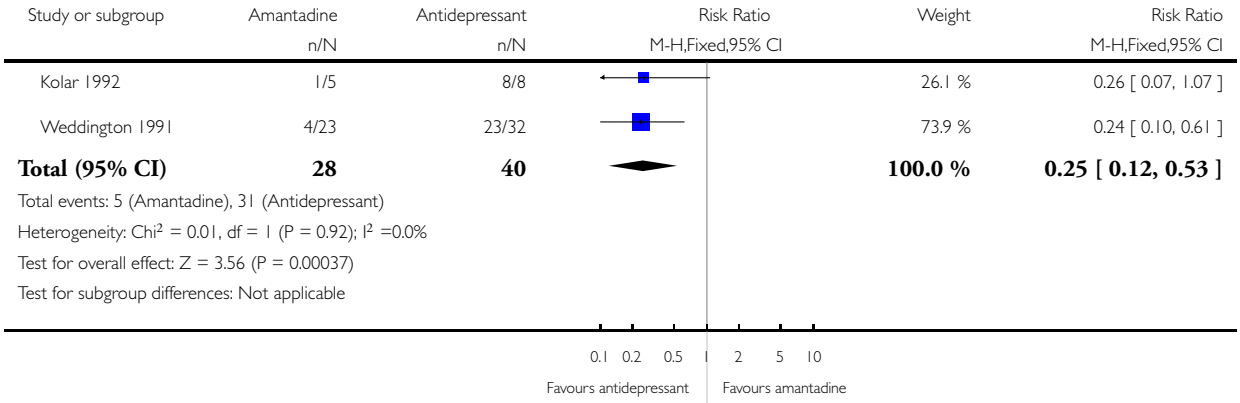
Test for subgroup differences: Not applicable

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

Review: Dopamine agonists for the treatment of cocaine dependence

Comparison: 5 Amantidine versus antidepressants

Outcome: 3 Abstinence (objective)



ADDITIONAL TABLES

Table 1. Assessment of risk of bias in the 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; minimization
	High risk	The investigators describe a non-random component in the sequence generation process such as: odd or even date of birth; date (or day) of admission; hospital or clinic record number; alternation; judgement of the clinician; results of a laboratory test or a series of tests; availability of the intervention
	Unclear risk	Insufficient information about the sequence generation process to permit judgement of low or high risk

Table 1. Assessment of risk of bias in the included studies (*Continued*)

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 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
	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;
5. incomplete outcome data (attrition bias) For all outcomes except retention in treatment or drop out	Low risk	No missing outcome data; Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias);

Table 1. Assessment of risk of bias in the included studies (*Continued*)

		Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; Missing data have been imputed using appropriate methods All randomised patients are reported/analysed in the group they were allocated to by randomisation irrespective of non-compliance and co-interventions (intention to treat)
	High risk	Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation;
	Unclear risk	Insufficient information to permit judgement of low or high risk (e.g. number randomised not stated, no reasons for missing data provided; number of drop out not reported for each group);
6 selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
	High risk	Not all of the study's pre-specified primary outcomes have been reported; One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; The study report fails to include results for a key outcome that would be expected to have been reported for such a study
	Unclear risk	Insufficient information to permit judgement of low or high risk

APPENDICES

Appendix 1. Search strategy 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

Appendix 2. Search strategies 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

Appendix 3. Search strategy 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)

Appendix 4. Search strategy 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

WHAT'S NEW

Last assessed as up-to-date: 12 October 2011.

Date	Event	Description
12 October 2011	New search has been performed	New authors, new searches, new studies
12 October 2011	New citation required and conclusions have changed	New authors, new searches, new studies

HISTORY

Protocol first published: Issue 1, 2001

Review first published: Issue 4, 2001

Date	Event	Description
21 April 2008	Amended	Converted to new review format.
25 February 2003	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Two author (Vecchi, Solimini) developed search strategy. Two authors (Vecchi, Solimini) inspected the search hits by reading titles and abstracts. Each potentially relevant study located in the search was obtained in full text and assessed for inclusion independently by two authors (Amato, Minozzi). Doubts were resolved by discussion between all the authors. Two authors (Minozzi, Amato) assessed study quality. Data were extracted independently by two authors (Amato, Minozzi). Any disagreement was discussed between all the authors. Pani has written the background and participated to results's discussion. Davoli and Zuccaro commented and emended the review.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- Department of Epidemiology, Lazio Regional Health Service, ASL RM E, Not specified.

External sources

- Italian Drug Agency, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review is a substantially update done by new authors several years after the first publication. Methods section is substantially changed according with the new features developed in these years within the Cochrane Collaboration.

NOTES

The authors did not update the review and did not answer to our reminders in order to update it. The topic is considered relevant and for that we decided to withdraw the review and make it available for new authors.

INDEX TERMS

Medical Subject Headings (MeSH)

Amantadine [therapeutic use]; Bromocriptine [therapeutic use]; Cocaine-Related Disorders [*drug therapy]; Dopamine Agonists [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans