MANAGEMENT OF SUBSTANCE DEPENDENCE

REVIEW SERIES

SYSTEMATIC REVIEW OF PHARMACOLOGICAL TREATMENT OF COCAINE DEPENDENCE

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ABSTRACT

Cocaine dependence is a common and serious condition, associated with severe medical, psychological and social problems, including the spread of infectious diseases. This series of systematic reviews will critically assess the efficacy of pharmacotherapy for treating cocaine dependence. The literature search strategy included: electronic searches of Cochrane Library holdings, EMBASE, MEDLINE, PsycLIT, Biological Abstracts and LILACS; scans of reference lists of relevant articles, personal communications, conference abstracts, unpublished trials from the pharmaceutical industry and book chapters on the treatment of cocaine dependence. Randomised controlled trials focusing on the use of carbamazepine, antidepressants, dopamine agonists, and other drugs used in the treatment of cocaine dependence were included. Trials in which patients had an additional diagnosis such as opiate dependence were also eligible. The reviewers extracted the data independently, and relative risks (RR), and weighted mean differences were estimated. Number needed to treat would be calculated for statistically significant outcomes. Qualitative assessments were carried out using a Cochrane validated checklist. Where possible, analysis was carried out according to the "intention to treat" principles. The reviewers assumed that people who died or dropped out had no improvement in their condition. The results indicate that there is no current evidence supporting the clinical use of CBZ, antidepressants, dopamine agonists mazindol, phenytoin, nimodipine, lithium, and NeuRecover-SA, in the treatment of cocaine dependence. Larger randomised investigation must be considered, while taking into account that these time-consuming efforts should be reserved for medications showing more relevant and promising evidence. Given the high dropout rate among the test population, clinicians may wish to consider adding psychotherapeutic supportive measures aimed at keeping patients in treatment programs.

ACKNOWLEDGEMENTS

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INTRODUCTION

RATIONALE FOR THIS SERIES OF SYSTEMATIC REVIEWS ON THE PHARMACOLOGICAL TREATMENT OF COCAINE DEPENDENCE

Systematic reviews of scientific research allow for the efficient integration of valid information and provide a basis for rational decision-making. The use of explicit, consistent methods when reviewing can limits bias (systematic errors) and reduces random errors (simple mistakes), thus providing more reliable results upon which to draw conclusions and make decisions. In addition, meta-analysis, or the use of statistical methods to summarise the results of several independent studies provides a more precise estimate of the effects of healthcare than that which can be derived from the individual studies included in a review.

In the 1970s and early 1980s, psychologists and social scientists developed systematic guidelines for minimising bias and random errors in research reviews. However, it was not until the late 1980s that attention was drawn to the poor scientific quality of healthcare review articles. Since the recognition of the need for systematic reviews in this field has grown rapidly. This is reflected by the current number of articles about review methods as well as the number of systematic reviews published in healthcare journals.

The Cochrane Collaboration is an international organisation that prepares, maintains and disseminates systematic reviews concerning the impact of health care or the effects of policy and practises on health. These reviews are designed to encompass every relevant randomised controlled trial, to critically appraise these works, and, if appropriate, to summarise them. A resulting overview is produced that is as free from bias as possible. The reviews focus on randomised controlled trials (RCTs) as they are the best available source of reliable information on the differential effects of different forms of healthcare.

Because of the widespread prevalence of cocaine dependence and its high social, psychological and physical morbidity, there is an urgent need to expand the treatment repertoire for this condition. A range of pharmacological treatments has been proposed. There is, however, a need for a critical appraisal and summary of RCT results in order to provide an unbiased overview of available evidence.

This review was conducted using the Cochrane Collaboration standards for preparing systematic reviews. An electronic version of this report will be published as a Cochrane Review, and will be updated to include new evidence as it emerges.

COCAINE DEPENDENCE

Cocaine consumption and related problems was an epidemic in the 1920s in the USA, disappearing by the end of that decade (Musto 1992). However, the use of cocaine increased again between 1976 and 1979, mainly in North America and some countries of South America. Since the early 1980s, cocaine abuse in the USA has again been at epidemic levels. Estimates from a recent National Household Survey on Drug Abuse based on a sample of 28,832 subjects indicate that there are 1.3 million cocaine users in the United States, more than five times the number of those addicted to heroin (Gold 1997).

Cocaine dependence has become a substantial public health problem, resulting in a significant number of medical, psychological and social problems; including the spread of infectious diseases (e.g. AIDS, hepatitis and tuberculosis), crime, violence and neonatal drug exposure. In consequence, there is an urgent need to expand the treatment repertoire for this condition. Although there is no consensus regarding how to treat cocaine dependence (Carroll 1994), effective pharmacotherapy can potentially play a major role within a broader treatment setting. The past decade has witnessed a sustained search for an effective pharmacotherapeutic agent for the treatment of cocaine dependence.

OUTLINE OF THIS SERIES OF REVIEWS

Various types of interventions have been assessed as potential treatments for cocaine dependence. In this series of systematic reviews, they have been grouped as follows:

(1)   Carbamazepine;

(2)   Antidepressants (such as desipramine, imipramine, fluoxetine, bupropion, etc.);

(3)   Dopamine agonists (such as bromocriptine and amantadine);

(4)   Miscellaneous.

METHODS

SEARCH STRATEGY: Electronic searches of Cochrane Library, EMBASE, MEDLINE, PsycLIT, Biological Abstracts and LILACS; scan of reference list of relevant articles; personal communication; conference abstracts; unpublished trials from the pharmaceutical industry; book chapters on the treatment of cocaine dependence.

(1)   Electronic databases: EMBASE (from 1980 - October 1997), LILACS (from 1982 - 1997), MEDLINE (from 1966 - October 1997), PsycLIT (from 1974 - July 1997), Biological Abstracts and Cochrane Library.

This review included published articles without language restrictions. The 'optimal' MEDLINE and EMBASE sensitive search strategies devised by the Cochrane Collaboration to identify randomised trials was used in conjunction with the following phrase in order to identify studies relevant to the pharmacological treatment of those with cocaine dependence:

    i. Cocaine or crack;

    ii. Abstinen* or dependen* or withdraw* or abus*;

    iii. 1 and 2 and, for the specific interventions (carbamezepine);

    iv. (carbamazepine or epitol or tegretol or tegretol CR or tegretard);

    v. 3 and 4.

The above phrase was also combined with references from other electronic databases, using specific phrases depending on the intervention evaluated.

(2)   Reference searching: the references of all identified studies were also used to identify other existing trials.

(3)   The register of trials kept by the Cochrane Schizophrenia Group and the Depression, Anxiety and Neurosis Group were also searched.

(4)   Conference abstracts were searched for references.

(5)   Personal Communications: in order to ensure that as many as possible RCTs were identified, the authors of the included studies were consulted to find out if they knew of any published or unpublished RCTs of carbamazepine on the treatment of cocaine dependence which had not yet been identified.

(6)   Attempts were made to obtain unpublished trials from the pharmaceutical industry.

(7)   Book chapters on the treatment of cocaine dependence (such as Lowinson 1997).

SELECTION CRITERIA: randomised controlled trials focusing on the use of various drugs for the treatment of cocaine dependence were included. Trials where patients had an additional diagnosis such as opiate dependence were also eligible.

TYPE OF STUDIES: All relevant randomised controlled trials.

TYPE OF PARTICIPANTS: People with any diagnosis for cocaine dependence, irrespective of gender, age or nationality. Trials including patients with additional diagnosis such as opiate dependence or those in methadone maintenance schemes were also eligible.

TYPES OF OUTCOME MEASURES: Where possible the outcomes were divided into 'clinically significant changes' or 'no stated change'. If the assessment was not possible and no other outcomes were provided (such as continuous data, without mean and SD), the authors were contacted and the study was put under 'awaiting assessment'. Outcomes of interest were:

(1) Acceptability of the treatment: measured by the number of people reporting adverse events and dropping out during the trial/ post randomisation exclusions.

(2) Efficacy
   i. Abstinence of cocaine use as measured by:
         - urine samples positive for cocaine metabolite (dichotomous);
         - self-report.
   ii. Craving:
         - weekly changes in cocaine craving (continuous);
         - subject-reported desire for cocaine (dichotomous);
         - self-report.
   iii. Severity of dependence
         - using scales such as the Addiction Severity Index (ASI);
         - retention time in treatment (continuous).
   iv. Amount of cocaine consumed (as measured by grams used or dollars spent)
   v. Mood states
         - changes on depression scales (such as Hamilton Depression Scale (HAM-D) (continuous).

(3) Other outcomes provided, such as school, job, criminal activity, relapse, death and quality of life measures.

All outcomes were grouped into time periods - short term (less than 6 weeks), medium term (6 weeks to 6 months) and long term (over 6 months).

SELECTION OF TRIALS: One reviewer (ARL) screened the abstracts of all publications obtained by the search strategy. A distinction was made between:

(1) eligible studies, including any pharmacological treatment comparison;

(2)   Pharmacological treatments without any control element or general treatment studies other than pharmacological.

For articles that were possibly RCTs the full article was obtained and inspected to assess their relevance to this review based on the criteria for inclusion.

QUALITY ASSESSMENT: In order to ensure that variation was not caused by systematic errors in the design of a study, two independent reviewers (ARL and BGOS) assessed the methodological quality of the selected trials. Quality was assessed using the criteria described in the Cochrane Handbook (Mulrow 1997). It is based on the evidence of a strong relationship among the potential for bias in the results and the allocation concealment (Schulz 1995) and is defined as below:

(1)   Low risk of bias (adequate allocation concealment);

(2)   Moderate risk of bias (some doubt about the results);

(3)   High risk of bias (inadequate allocation concealment).

For the purpose of the analysis in this review, trials were included if they met the criteria A or B of the Handbook.

DATA COLLECTION AND ANALYSIS: the reviewers extracted the data independently and Relative Risks, weighted mean difference and number needed to treat were estimated. Qualitative assessments were carried out using a Cochrane validated checklist. The reviewers assumed that people who died or dropped out had no improvement. Where possible, analysis was carried out according to the "intention to treat" principles.

DATA MANAGEMENT: Any disagreement among the reviewers concerning data was discussed, the decisions documented and, where necessary, the authors of the studies were contacted to help resolve the issue. All exclusion/ dropouts were identified. If no information was available (either from the report or from the authors), it was assumed that drop out was because of side effects/ treatment failure. The sensitivity of the results was tested to see if the inclusion of this assumption caused any substantial changes.

In the case of trials using a crossover design, to exclude the potential additive effect in the second or later stages on these trials, only data from the first stage was analysed.

ANALYSIS: Dichotomous outcomes were analysed calculating relative risks for each trial with the uncertainty in each result being expressed by their confidence intervals. The relative risks from the individual trials were combined through meta-analysis.

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Continuous outcomes were analysed according to their difference in mean treatment effects and its standard difference. Skewed data are not used, as they are poorly analysed.

Heterogeneity in the results of the trials was assessed both by graphical inspection and by calculating a test of heterogeneity. Possible reasons for heterogeneity were pre-specified. Responses differs:

(1)   According to the different drugs;

(2)   When psychosocial therapies are provided in conjunction with prescribed drugs;

(3)   According to the characteristics of patients participating in trials and;

(4)   Depending on length of treatment. Heterogenity was assessed by looking at separate subgroups of trials.

Tables were used to display characteristics of eligible trials including those excluded with the reasons for exclusion. Outcomes were also presented graphically. A review manager software developed by the Cochrane Collaboration was used to organise and process the results.

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CARBAMAZEPINE FOR COCAINE DEPENDENCE

SUMMARY

The anti-convulsant carbamazepine, a tricyclic medication that is widely used to treat a variety of neurological and psychiatric disorders, has also been used to treat cocaine dependence. However, its effectiveness has not been established (Montoya 1995).

OBJECTIVES: To investigate the efficacy and acceptability of carbamazepine in the treatment of cocaine dependence when compared with placebo.

SELECTION CRITERIA: All randomised controlled trials focusing on the use of carbamazepine drugs versus placebo for the treatment of cocaine dependence were included. Trials where patients had an additional diagnosis such as opiate dependence were also eligible.

TYPES OF INTERVENTIONS:

(1)   Carbamazepine: any dose and mode or pattern of administration;

(2)   Placebo;

(3)   Other medications eventually used in comparison to carbamazepine.

MAIN RESULTS: 5 studies were included in the review, with 455 participants randomised. No differences were found regarding positive urine samples for cocaine metabolites. Dropouts were high in both groups, with up to 70% in the placebo group. Fewer dropouts occurred in the Carbamazepine group (RR 0.87, 95% CI 0.71-1.06). When they were due to side effects, no differences were found between the interventions.

CONCLUSIONS: There is no current evidence supporting the clinical use of CBZ in the treatment of cocaine dependence. Larger randomised investigations must be considered taking into account that these time-consuming efforts should be reserved for medications showing better promise.

DESCRIPTION OF STUDIES

EXCLUDED STUDY: Hatsukami (1990) is a randomised, crossover study, comparing carbamazepine versus placebo, for male cocaine abusers (N=6), using 40 mg/day of cocaine. There is no clear data just on the first arm of the crossover, and the outcomes are only related to the effects of carbamazepine on the acute use of cocaine, this not being the objective of this review.

INCLUDED STUDIES: It was possible to extract data from 5 studies.

DURATION OF TRIALS: From 20 days to 6 months.

SETTING: All trials were conducted with outpatients, at the community level.

PARTICIPANTS: 455 people meeting DSM-III-R criteria for cocaine dependence were randomised for the interventions. Trials included participants with other psychiatric diagnosis such as alcohol dependence, depression and generalised anxiety. 79% (361) participants were male and 58% black. Age range was 18-60 years.

INTERVENTIONS: In two trials (Kranzler, 1995 and Montoya, 1995) carbamazepine doses were fixed in 600 and 800 mg/day respectively. In Cornish (1995), doses started at 200 mg/day, with gradual increases in order to reach serum levels of 4-12 ug/ml. Two distinct doses (400 and 800 mg/ day) of CBZ corresponding to two arms were adopted in Halikas' trial (1997). Dose was unknown in Campbell's trial (1994).

OUTCOMES: Outcomes, as reported by authors of the trials, were either dichotomous or continuous. The following scales were used in the relevant studies:

(1)   Craving (subject-reported desire for cocaine using a 20-point Interval analogue scale; Minnesota Cocaine Craving Scale);

(2)   Drug Impairment Rating Scale for cocaine (DIRS-C);

(3)   Halikas Drug Impairment Rating Scale (HALDIRS);

(4)   Beck Depression Inventory (BDI);

(5)   Spielberg State Anxiety Inventory (SSA);

(6)   Symptom Check List-90-Revised (SCL-90-R);

(7)   Patient Global Improvement (PGI);

(8)   Addiction Severity Index (ASI).

However, relevant data was provided for SSA, ASI and BDI only. Skewed data (ASI and BDI) could not be presented in graphical form and were described in the 'other data' section. In Halikas (1997), many continuous outcomes were described in terms of means without corresponding standard deviations, log (odds ratio), or actual measures units for baseline point and linear change per visit. Such data could not be summarised and the p-value for each comparison was unclear. Further relevant information for these studies is shown in Table 1.

Table 1. Carbamazepine for cocaine dependence: characteristics of included randomised controlled trials.

AUTHOR/ YEAR	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOMES USED	OUTCOMES UNABLE TO USE
Campbell, (1994)	Allocation:computer -generated list of random numbers; Blindness: double; Duration: 6 months; Design:three parallel groups; Analysis: non ITT.	Diagnosis: cocaine dependence(DSM-III-R); Number: 65; Age: 32 years (range 20 - 60); Sex: 63% male; Race: 90% black; Setting: community; History: co-morbidity - alcohol dependence (n=16), major depression (11), antisocial personality disorder (16).	1. Desipramine (n=21; dose unknown); 2. Carbamazepine (n=19; dose unknown) 3. Placebo (n=25).	Duration of treatment (no SD)	Urine samples positive for cocaine metabolite Drop out
Cornish, (1995)	Allocation: randomised; Blindness: double; Duration: 10 weeks; Design: 2 parallel groups; Analysis: non ITT.	Diagnosis: cocaine dependence (DSM-III-R); Number: 95; Age: range 21-51 years; Sex: 98% males; Race: 98% black; Setting: two studies sites, community; History: subjects were recruited from individual seeking outpatient treatment for cocaine dependence.	1. Carbamazepine (n=37). Dose started at 200 mg/day, being increased in order to reach serum levels of 4-12 ug/ml 2. Placebo(n=45)	Death No retention in treatment Positive urine sample for cocaine metabolite Side-effects	Craving (subject-reported desire for cocaine using a 20-point Interval analogue scale)

Table 1: Carbamazepine for cocaine dependence: characteristics of included randomised controlled trials.

AUTHOR/ YEAR	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOMES USED	OUTCOMES UNABLE TO USE
Hallikas 1997	Randomisation: by a block design, no details on allocation concealment; Blindness: double blind; Duration: 12 weeks; Design: 3 parallel groups; Analysis: non-ITT - 33 subjects who failed to return in visit 1 after baseline were replaced in the randomisation.	Diagnosis: cocaine dependence (DSM-III-R); Number: 183; Age: mean 32.5 years; Sex: 71% males; Race: 66.1% white; Setting: community; History: subjects had at least an eighth grade education. Psychosocial interventions were offered to participants.	1. Carbamazepine 400 mg (n=62). 2. Carbamazepine 800 mg (n=58). 3. Placebo(n=63)	No retention in treatment Positive urine sample for cocaine metabolite Severe dermatologic reaction	
Kranzler 1995	Allocation: randomised, done by a research pharmacist not involved in the clinical care of the participants. Blindness: double Duration: 12 weeks Design: 2 parallel groups Analysis: ITT	Diagnosis: cocaine dependence (DSM-III-R); Number: 40; Age: range 18-45 years; Sex: 100% males; Race: 32% black; Setting: community; History: subjects used at least 4 g of cocaine during the preceding month.	1. Carbamazepine 600 mg (n=20) 2. Placebo (n=20)	Urine samples positive for cocaine metabolite No retention in treatment Number of people presenting at least one side effect Side-effects ASI, BDI, SAS Days of cocaine use Intensity of cocaine use	Self reported cocaine use Amount of cocaine used per day

Table 1: Carbamazepine for cocaine dependence: characteristics of included randomised controlled trials.

AUTHOR/ YEAR	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOMES USED	OUTCOMES UNABLE TO USE
Montoya (1994)	Randomised: yes, but no information on allocation concealment Blindness: double-blind Duration: 8 weeks Design: 2 parallel group Analysis: non ITT	Diagnosis: cocaine dependence (DSM-III-R) Number: 72 Age: mean 33,2 years Sex: 79% males Race: 68% black Setting: community History: at least 14 g of self-reported cocaine use in the prior 3 months	1. Carbamazepine 800 mg/day (n=28) 2. Placebo (n=34)	No retention in treatment	Urine samples positive for cocaine metabolite Self report of drug use Craving (MCCS) Mood states (BDI) Side-effects Retention in treatment Symptom Check List-90-Revised Grams / money spent

GLOSSARY

ASI: Addiction Severity Index
BDI: Beck Depression Inventory score
SSA: Spielberg State Anxiety score
MCCS: Minnesota Cocaine Craving Scale
DSM-III-R: Diagnostic and Statistical Manual 3rd edition - American Psychiatric Association
ITT: Intention to treat analysis

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METHODOLOGICAL QUALITY

RANDOMISATION: Only one study described adequate concealment of allocation: in Kranzler (1995), a research pharmacist not involved in the clinical care of the participants did randomisation. Campbell (1994) used a computer-generated list of random numbers. Halikas (1997) used a randomised block design. Cornish (1995) and Montoya (1995) did not give details on randomisation and allocation procedures.

BLINDING: All the included studies used a double-blind design. Blinding was tested in one trial (Halikas, 1997).

DESCRIPTION OF NO RETENTION IN TREATMENT: With the exception of Campbell (1994), all studies included descriptions of those who dropped out before the end of the trial protocol.

OUTCOME REPORTING: Many outcomes could not be summarised because they were presented in graphical form or only on statistical tests and p-values. For most of the continuous variables, standard deviation was not provided.

RESULTS

THE SEARCH: 1014 citations were found through the electronic search. Only 8 were related to carbamazepine and placebo and all of these were obtained. 7 different studies were identified from these citations and 5 were included in the review.

DEATH: Death by suicide was described in one study (Cornish 1995, N=82), occurring with one participant using carbamazepine.

POSITIVE URINE SAMPLE FOR COCAINE METABOLITES: The cut-off value considered to determine a positive test sample was 300 mg/ml in the urine. No differences were established when 242 participants, from three studies, were randomised (Figure 1.1).

PATTERN OF COCAINE USE: The following outcomes were used to assess the pattern of cocaine use and craving: duration of treatment in weeks (Campbell, 1994); amount of grams used per day (Kranzler, 1995), days of cocaine use (Kranzler, 1995); ASI drug scores at the end of the trial (Kranzler. 1995), craving intensity frequency (Halikas, 1997). These data were skewed and were not summarised. Halikas' (1997) study found improvements trends in decrease of craving intensity and duration and in decrease of self-report cocaine use favouring 400 mg of Carbamazepine when compared to placebo.

Figure 1.1. Carbamazepine for cocaine dependence: positive urine sample for cocaine metabolites

Kranzler 1995

Cornish 1995

DL pooled relative risk = 1,05 (95% CI =0,62 to 1,77)
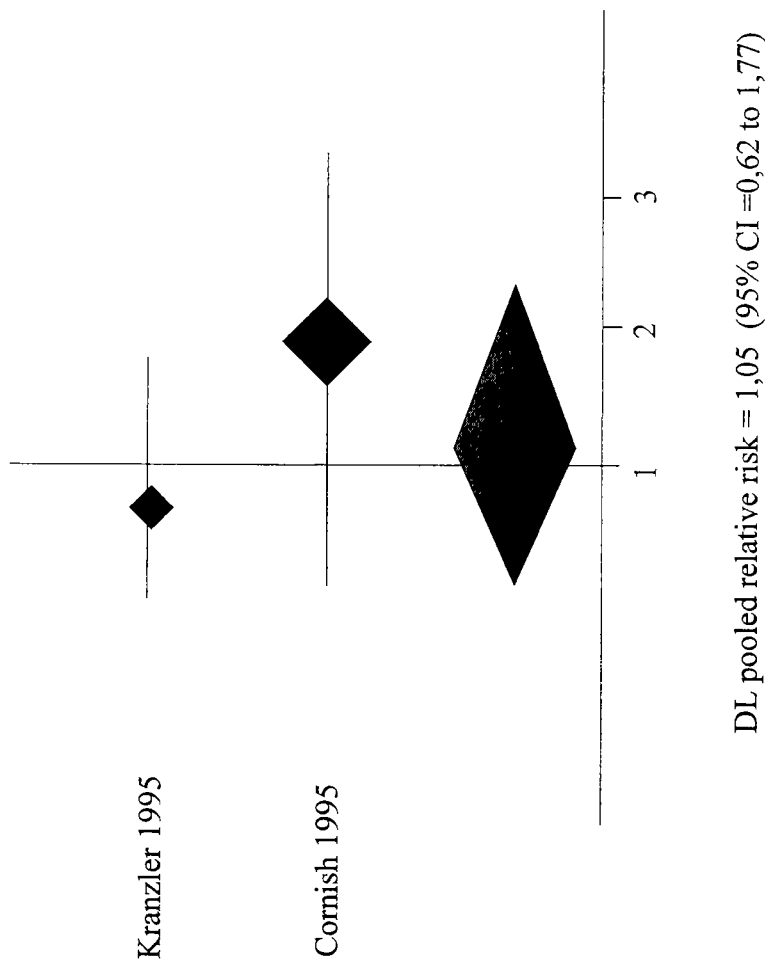
OTHER CLINICAL RATINGS: Halikas (1997) evaluated some clinical aspects of those using cocaine. The following scales were used: Drug Impairment Rating Scale for Cocaine (DIRS-C) and Clinical Global Improvement (CGI), but no statistical differences were found between placebo and CBZ. Therapeutic Effects, as measured by a 4-point scale, were evaluated and favoured placebo when compared to CBZ 400 mg (p=0.009).

BEHAVIOUR: Two scales were used to characterise depression and anxiety, BDI and SSA respectively. BDI data was too skewed to be presented graphically. SSA slightly favoured carbamazepine, but did not reach statistical significance.

NO RETENTION IN TREATMENT: Less drop out occurred in the Carbamazepine group (RR 0.88, 95%CI 0.75-1.03). When no retention in treatment was due to side effects no differences were found (Figure 1.2).

SIDE EFFECTS: Several side effects were described in the trials, including dermatological hypersensitivity reaction, dizziness, drowsiness, dry mouth, headache, nausea, and vomiting, and there were no statistically significant differences between carbamazepine and placebo. The number of participants presenting at least one side effect, reported by Kranzler (1995), was higher in the carbamazepine group, without reaching statistical significance.

DISCUSSION

The efficacy of carbamazepine for the treatment of cocaine dependent patients was first suggested by an open trial with 35 participants (Halikas, 1989). This same author conducted a crossover randomised controlled study two years later confirming this finding (n=32). Such promising results, however, were based on limited methods, the effects were modest, and the studies done by a single group. Despite this rationale and absence of a solid research base, the unfortunate consequence of the early publicity was that carbamazepine made its way into physicians' practices (Johanson 1995). Further randomised investigation from 5 RCTs, and involving 455 subjects suggest lack of evidence regarding the efficacy of carbamazepine. Type II error could be an explanation for such findings but other factors such as illness behaviour must also to be considered.

The most evident methodological problems for these studies concern the high dropout rates. Although slightly favouring carbamazepine, these rates were high for both those taking carbamazepine (61%) and placebo (69%).

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Figure 1.2. Carbamazepine for cocaine dependence: no retention in treatment.
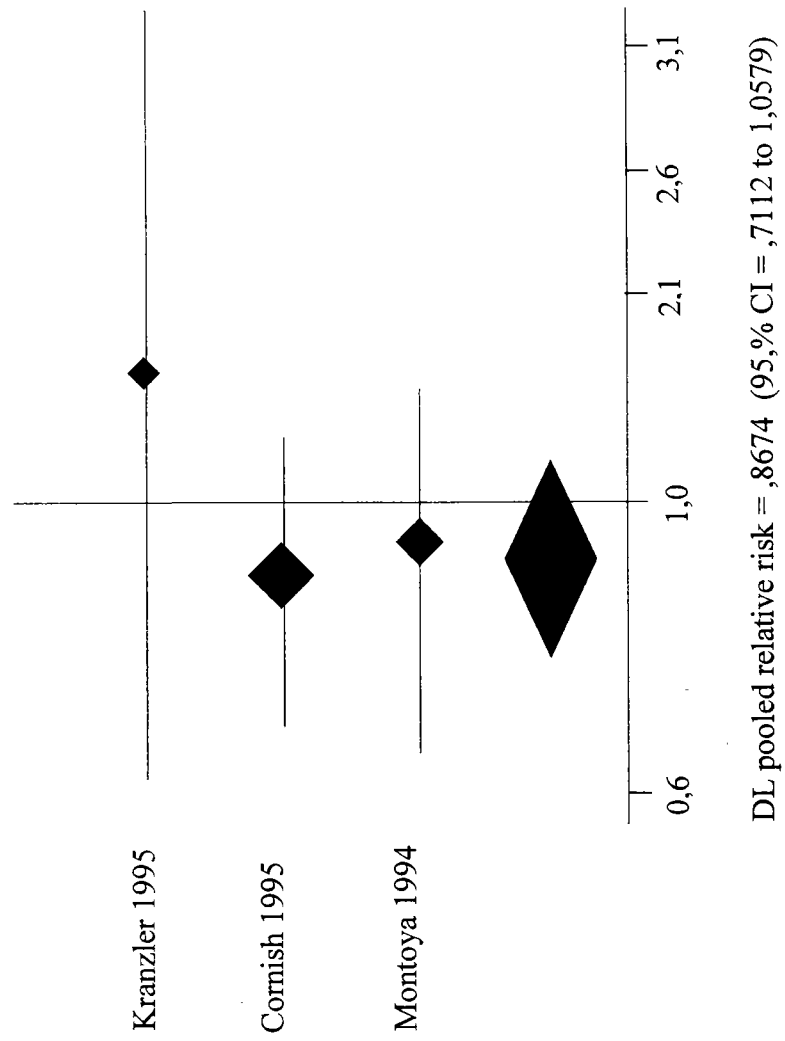
Kranzler 1995

Cornish 1995

Montoya 1994

0,6   1,0   2,1   2,6   3,1

DL pooled relative risk = ,8674 (95,% CI = ,7112 to 1,0579)

The most evident methodological problems for these studies concern the high dropout rates. Although slightly favouring carbamazepine, these rates were high for both those taking carbamazepine (61%) and placebo (69%). These high dropout rates may be inherent to the type of drug problem and to its severity. The high drop rates in both groups indicate the need for the development of strategies to retain individuals who are cocaine dependent in treatment.

In the addiction field, there is a high correlation between compliance with prescribed treatment and clinical outcome (Meyer, 1992). In open trials such as the one conducted by Halikas (1997) patients may be motivated and are not representative of cocaine dependent patients in the general population. Participants in the studies included in this review may manifest vastly differing degrees of motivation for change. Such motivation may significantly improve overall outcome but to date this has not been well demonstrated empirically.

Ideally, successful pharmacological intervention should act independently of level of patient motivation for change. Theoretically, motivation need not be a prerequisite for the use of anti craving medication (Halikas, 1991).

Halikas (1997) found significant results favouring the use 400 mg of Carbamazepine, although therapeutic effects as assessed by clinicians showed that the placebo group performed significantly better. In the same trial, a number of continuous outcome variables were subjected to sophisticated regression analysis. However, the most consistent efficacy outcome – positive analysis – did not show any significant difference between groups, even adopting the most positive results from Halikas (400 mg/day).

IMPLICATIONS FOR PRACTICE

The urgent demand by clinicians, patients, families, and the community as a whole for an adequate treatment for cocaine dependence may lead to adoption of therapeutic regimes even if the evidence of their efficiency is weak. Alternatively, it is plausible that carbamazepine illustrates a common problem of extrapolating results from pre clinical studies to clinical effects in adults, which are not necessarily related to demonstrated and significant clinical effects.

Although caution is needed when assessing results from a limited number of clinical trials, there is no current evidence supporting the clinical use of CBZ in the treatment of cocaine dependence.

IMPLICATIONS FOR RESEARCH

In general, the overall quality of the included studies was reasonable. The absence of clinical effects based on a small numbers of trials may lead to a general conclusion that larger randomised controlled trials are needed. However, in light of the data reviewed, it could be that this is not justified, due to the lack of any clinically relevant results from carbamazepine trials. With nearly 500 subjects randomised, more than trends and a small number of significant results, which the current evidence relies on, is needed. Larger randomised investigations are expensive and time-consuming and should perhaps be reserved for medications showing more relevant and promising evidence.

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ANTIDEPRESSANTS FOR COCAINE DEPENDENCE

SUMMARY

While the administration of cocaine acutely increases intercellular dopamine, serotonin, and norepinephrine levels by blocking their pre-synaptic reuptake (Gold, 1997), chronic cocaine abuse leads to down-regulation of monoamine systems. Post-cocaine use depression and cocaine craving may be linked to this down-regulation.

These pre-clinical findings are the theoretical foundations on which the use of antidepressants for the treatment of cocaine dependence is based. Under this assumption, antidepressant pharmacotherapy, by increasing monoamine levels, may alleviate cocaine abstinence symptomatology, as well as relieving dysphoria and associated craving by general antidepressant action (Margolin 1995).

Despite such encouraging pre-clinical evidence, to date no particular antidepressant has been shown to be clearly effective and most of the individual studies do not show significant results.

OBJECTIVES: To conduct a systematic review of all RCTs on the use of antidepressants for treating cocaine dependence.

SELECTION CRITERIA: The inclusion criteria for all randomised controlled trials were that they should focus on the use of antidepressants for treatment of cocaine dependence. Trials including patients with additional diagnosis such as opiate dependence were also eligible.

TYPES OF INTERVENTIONS:

(1)   Any antidepressant drugs
        i. Tricyclic and related antidepressant drugs;
        ii. Monoamine-oxidase inhibitors (MAOIs);
        iii. SSRIs and related antidepressants.

(2)   Placebo

(3)   Other medications eventually used in comparison to antidepressants

MAIN RESULTS: 18 studies were included in the review, with 1,177 participants randomised. Positive urine samples for cocaine metabolites were the main efficacy measure, with no significant results obtained regardless of the type of antidepressant. Compared to other drugs, desipramine performed better, but showed only a non-significant improvement trend with heterogeneity present, as revealed by the chi-square test (8.6, df=3; p=0.04). One single trial showed imipramine performed better than placebo in terms of clinical response, according to patient self-reporting. A similar rate of retention in treatment was found

for both patients taking desipramine or placebo. Results from a single trial suggest fluoxetine patients on SSRIs are less likely to dropout. Similar results were obtained for trials where patients had additional diagnoses of opioid dependence and/or were in methadone maintenance treatment.

CONCLUSIONS: There is no current evidence supporting the clinical use of antidepressants in the treatment of cocaine dependence. Given the high rate of dropouts in this population, clinicians may consider adding psychotherapeutic supportive measures aiming at keeping patients in treatment.

DESCRIPTION OF STUDIES

EXCLUDED STUDIES: Seven studies were excluded in this review for a series of reasons, including the absence of randomisation, and where assessment of subjective and physiological effects was the aim of the study.

INCLUDED STUDIES: It was possible to extract data from 18 studies.

DURATION OF TRIALS: From 40 days - 6 months.

SETTING: Most of trials were conducted with outpatients, at the community level or in mental health centres. In some trials (Hall 1994; Jenkins 1992; McElroy 1989; Triffleman 1992), patients were hospitalised at the beginning of study.

PARTICIPANTS: 1,177 people suffering from cocaine dependence were randomised for the interventions. Psychiatric comorbidity other than opiate dependence were reported in most of the trials, including antisocial personality disorder, alcohol dependence, depression and generalised anxiety. Male gender and African-American origin were predominant characteristics. Age range was 20-60 years.

INTERVENTIONS: Desipramine was the main antidepressant studied in the RCTs included in this review (12). Doses ranged from 150 to 300 mg/day, and were unknown in the Campbell (1994) study.
Fluoxetine was used in two trials, doses ranging from 20 to 60 mg/day. Three distinct doses (20, 40 and 60 mg/day) of fluoxetine corresponding to three arms were adopted in Covi's trial (1993).
Ritanserin (10mg/day), gepirona (16mg/day), bupropion (300mg/day), and imipramine (150-300 mg/day) therapeutic effects were investigated in one trial each.

OUTCOMES: Outcomes were either dichotomous or continuous, as reported by trialists. The following scales were used:

(1)   Beck Depression Inventory (BDI);

(2)   Craving related scales (subject-reported desire for cocaine using a 20-point Interval analogue scale; Minnesota Cocaine Craving Scale);

(3)   Drug Impairment Rating Scale for cocaine (DIRS-C);

(4)   Halikas Drug Impairment Rating Scale (HALDIRS);

(5)   National Institute of Mental Health Diagnostic Interview Schedule (NIMH DIS);

(6)   Cocaine Craving Scale (CCS);

(7)   Cocaine Craving Intensity (CCI);

(8)   Cocaine Craving Frequency (CCF);

(9)   Clinical Global Improvement (CGI);

(10)   Quantitative Cocaine Inventory (QCI);

(11)   Yale Quantitative Cocaine Inventory, modified version (Batki et al., 1991, 1993, 1994);

(12)   Hamilton Depression Scale (HAM-D);

(13)   Hamilton Anxiety Scale (HAS);

(14)   Profile of Mood States (POMS);

(15)   Brief Psychiatric Rating Scale (BPRS).

Data related to the Addiction Severity Index (ASI) were used, as some of the sub-items were not skewed. However, these concern only two trials (Carroll 1994, Margolin 1995).

Many continuous outcomes were described in terms of means without corresponding standard deviations. Such data could not be summarised and the p-value for each comparison was unclear.

Some continuous outcomes related to cocaine use could be reported in this review (percentage of abstinent days, days of cocaine use per week and craving intensity). However, they were found in two trials (Carrol 1994; Batki 1996) and it was not possible to perform meta-analysis.

The most relevant dichotomous outcomes were:

(1)   Positive urine sample for cocaine metabolites;

(2)   Non response (self-report);

(3)   Non retention in treatment;

(4)   Non retention in treatment due to side effects.

Table 2. Antidepressants for cocaine dependence: characteristics of included randomised controlled trials.

AUTHOR/ YEAR	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOMES USED	OUTCOMES UNABLE TO USE
Arndt 1992*	Allocation: subjects were randomly assigned to active medication or placebo in a 2:1 ratio Blindness: double Duration: 12 weeks Design: two parallel groups Analysis: non intention-to-treat	Diagnosis: cocaine abuse (DSM-III) in methadone-maintained treatment for heroin dependence Number: 79 Age: 22 - 59 years; mean 40,5 Sex: 100% males Race: 90% african-american Setting: outpatients History: 51% of patients met DSM-III criteria for antisocial personality disorder.	1. Desipramine 250-300 mg/day (n= 36) 2. Placebo (n=23)	USED No retention in treatment No retention in treatment for side effect	ASI; BDI; NIMH DIS; CCS; QCI; Urine Toxicology Screenings
Batki 1996	Allocation: randomised Blindness: double Duration: 12 weeks Design: 2 parallel groups Analysis: non ITT	Diagnosis: cocaine dependence (DSM-III) Number: 32 Age: 34 years Sex: 66% males Race: 53% african-american Setting: outpatients History: 12 participants with major depressive disorder (DSM-III-R), 6 with antisocial personality disorder, 6 with alcohol abuse dependence.	1. Fluoxetine 40 mg/day (20mg on the first week) (n=16) 2. Placebo (n=16)	USED No retention in treatment QCI modified version (days used, craving, quality of high)	Urine and plasma cocaine and benzoylegonine levels - not objective of the review Hamilton Depression Scale - numbers unclear Hamilton Anxiety Scale - numbers unclear

Table 2. Antidepressants for cocaine dependence: characteristics of included randomised controlled trials.

AUTHOR/ YEAR	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOMES USED	OUTCOMES UNABLE TO USE
Campbell 1994	Allocation: computer-generated list of random numbers Blindness: double Duration: 6 months Design: three parallel groups Analysis: non ITT	Diagnosis: cocaine dependence (DSM-III-R) Number: 65 Age: 32 years (range 20 - 60) Sex: 63% male Race: 90% african-american. Setting: outpatients History: 16 subjects had current diagnosis of alcohol dependence, 11 major depression, 2 generalised anxiety disorder, and 16 antisocial personality disorder.	1. Desipramine (n=21; dose unknown) 2. Carbamazepine (n=19; dose unknown) 3. Placebo (n=25)	Duration of treatment (no SD)	Positive urine samples for cocaine metabolites No retention in treatment Hours of treatment
Carroll 1994	Allocation: randomised Blindness: double blind Duration: 12 weeks Design: 4 parallel groups Analyses: non ITT	Diagnosis: cocaine dependence (DSM-III-R) Number: 139 Age: ~29 years Sex: male 73% Race: 46% Caucasians Setting: outpatients History: 49% had antisocial personality, 65% any other personality disorder, 48% alcohol dependence, 20% affective disorder, 13% anxiety disorder.	1. Desipramine (mean 200 mg/day) + RP (n=29) 2. Desipramine (mean 200 mg/day) + CM (n= 25) 3. Placebo + RP (n=29) 4. Placebo + CM (n=27)	No retention in treatment Cocaine use during treatment ASI (skewed data)	Percentage abstinent days Positive urine samples for cocaine metabolites Longest consecutive days of abstinence

Table 2. Antidepressants for cocaine dependence: characteristics of included randomised controlled trials.

AUTHOR/ YEAR	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOMES USED	OUTCOMES UNABLE TO USE
Covi 1993	Allocation: randomised; allocation was performed by a person who was not involved in recruitment of patients. Blindness: double Duration: 12 weeks Design: 4 parallel groups Analysis: non ITT	Diagnosis: cocaine dependence (DSM-III-R) Number: 45 Age: mean 30.0 (4.9) years Sex: male 80% Race: white 55.5% Setting: community History: 66.6% had tobacco dependence, 22% alcohol dependence, 18% anxiety disorders, 7% antisocial personality disorder.	1. Fluoxetine 20 mg (n=10) 2. Fluoxetine 40 mg (n=11) 3. Fluoxetine 60 mg (n=10) 4. Active Placebo (diphenhydramine) (n=14)	Urine positive for cocaine metabolites	No retention in treatment Side effects. ASI; POMS; Craving.
Ehrman 1996	Allocation: randomised Blindness: double Duration: 4 weeks (medical phase) Design: 2 parallel groups Analysis: non ITT	Diagnosis: cocaine dependence (DSM-III-R) Number: 80 Age: ~37 years Sex: 100% males Race: 95.5% african-american Setting: outpatient History: regular cocaine use ~6 years	1. Ritanserin 10 mg/day (n=40) 2. Placebo (n=40)	No retention in treatment	Self reported withdrawal, and craving Clinical measures

Table 2. Antidepressants for cocaine dependence: characteristics of included randomised controlled trials.

AUTHOR/ YEAR	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOMES USED	OUTCOMES UNABLE TO USE
Gawin 1989	Allocation: randomised Blindness: double Duration: 6 weeks Design: 3 parallel groups Analysis: non ITT	Diagnosis: cocaine dependence (DSM-III-R) Number: 100 Age: ~29 years Sex: male 76% Race: 71% Caucasians Setting: community History: most participants had other diagnosis such as attention deficit disorder.	1. Desipramine 2,5 mg/kg (n=31) 2. Lithium Carbonate 600 mg (n=37) 3. Placebo-atropine 0.1 mg (n=32)	Positive urine samples for cocaine metabolites Duration of treatment	No retention in treatment Reduction in craving
Giannini 1986	Allocation: randomisation performed using a 'Texas Instrument Programmable 58' random selection program Blindness: double Duration: 40 days Design: 4 parallel groups Analysis: ITT	Diagnosis: 20 chronic cocaine abusers and 20 chronic phencyclidine (PCP) abusers Number: 40 Age: range 20-34 years Sex: 100% male Race: 100% Caucasians Setting: community History: abusers used only that particular drug at least 3 times weekly and had a history of abuse of at least one year.	Cocaine group: 1. Desipramine 150 mg/day (n=10) 2. Placebo (diphenhydramine) (n=10) PCP group: 1. Desipramine 150 mg/day (n=10) 2. Placebo (diphenhydramine) (n=10)	No retention in treatment Depression	

Table 2. Antidepressants for cocaine dependence: characteristics of included randomised controlled trials.

AUTHOR/ YEAR	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOMES USED	OUTCOMES UNABLE TO USE
Giannini 1987	Allocation: randomisation performed using a 'Texas Instrument Programmable 68' random program Blindness: double Duration: 45 days Design: 2 parallel groups Analysis: ITT	Diagnosis: space-base (combination of free-base cocaine and phencyclidine) abusers Number: 20 Age: range 21-28 years Sex: 100% male Race: 100% Caucasians Setting: private-practice psychiatry group. History: abusers smoked space-base on a twice week or more frequency.	1. Desipramine 200mg/day (n=10) 2. Placebo (n=10)	Non abstinent No retention in treatment	BPRS
Hall 1994	Allocation: randomised Blindness : double Duration: 12 weeks Design: 4 parallel groups Analysis: ITT	Diagnosis: cocaine dependence (DSM-III-R) Number: 94 Age: ~38 years Sex: male100% Race: african-american 85% Setting: inpatient at beginning (~2 weeks) History: primary cocaine abusers; patients who abused other drugs in addition to cocaine were included.	1. Desipramine 200 mg - Continuity (n= 23) 2. Desipramine 200 mg - Standard (n= 22) 3. Placebo - Continuity (n= 28) 4. Placebo - Standard (n= 21)	Positive urine sample for cocaine metabolites Non entrance in outpatient program (not leaving the hospital)	No retention in treatment

Table 2. Antidepressants for cocaine dependence: characteristics of included randomised controlled trials.

AUTHOR/ YEAR	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOMES USED	OUTCOMES UNABLE TO USE
Jenkins 1992	Allocation: randomised Blindness: double Duration: 12 weeks Design: 2 parallel groups Analysis: non ITT Multicenter (4 centers)	Diagnosis: cocaine dependence (DSM-III-R) Number: 60 Age: mean 30.8 years Sex: 95% males Race: 66% african-american Setting: inpatients in the first week of the trial History: mean education 13,5 years. It was considered desirable for patients to be employed and live in a moderately stable social situation, and not have antisocial Personality Disorder.	1. Gepirona: mean dose 16.25 mg/day (n=20) 2. Placebo (n=21)	No retention in treatment Duration of treatment Urine positive for cocaine metabolites (week 6) No global improvement (CGI)	QCI, CCS, ASI, HAM-D, HAM-A
Kolar 1992*	Allocation: randomised Blindness: double Duration: 12 weeks for desipramine and placebo; 8 weeks for amantadine followed by 4 weeks of placebo Design: 3 parallel groups Analysis: non ITT	Diagnosis: cocaine dependence (DSM-III-R) Methadone-maintained patients. Number: 24 Age: mean 34.8 years Sex: 85% male Race: african-american 68% Setting: outpatients History: patients had used cocaine on average for 10 years. Other diagnosis were found such as attention deficit disorder, affective and anxiety disorders.	1. Desipramine 200 mg (n=8) 2. Amantadine 200 mg followed by placebo (n= 5) 3. Placebo (n=9)	No retention in treatment Positive urine for cocaine metabolites Participants presenting at least one side effect	BDI Cocaine use in dollars spent and grams Cocaine craving Side-effects

Table 2. Antidepressants for cocaine dependence: characteristics of included randomised controlled trials.

AUTHOR/ YEAR	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOMES USED	OUTCOMES UNABLE TO USE
Kosten 1992a*	Allocation: randomised Blindness: double Duration: 12 weeks Design: 3 parallel groups Analysis: non ITT	Diagnosis: opioid and cocaine dependence (DSM-III-R) Number: 94 Sex: male 52% Age: mean age 32 (0,5 years) Race: 82% white Setting: outpatients History: additional diagnosis: antisocial personality disorder (20%); major depression (5%), dysthymia (22%).	1. Desipramine 150 mg (n=30) 2. Amantadine 300mg (n= 33) 3. Placebo (n=31)	Positive urine sample for cocaine metabolites No retention in treatment No retention in treatment for side effect	Cocaine craving
Margolin 1995*	Allocation: quasi-randomised (subjects were stratified by presence of antisocial personality disorder and sequentially randomised to receive either bupropion or placebo) Blindness: double Duration: 12 weeks Design: 2 parallel groups Analysis: ITT Multicenter study	Diagnosis: cocaine dependence (DSM-III-R), in methadone-maintained treatment for heroin dependence Number: 149 Age: mean 37.2 years Sex: 62% males Race: 45% Caucasians; 12% african-american Setting: outpatients History: About 50% met criteria for antisocial personality disorder.	1. Bupropion 300mg/day (n=74) 2. Placebo (n=75)	No retention in treatment No retention in treatment for side effect Hamilton Depression Rating Scale ASI Craving	Urine positive for cocaine metabolites Side effects Self report use of cocaine

Table 2. Antidepressants for cocaine dependence: characteristics of included randomised controlled trials.

AUTHOR/ YEAR	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOMES USED	OUTCOMES UNABLE TO USE
McElroy 1989	Allocation: randomised Blindness: double Duration: 24 weeks Design: cross-over (at 12 weeks) Analysis: non ITT	Diagnosis: cocaine dependence (DSM-III-R) Number: 15 Age: 29.5 (5.7) years Sex: 73% male Race: unclear Setting: inpatient at beginning History: average duration of cocaine use was 5 years. All patients met criteria for current or past abuse of other drugs.	1. Desipramine 200 mg (n=9) 2. Placebo (n=6)	Positive urine samples for cocaine metabolites No retention in treatment No retention in treatment for side effect	CCI; CCF; BDI; HAM-D
Nunes 1995	Allocation: randomised, stratified, administered by a nurse, not involved in the recruitment. Blindness: double Duration: 12 weeks Design: 2 parallel groups Analysis: ITT	Diagnosis: cocaine abuse (DSM-III-R) Number: 113 Age: ~32 years Sex: Male 73% Race: 52% Caucasian Setting: outpatients History: depressive disorder was found in 61% of participants.	1. Imipramine 150-300mg (n=59) 2. Placebo (n=54)	No retention in treatment No retention in treatment for side effect No response	Self report cocaine use Cocaine craving Cocaine high Depression
O'Brien 1988	Allocation: randomised, no details on allocation concealment Blindness: double; assessed at follow-up Duration: 12 weeks Design: two parallel groups Analysis: non ITT	Diagnosis: cocaine dependence (DSM III R) in methadone-maintenance treatment Number: 47 Age: 29 to 50 years Sex: male 100% Race and setting: unknown History: patients with sedative/alcohol dependence were excluded. They had been abusing cocaine for 3 or more months.	1. Desipramine (n=24) 2. Placebo (n=14)	No retention in treatment	ASI BDI Positive urine samples for cocaine metabolites

Table 2. Antidepressants for cocaine dependence: characteristics of included randomised controlled trials.

AUTHOR/ YEAR	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOMES USED	OUTCOMES UNABLE TO USE
Tennant 1985	Allocation: randomised, but no details on allocation concealment were provided. Blindness: double blind. Duration: 12 days for desipramine patients, 15 for placebo. Design: two parallel groups. Analysis: unclear.	Diagnosis: cocaine dependence. Number: 22. Age: unknown. Sex: unknown. Race: unknown. Setting: unknown. History: patients with drug/alcohol dependence were excluded.	1. Desipramine (n=11) 2. Placebo (n=11)	Positive urine samples for cocaine metabolites. No retention in treatment	Data extracted from abstract and Levin (1991). Authors contacted.
Triffleman 1992	Allocation: randomised (2X2). Blindness: double. Duration: 8 weeks. Design: 2 parallel groups. Analysis: non ITT	Diagnosis: crack-cocaine dependence. Number: 82. Age: unclear. Sex: male 100%. Race: african- american 85%. Setting: inpatient for 2 weeks. History: 76% unemployed and 32% homeless.	1. Desipramine 200 mg qD (n= 41) 2. Placebo (n=41)	Duration of treatment	No retention in treatment.

Table 2. Antidepressants for cocaine dependence: characteristics of included randomised controlled trials.

AUTHOR/ YEAR	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOMES USED	OUTCOMES UNABLE TO USE
Weddingt on 1992	Allocation: randomised, administered by a person not involved with recruitment of patients, using serially numbered, opaque, envelopes. Blindness: single Duration: 12 weeks Design: 3 parallel groups Analysis: non ITT	Diagnosis: cocaine dependence (DSM-III-R) Number: 83 Age: ~30 years Sex: male 76% Race: white 69% Setting: outpatients History: Additional diagnosis included attention deficit disorder, affective and anxiety disorders.	1. Desipramine 200 mg (n= 32) 2. Amantadine 400 mg followed placebo (n=23) 3. Placebo (n= 28)	Positive urine sample for cocaine metabolites No retention in treatment Duration of treatment Participants presenting at least one side effect	Craving for cocaine Depression scores

GLOSSARY:
*Studies including patients in methadone maintenance treatment or opioid dependents.
ASI - Addiction Severity Index
BDI - Beck Depression Inventory
BPRS - Brief Psychiatric Rating Scale
CCS - Cocaine Craving Scale
CCI - Cocaine Craving Intensity
CCF - Cocaine Craving Frequency
CGI - Clinical Global Improvement
DSM-III - Diagnostic and Statistic Manual (American Psychiatric Association), third edition
DSM-III-R - Diagnostic and Statistic Manual (American Psychiatric Association), third edition revised
HAM-D - Hamilton Depression Scale
NIMH DIS - National Institute of Mental Health Diagnostic Interview Schedule
POMS - Profile of Mood States
QCI - Quantitative Cocaine Inventory
QCI modified- Yale Quantitative Cocaine Inventory, modified version (Batki et al., 1991, 1993, 1994)

METHODOLOGICAL QUALITY

RANDOMISATION: All but one study (Margolin 1995) were randomised. In the Margolin study, a quasi-randomised design was employed - subjects were stratified by the presence of personality disorders and sequentially randomised. This trial was rated as 'C' according to the Mulrow quality assessment. In three studies (Covi 1993; Nunes 1995; Weddington 1991), allocation was performed by a person who was not involved in recruitment of patients, so these trials were rated as 'A' - adequate allocation concealment. All remaining studies did not describe the concealment of allocation and were classified as 'B'. A computer-generated list of random numbers was used in Campbell (1994). Two trials (Giannini 1986; 1987) used the 'Texas Instrument Programmable random selection program'.

Nunes (1995) stratified patients by route of administration and by categories of depressive disorder.

BLINDING: 15 studies used a double-blind design. Weddington (1992) used single blindness. In two trials, this information was not available (Carrol 1994; Hall 1994).

ACTIVE PLACEBO: Covi (1993) used diphenhydramine as an active placebo.

DESCRIPTION OF RETENTION IN TREATMENT: Five studies (Campbell 1994; Covi 1993; Gawin 1989; Hall 1994; Triffleman 1992) did not describe those who dropped out before the end of the trial protocol. Dropout rates ranged from 0% (Giannini 1987 - patients from a private practice psychiatric group) to 72% (Batki 1996), suggesting that a very heterogeneous set of populations were compared.

OUTCOME REPORTING: Many outcomes could not be summarised because they were presented in graphical form or only by statistical tests and p-values. For most of continuous variables, standard deviation was not provided or data were skewed.

RESULTS

Given the heterogeneity of patients, diagnosis, and settings, subgroup analysis was performed separately for two groups:

(1)   Trials where patients had a primary diagnosis of cocaine dependence (without opioid dependence or methadone maintenance treatment);

(2)   Trials where patients were diagnosed for both cocaine and opioid dependence or were in methadone maintenance treatment.

PRIMARY COCAINE DEPENDENCE

EFFICACY MEASURES:

(1)   Positive urine sample for cocaine metabolites

No significant results were obtained for this restringing outcome, regardless of the type of antidepressant administered. It seems that desipramine results were better than those found for other drugs (five trials, 188 patients), when compared to placebo (figure 2.1). However, this was a non significant finding (RR=0.86; 95% CI 0.57-1.31).

In a preliminary analysis, all seven desipramine trials (266 participants) were included regardless of the presence of additional opiate dependence (figure 2.2). A trend was found favouring desipramine (RR=0.82; 95% CI 0.6-1.13), but with significant heterogeneity (chi-square=12.7; df=6; p=0.048). One trial (Kolar 1992) showed an extreme positive value favouring desipramine. Excluding this study, there is no remaining heterogeneity.

(2)   Non response/ abstinence

Clinical response according to patient's self-report was more likely to occur in patients taking imipramine than placebo, but this finding was only found in one trial (Nunes 1995). Abstinence, a similar outcome obtained by self-report, did not show significant differences between desipramine and placebo (Giannini 1987).

(3)   No clinical improvement

No significant results were found between gepirone and placebo (Jenkins 1992) in one trial using CGI, a non-specific criteria for improvement.

(4)   Continuous outcomes

Statistically significant results could not be found when continuous outcomes were analysed, i.e.percentage of abstinent days (antidepressant desipramine), days of cocaine use per week (fluoxetine) and craving intensity (fluoxetine).

ACCEPTABILITY

(1)   Non-retention in treatment

A similar rate of patients remaining in treatment was found for patients taking either desipramine or placebo. Results from one trial suggest fluoxetine patients on SSRIs are less likely to dropout. No significant

Figure 2.1. Positive urine samples for cocaine metabolites: desipramine results from primary cocaine dependence trials.

Weddington 1992

Hall 1994

Gawin 1989

McElroy 1989

Tennant 1985
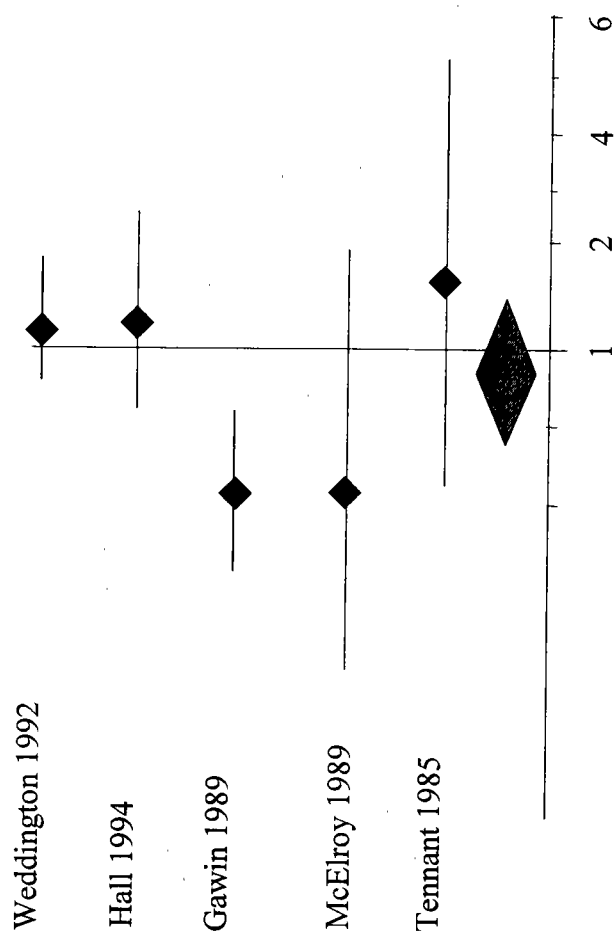
DL pooled relative risk = 0,86 (95,% CI = 0,57 to 1,31)

Figure 2.2. Positive urine samples for cocaine metabolites: desipramine results from all trials.

McElroy 1989

Tennant 1985

Weddington 1992

Kosten 1992a*

Gawin 1989

Kolar 1992*

Hall 1994

1   2   4   6

DL pooled relative risk = 0,82   (95% CI = 0,60 to 1,13)
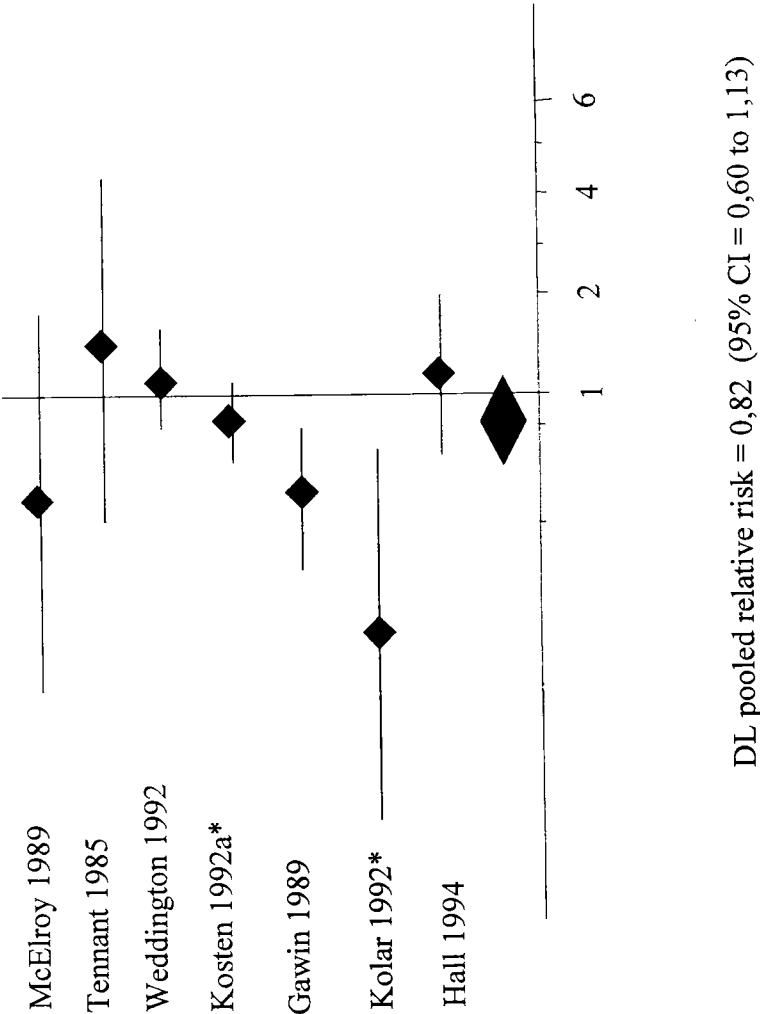
results were obtained for gepirone, ritanserin, imipramine, but these results are from single trials and involve a limited number of patients.

Similar results were found for dropout rates due to side effects.

Results from trials comparing desipramine to placebo are presented on figure 2.4.

(2)   Side effects

Only two trials (McElroy 1989; Weddington 1992) reported relevant data on side effects. A trend was found suggesting that patients on desipramine were more likely to present at least one side effect during the trial (RR=1.65; 95% CI 0.98-2.79).

COCAINE / OPIOID DEPENDENCE

EFFICACY MEASURES

(1)   Positive urine sample

Data from two RCTs (Kolar 1992; Kosten 1992) involving 78 patients showed no significant final differences between desipramine and placebo regarding the presence of cocaine metabolites in the urine samples. An extreme positive value was found in Kolar (1992), but this study was carried out on a reduced number of patients (n=17).

Relevant data concerning efficacy could not be obtained for bupropion.

ACCEPTABILITY

(1)   Non-retention in treatment

No significant differences were found irrespective of the drug (bupropion or desipramine), including the dropouts which were due to side effects. Data from trials comparing desipramine to placebo are presented on figure 2.5.

(2)   Side effects

In Kolar (1992), non-significant differences were found between desipramine and placebo in terms of the number of patients who reported at least one side effect during the trial.

Figure 2.3. Retention in treatment: desipramine versus placebo (trials with diagnosis of primary cocaine dependence).

McElroy 1989

Weddington 1992

0,5 1,0 2,0 2,5
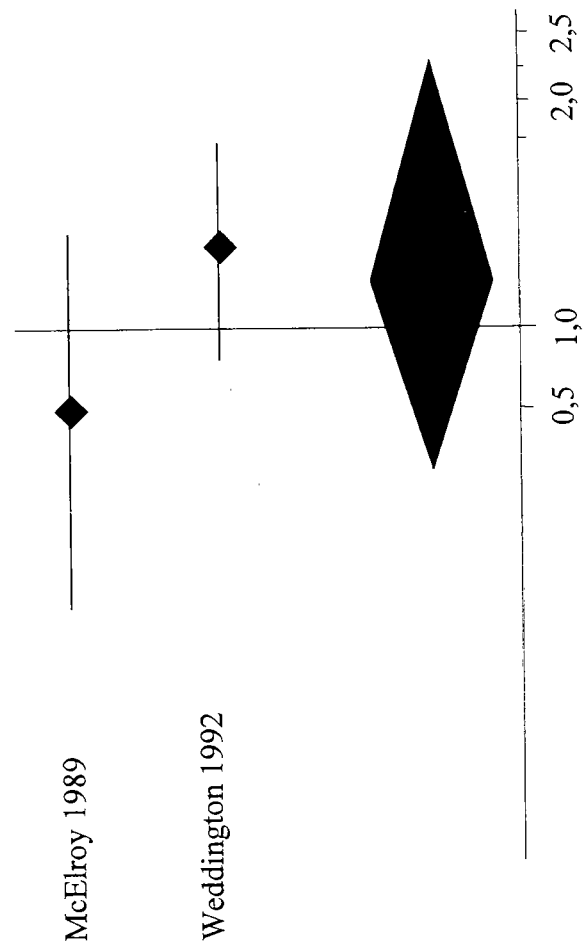
DL pooled relative risk = 1,15 (95,% CI =0,55 to 2,40)

Figure 2.4. Positive urine samples for cocaine metabolites: desipramine results from trials with opioid dependence/methadone maintenance patients.

Kolar 1992

Kosten 1992

1   2   3
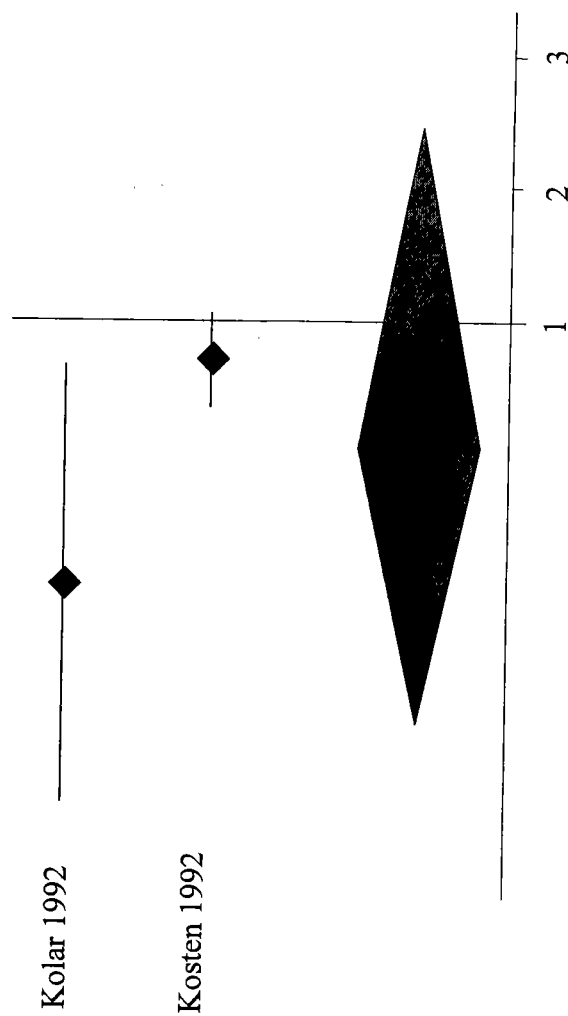
DL pooled relative risk = 0,44 (95% CI = 0,07 to 2,93)

Figure 2.5. Retention in treatment: desipramine versus placebo (trials with patients on methadone maintenance).
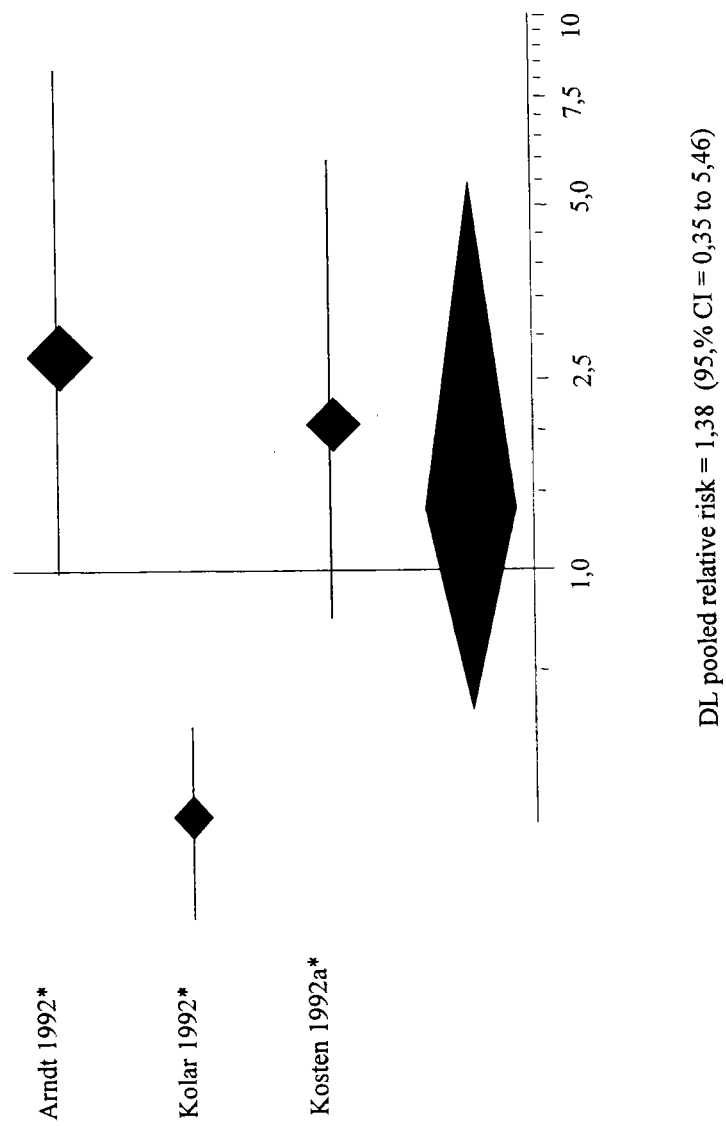
DISCUSSION

METHODOLOGICAL CONSIDERATIONS: The interest in the use of pharmacological therapy for treating cocaine dependence has increased over the last 15 years. Results from animal populations have suggested that antidepressants could be useful in the process of cocaine use withdrawal (Giannini 1986). Since then, randomised controlled trials have addressed the issue of clinical efficacy for a range of antidepressants, particularly desipramine.

A meta-analysis of desipramine for the treatment of cocaine addiction (Levin 1991), including seven randomised studies with a total of 200 patients, found that desipramine is no better than placebo in retaining patients in treatment. However, it was also suggested that while patients were in treatment, desipramine is helpful in promoting abstinence (data from six trials). The authors state that the 'Fail-safe N' - which provides an estimate of the number of additional negative studies that would be required to reverse a positive meta-analytic finding - in connection with desipramine efficacy is 16. In other words, 16 studies finding no advantage to desipramine compared with placebo would be necessary to negate this finding.

Levin's findings were discussed by Delucchi (1992), who pointed out a number of limitations in the meta-analysis. The main problem was the use of an incorrect method for combining the studies chosen by the authors. For each study, probability levels (p values) for observed effects were first transformed to Z scores, and then the weighted Stouffer method was applied. However, if data comes from a 2 X 2 table, such a method is not appropriate. In addition, this method is not recommended for a meta-analysis because it does not convey any information about the size of the effect itself (Delucchi 1992). Moreover, the main outcome measure - abstinence - was defined in many different ways across the studies.

There are clear discrepancies between the results and conclusions of Levin's review and the present one. Different methods of combining studies were used, but other differences also need to be mentioned:

(1) The first review was published 8 years ago, and further randomised evidence has since become available: this review includes 12 RCTs (8 studies with available data for efficacy);

(2) Efficacy data used in this review were combined only when authors defined efficacy in a similar and comparable way. All eight studies used the number of patients with positive samples for cocaine metabolites at the end of the trial. Therefore, the estimates from the first meta-analysis could be inflated by less

restrictive definitions of efficacy. Alternatively, our results can be considered conservative ones, given the selection of outcomes, criteria for pooling analysis and the use of the random effects model, which takes into account heterogeneity between trials.

A range of factors makes it difficult to draw conclusions from any synthesis of treatments for cocaine dependence. These include differences in psychiatric and substance use diagnoses, study quality and design, definitions of outcome variables, and varying amounts of psychotherapy provided in conjunction with medications.

EFFICACY FINDINGS: Data from 18 RCTs involving 1177 subjects suggest lack of evidence regarding the efficacy of antidepressants compared to placebo. Just 3 trials (Gawin 89, Giannini 86, Giannini 87) showed statistical significant differences favouring the intervention (Desipramine) in efficacy measures when compared to placebo. Most of the trials showed a similar decrease in cocaine use and craving for placebo and the active drug. When relapse in cocaine free patients was evaluated, the same pattern of response was found (McElroy 89).

Desipramine results are the focus of this discussion, given the higher number of studies for this drug (12), and the fact that it was possible to perform meta-analysis for some of the outcomes.

As far as the more restrictive efficacy measure - the number of subjects with positive urine samples for cocaine metabolites at the end of the trial - is concerned, results varied according to the type of participant. Two levels of heterogeneity must to be considered: in a preliminary analysis, when all desipramine trials with urinalysis data available were included, significant heterogeneity was present (chi-square=12.7; df=6; p=0.048). This result favoured desipramine, but it was statistically non-significant (RR=0.82; 95% CI 0.6-1.13). As expected, such findings could be related to differences between populations (primary cocaine dependence and patients with cocaine and opioid dependence, in methadone maintenance treatment). When trials were analysed separately according to the presence of an additional diagnosis of opioid dependence, the result on heterogeneity held for the studies (Kolar and Kosten), including patients on methadone maintenance treatment (chi-square=4.24; df=1; p=0.04). Kolar, a small RCT (n=17), showed an extreme non-significant positive result favouring desipramine (RR=0.16; 95% CI 0.02-1.04). The results for trials with primary cocaine dependence patients were more homogeneous, with no significant differences between desipramine and placebo.

Though it could be expected that patients who had a history of opioid use were more likely to relapse when treated with antidepressants (Arndt 1992), current results were unable to confirm any relevant differences for any of the efficacy and acceptability measures.

There is still a limited number of RCTs assessing other agents such as fluoxetine, ritanserin, gepirona, bupropion, and imipramine. Previous experience with depression suggests they may have similar effects regardless of the proposed mechanism of action. When trials reported results on urinalysis (Jenkins 1992, Covi 1993) Gepirone and Fluoxetine performances were very similar to those found for desipramine trials.

ACCEPTABILITY FINDINGS: Consistent with results from our previous systematic review on Carbamazepine for cocaine dependence, it was found in this review that a high percentage of cocaine dependent patients were not able to complete the trial. One significant result was found by Batki (1996): a higher percentage of patients on fluoxetine completed the study, in comparison with placebo (RR=0.53; 95% CI 0.32-0.88). SSRIs are supposed to have a better acceptability, but this finding needs replication.

The lowest dropout rate (10%) was found by Giannini (1986). In this small study (n=20), participants had a history of cocaine abuse of at least one year, and received supportive counselling at five days intervals. Batki (1996) found the highest dropout rate: 72%. Most of the subjects in this trial (n=32) had other psychiatric disorders such as major depressive disorder (40%), antisocial personality disorder (20%) and alcohol abuse and dependence (20%), and got paid to participate in the study - $10 for the intake and each of the weekly assessments.

This finding is biased by the fact that very heterogeneous populations have typically been the subjects of clinical studies, and reinforces the view that a specific set of conditions may be associated with higher percentages of dropouts, including factors of co-morbidity, the absence of psychosocial support, and the method of recruitment. As Margolin (1995) pointed out, it seems unlikely that medications, with the possible exception of a cocaine-specific blocking or maintenance agent, will have a significant impact on behaviour if there is an absence of motivation for behavioural change. It is plausible that the best results can be expected in highly motivated populations.

IMPLICATIONS FOR PRACTICE

With the evidence currently available, there is no data supporting the efficacy of antidepressants for cocaine dependence. These drugs are not promising as a base for treatment of unselected cocaine abusers.

Although the efficacy of desipramine has been suggested in individual studies (Kolar 1992, Gawin 1989), the results of this review do not support their efficacy as single interventions for cocaine dependence. It seems unlikely that, in the absence of motivation for behaviour change, pharmacological agents, with the possible exception of cocaine-specific blocking or maintenance agents, are able to promote a significant improvement in behaviour.

The value of antidepressants, prescribed in conjunction with a more potent psychosocial intervention, remains unknown. However, until further efficacy and effectiveness studies are available, clinicians may consider adding psychotherapeutic supportive measures aiming to keep patients in treatment. Such advice does not rely on any direct evidence of the efficacy, but does consider the best available evidence, the high dropout rates and illness behaviour associated with cocaine use.

IMPLICATIONS FOR RESEARCH

In general, the overall quality of the included studies was reasonable. The unusually high dropout rates across studies and drugs, rather than reflecting a simple methodological flaw, may suggest that specific compliance promoting approaches are needed to investigate clinical effects of drugs for the treatment of cocaine dependence.

The data points to a need for further studies. First, if there is no evidence that desipramine, a tricyclic drug associated with a number of side effects, is any better than other antidepressants, it may be useful to investigate the possible treatment role of newer drugs, with better adverse events profile.

If compliance can be improved through psychosocial interventions, what would then be the optimal duration of pharmacological treatment? Is medication still useful after the natural resolution of the withdrawal phase of abstinence symptoms?

Antidepressants are not direct cocaine antagonists. Unlike methadone for opiate dependence, they are not a substitution of a long acting but are abusable agonist from the same class of the drugs. However, larger randomised controlled trials may address the question of whether they represent a new class of substance abuse treatments which are able to accelerate the process of central nervous system normalisation after long-term substance abuse.

In reviewing RCTs on the treatment of cocaine dependence, some outcome measures seem to be more reliable and useful than others. Trialists can choose to use continuous data from one craving or psychiatric scale, relying mainly one those that are widely used and

validated. ASI scale seems to be a useful, given it is designed to assess the problem of severity in seven areas commonly affected by addiction.

Dichotomous variables can be more easily interpreted by clinicians, and provide estimations of effect size and number needed to treat/harm, particularly in respect to:

(1)   The number of subjects with positive urine samples for cocaine metabolites at endpoint;

(2)   Self-reported use of cocaine - although less reliable, these results can be compared to those from urinalysis;

(3)   Retention in treatment (overall);

(4)   Retention in treatment for side effects.

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DOPAMINE AGONISTS FOR COCAINE DEPENDENCE

SUMMARY

Therapeutic management of the cocaine addiction include an initial period of abstinence from the drug. During this phase the subjects may experience, in addition to an intense craving for cocaine, symptoms such as depression, fatigue, irritability, anorexia, and sleep disturbances. It has been demonstrated that the acute use of cocaine may enhance dopamine transmission and chronically decrease dopamine concentrations in the brain. Pharmacological treatment that affects dopamine could theoretically reduce these symptoms and contribute to a more successful therapeutic approach (Giannini 1986).

Most agents used to treat cocaine abuse target the DA system because of its role in reinforcement. When chronic cocaine self-administration is stopped, DA in the DA system may decrease synaptic transmitter levels. Considering that these changes may be related to cocaine craving and the risk of relapse (Gold 1997), dopamine agonists may be an option for the treatment of cocaine use. Data from animal studies suggest drugs such as bromocriptine attenuates the decrease of brain activity of mesolimbic structures in rats who have been acutely withdrawn after repeated doses of cocaine (Jaffe 1995).

OBJECTIVES

(1)   To investigate the efficacy and acceptability of dopamine agonists for treating cocaine dependence when compared with placebo, other medications used as comparison groups or psychosocial interventions such as counselling;

(2)   Where possible, perform a meta-analytic synthesis of the studies.

TYPES OF INTERVENTIONS:

(1)   Any dopamine agonist drug
        i. Amantadine;
        ii. Bromocriptine.

(2)   Placebo

(3)   Other medications used as comparison groups

MAIN RESULTS: Twelve studies were included, with a total of 587 participants randomised. In most of trials amantadine and bromocriptine were compared to a placebo. In two studies, amantadine was directly compared to bromocriptine, while in three others, amantadine was compared to the antidepressant desipramine. The main efficacy measure presented was positive urine sample for cocaine metabolites, with no significant differences between the different interventions. When retention in treatment was assessed as an acceptability measure, similar

rates were found for both placebo and active drugs. No significant differences were found between trials where participants had primary cocaine dependence or had additional diagnosis of opioid dependence and/or were in methadone maintenance treatment.

CONCLUSIONS: Current evidence does not support the clinical use of dopamine agonists in the treatment of cocaine dependence. Given the high rate of dropouts in this population, clinicians may consider adding psychotherapeutic supportive measures aiming to keep patients in treatment.

DESCRIPTION OF THE STUDIES

EXCLUDED STUDIES: Eleven studies were excluded in this review. Four studies were not randomised. In another seven studies, long term treatment or clinical data were not the aim of the trial. These studies were conducted in order to assess acute cocaine cue reactivity to different medications.

AWAITING ASSESSMENT: Five studies are awaiting assessment. In two (Gillin 1994, Malcolm 1997) allocation procedures are unclear, they do not specify if they are randomised trials. In Alim 1995, Giannini 1987-a, Giannini 1987-b, outcomes are not presented in a sufficiently clear form to be presented in this review.

INCLUDED STUDIES: Substantive descriptions of included studies can be found in table 3.

It was possible to extract data from 12 studies. The duration of trials ranged from 10 days to 12 weeks.

Setting: nine trials were conducted with outpatients, at the community level or in mental health centers. Subjects were in day hospital in one trial (Alterman 1992). Eiler (1995) and Kranzler (1992) were conducted with inpatients.

PARTICIPANTS: 587 cocaine dependent subjects were randomised for the interventions. Most of trials (73%) used DSM-III-R criteria for clinical diagnosis. Patients usually reported abuse or dependence of other drugs, particularly alcohol. Psychiatric diagnoses other than opiate dependence were reported in some trials. Kolar (1992) and Weddington (1991) included Attention Deficit Disorder, Affective and Anxiety Disorder. Participants with anti social disorders were included in two trials (Giannini 1989, Kosten). Kampman (1996) included subjects with alcohol and marijuana dependence.

Table 3. Dopamine agonists for cocaine dependence: characteristics of included randomised controlled trials.

AUTHOR /YEAR	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOMES USED	OUTCOMES UNABLE TO USE
Alterman 1992	Allocation: 'random assignment was completed by a research technician using a constrained block randomisation procedure' Blindness: double Duration: 2 weeks (mean 10,5 days) Design: 2 parallel groups Analysis: ITT	Diagnosis: cocaine dependence (DSM-III-R) Number: 42 Age: average 35 years Sex: male 100% Race: african-american 90% Setting: day hospital patients History: reported used of cocaine 15 days in the past 30 and using cocaine regularly for about 3 years.	1. Amantadine 200-400 mg (n=21) 2. Placebo (n=21)	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
Eiler 1995	Allocation: randomised Blindness: double Duration: 18 days Design: 2 parallel groups Analysis: non ITT	Diagnosis: cocaine dependence (DSM-III-R) Number: 63 Age: mean 35.6 years Sex: male 100% Race: black 86% Setting: inpatients History: last cocaine use was within 6 days before entrance in the study. Alcohol abuse could be present, but not alcohol dependence.	1. Bromocriptine 2.5-10 mg/day (n=32) 2. Placebo (n=31)	No retention in treatment No retention in treatment for side effect	SCL-90-R BDI Craving

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Table 3. Dopamine agonists for cocaine dependence: characteristics of included randomised controlled trials.

AUTHOR /YEAR	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOMES USED	OUTCOMES UNABLE TO USE
Giannini 1989	Allocation: randomised using a "Texas Instrument Programmable 68" random computer program Blindness: double Duration: 30 days design: 3 parallel groups Analysis: ITT	Diagnosis: cocaine abusers Number: 30 Age: range 24-32 years Sex: male 100% Race: Caucasians 100% Setting: outpatient History: intranasal use on a daily basis for at least 6 months before being withdrawn. 2 subjects in the bromocriptine group and placebo group met DSM-III-R criteria for antisocial personality disorder.	1. Amantadine 400 mg/day (n=10) 2. Bromocriptine 10 mg/day (n= 10) 3. Placebo (n=10)	Craving Side effects	BPRS
Handelsm an 1995-1	Allocation: randomised after one week period of placebo use Blindness: double Duration: 8 weeks Design: 3 parallel groups Analysis: non ITT	Diagnosis: cocaine dependence (DSM-III-R). Methadone-maintained patients in treatment for heroine dependence. Number: 67 Age: ~36 years Sex: male 100% Race: unclear Setting: outpatients History: active cocaine dependence in the three-month period prior to the trial	1. Amantadine 200 mg/day (n=19) 2. Amantadine 400 mg/day (n=23) 3. Placebo (n=25)	No retention in treatment BDI SCL-90	Positive urine sample for cocaine metabolites Craving ASI Side effects

Table 3. Dopamine agonists for cocaine dependence: characteristics of included randomised controlled trials.

AUTHOR /YEAR	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOMES USED	OUTCOMES UNABLE TO USE
Handelsman 1997	Allocation: randomised Blindness: double Duration: 5 weeks Design: 2 parallel groups Analysis: non ITT	Diagnosis: cocaine abuse or dependence (DSM-III-R). Methadone-maintained patients in treatment for heroine dependence. Number: 60 Age: ~39 years Sex: male 100% Race: 24% black Setting: outpatients History: subjects were using cocaine in the last 30 days, before entrance in the study	1. Bromocriptine 5 mg (n=24) 2. Placebo (n=26)	No retention in treatment	Positive urine sample for cocaine metabolites Craving POMS PANAS
Kampman 1996	Allocation: randomised, utilising a stratified block procedure Blindness: double Duration: 4 weeks Design: 2 parallel groups Analysis: ITT for urine samples	Diagnosis: cocaine dependence (DSM-III-R) Number: 61 Age: ~35 years Sex: Male in amantadine group 87%; in placebo group 77% Race: african-american in amantadine group 67%; in placebo group 71% Setting: outpatients History: cocaine use within 10 days of entering the study. Alcohol and marijuana dependent were not excluded.	1. Amantadine 300 mg (n=30) 2. Placebo (n=31)	No retention in treatment Non abstinent ASI BDI BAI	Positive urine sample for cocaine metabolites Cocaine craving Side effects

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Table 3. Dopamine agonists for cocaine dependence: characteristics of included randomised controlled trials.

AUTHOR /YEAR	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOMES USED	OUTCOMES UNABLE TO USE
Kolar 1992	Allocation: randomised Blindness: double Duration: 12 weeks for desipramine and placebo; 8 weeks for amantadine followed by 4 weeks of placebo Design: 3 parallel groups Analysis: non ITT Pilot study	Diagnosis: cocaine dependence (DSM-III-R) Methadone-maintained patients in treatment for heroin dependence Number: 24 Age: mean 34.8 years Sex: 85% male Race: african-american 68% Setting: outpatients History: average use of cocaine 10 years. Other diagnosis: attention deficit disorder, affective and anxiety disorders.	1. Desipramine 200 mg (n=8) 2. Amantadine 200 mg followed by placebo (n= 5) 3. Placebo (n=9)	Positive urine sample for cocaine metabolites No retention in treatment	
Kosten 1992	Allocation: randomised Blindness: double Duration: 12 weeks Design: 3 parallel groups Analysis: ITT	Diagnosis: opioid and cocaine dependence (DSM-III-R) Number: 94 Sex: male 52% Age: mean age 32 (0,5 years) Race: 82% white Setting: outpatients History: additional diagnosis - antisocial personality disorder (20%); major depression (5%), dysthymia (22%).	1. Desipramine 150 mg (n=30) 2. Amantadine 300mg (n= 33) 3. Placebo (n=31)	Positive urine sample for cocaine metabolites No retention in treatment No retention in treatment for side effect	

Table 3. Dopamine agonists for cocaine dependence: characteristics of included randomised controlled trials.

AUTHOR /YEAR	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOMES USED	OUTCOMES UNABLE TO USE
Kranzler 1992	Allocation: randomised. capsules identical in appearance were administered by nursing staff who were blind to treatment group assignment Blindness: double Duration: 21 days Design: 2 parallel groups Analysis: non ITT	Diagnosis: cocaine dependence (DSM-III-R) Number: 20 Age: mean 27.7 years Sex: male 100% Race: white 85% Setting: inpatient History: Participants had used an average of 3 g of cocaine during the month prior to the admission.	1. Bromocriptine 2.5 mg (n=10) 2. Placebo (n=10)	Participants presenting at least one side effect Side effects	Subjective measures Physiological measures
Moscovitz 1993	Allocation: randomised. A pharmacist who had no contact with the subjects or the test data, coded the study medications. Blindness: double Duration: 2 weeks Design: 2 parallel groups Analysis: non ITT	Diagnosis: cocaine users Number: 29 Age: ~37 years Sex: male 100% Race: unclear Setting: outpatient History: participants used cocaine at least four times per week for the previous month.	1. Bromocriptine 3.75 mg/day (n= 14) 2. Placebo (n=15)	Positive urine sample for cocaine metabolites No retention in treatment Participants presenting at least one side effect	

Table 3. Dopamine agonists for cocaine dependence: characteristics of included randomised controlled trials.

AUTHOR /YEAR	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOMES USED	OUTCOMES UNABLE TO USE
Tennant 1987	Allocation: randomised, using a coin flip. Blindness: double. Duration: 10 days. Design: 2 parallel groups. Analysis: ITT	Diagnosis: cocaine dependence. Number: 14. Age: range 16-38 years. Sex: unclear. Race: unclear. Setting: outpatients. History: subjects used cocaine at least 4 times per day for the 30 days prior to the admission. They had to believe they were dependent on cocaine and needed medical assistance to withdraw.	1. Amantadine 100mg/day (n=7). 2. Bromocriptine 2.5 mg/day (n=7)	Positive urine sample for cocaine metabolite. No retention in treatment. Side effects. Number of participants presenting at least one side effect. Subjective report	
Weddingt on 1991	Allocation randomised, administered by a person not involved with recruitment of patients, using serially numbered, opaque, envelopes. Blindness: single. Duration: 12 weeks. Design: 3 parallel groups. Analysis: non ITT	Diagnosis: cocaine dependence (DSM-III-R). Number: 83. Age: ~30 years. Sex: male 76%. Race: white 69%. Setting: outpatients. History: cocaine use was one gram or more per week for 12 weeks. Additional diagnosis were found including attention deficit disorder, affective and anxiety disorders.	1. Desipramine 200 mg (n= 32). 2. Amantadine 400 mg followed placebo (n=23). 3. Placebo (n= 28)	Positive urine sample for cocaine metabolites. No retention in treatment. Duration of treatment. Participants presenting at least one side effect	Craving for cocaine. Depression scores

GLOSSARY:

ASI - Addiction Severity Index   PANAS - Positive Affect Negative Affect Scale
BAI - Beck Anxiety Inventory   DSM-III-R - Diagnostic and Statistic Manual (American Psychiatric Association), third edition revised
BDI - Beck Depression Inventory   HDRS -Hamilton Depression Scale
CSR - Cocaine Status Report   POMS - Profile of Mood States

Participants with alcohol abuse, not dependence, were included in Alterman (1992) and Eiler (1995) . Male gender was predominant for most of trials; seven studies did not include females. Most trials presented mean age of participants around 30/ 35 years.

INTERVENTIONS: Amantadine was compared to a placebo in three trials (Alterman 1992, Handelsman 1995, Kampman 1996). Two distinct doses (200 and 400 mg/day) corresponding to two arms were adopted in Handelsman's (1995). Three arm placebo controlled studies (with two active drugs) provided further comparisons with other dopamine agonists (amantadine and bromocriptine - Giannini 1989) or antidepressants (desipramine - Kolar 1992, Kosten 1992, Weddington 1991). Amantadine doses ranged from 100 to 400 mg/day.

Four RCTs compared bromocriptine with placebo only (Eiler 1995, Handelsman 1997, Kranzler 1992, Moscovitz 1993). Dose ranged from 2.5 to 10 mg/day.

Tennant (1987) compared amantadine to bromocriptine with no placebo group.

OUTCOMES: Outcomes were either dichotomous or continuous, as reported by trialists. The following scales were used in relevant studies:

(1)   Addiction Severity Index (ASI);

(2)   Beck Anxiety Inventory (BAI);

(3)   Beck Depression Inventory (BDI);

(4)   Cocaine Status Report (CSR);

(5)   Hamilton Depression Scale (HDRS);

(6)   Positive Affect Negative Affect Scale (PANAS);

(7)   Profile of Mood States (POMS).

For most of these scales data were skewed and could not be presented on graphical form or even subject to meta-analysis. Many continuous outcomes were described in terms of means without corresponding standard deviations.

The most relevant dichotomous outcomes were:

(1)   Positive urine sample for cocaine metabolites;

(2)   No retention in treatment;

(3)   No retention in treatment for side effects.

METHODOLOGICAL QUALITY

RANDOMISATION: All trials were randomised using a number of techniques: constrained block randomisation (Alterman 1992), Texas Instrument Programmable random selection program (Giannini 1989),

stratified block procedure (Kampmam 1996), and coin flip (Tennant 1987). Three studies described adequate concealment of allocation (Kranzler 1992, Moscovitz 1993, Weddington 1991). A one-week washout period was used in Handelsman (1995).

BLINDING: Double-blind design was adopted in all but one (Weddington 1991, single-blind) study.

ACTIVE PLACEBOS: No study used active placebos.

DESCRIPTION OF NO RETENTION IN TREATMENT: Two studies (Giannini 1989, Kranzler 1992) did not describe those who dropped out before the end of the trial protocol. Dropout rates ranged from 10% (Handelsmam 1995) to 84% (Weddington 1991), suggesting that a very heterogeneous set of populations were compared.

OUTCOME REPORTING: Many outcomes could not be summarised because they were presented in graphical form or only on statistical tests and p-values. For most of continuous variables, standard deviation was not provided or data were skewed.

RESULTS

Results will be described for each of the dopamine agonists against placebo separately; and then direct comparisons will be made.
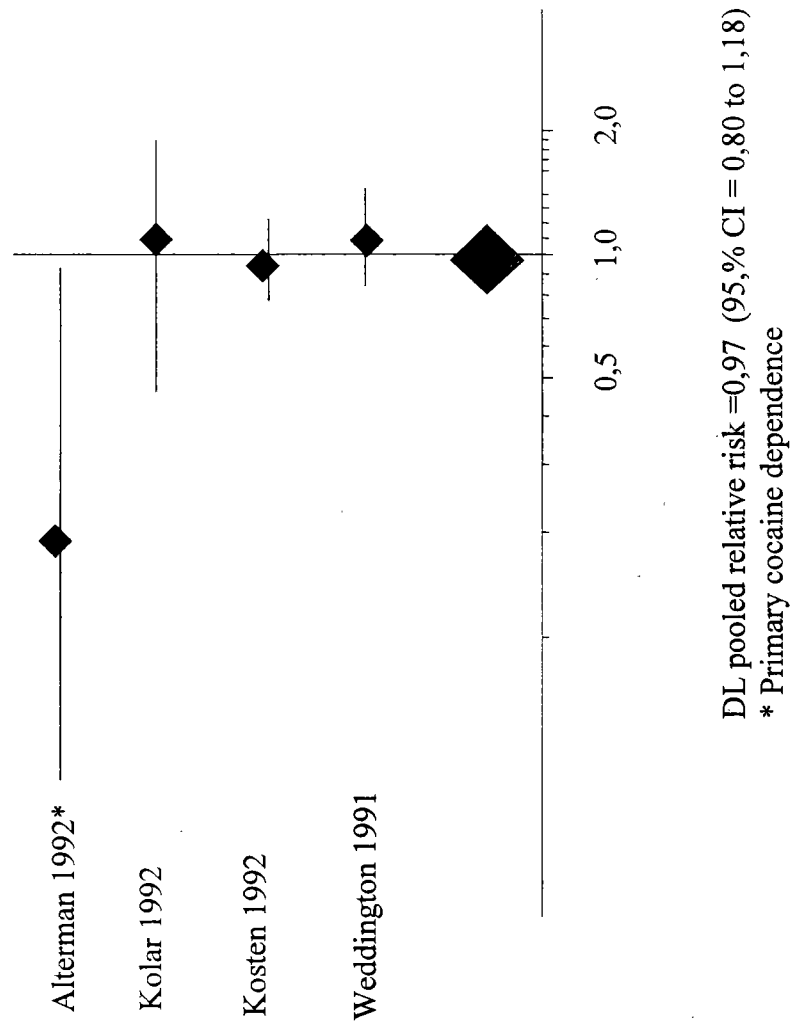
AMANTADINE

EFFICACY MEASURES

(1)   Positive urine samples for cocaine metabolites
Alterman (1992) reported a non-significant extreme result, but only 30 cocaine dependent and opioid dependent/methadone maintained patients were evaluated in this trial. A global comparison including all trials related to positive urine samples for cocaine metabolites can be seen in table 3.1.

(2)   Non abstinence
Kampmam found no differences in terms of abstinence as self-reported by patient between amantadine and placebo groups (n=61).

Figure 3.1. Positive urine samples for cocaine metabolites: all amantadine trials.

Alterman 1992*

Kolar 1992

Kosten 1992

Weddington 1991

0,5   1,0   2,0

DL pooled relative risk =0,97 (95,% CI = 0,80 to 1,18)
* Primary cocaine dependence

(3)   Craving

A small trial (Giannini 1989) found no differences between amantadine and placebo in terms of self-reported craving.

(4)   Continuous outcomes

Non-significant results were found in all domains of ASI, BDI (depression) and BAI (anxiety).

ACCEPTABILITY

(1)   Non-retention in treatment: similar dropout rates were found for patient groups taking either amantadine or a placebo (figure 3.1).

In four trials (Kolar 1992, Kosten 1992, Weddington 1991, Handelsman 1995), participants had an additional diagnosis of opioid dependence and/or were in methadone maintenance treatment. Results were very similar to those described above. The highest percentage of dropouts was reported in Weddington (1991): 84% did not complete the study.

(2)   Side effects: Giannini (1989) did not find statistically significant differences between amantadine and placebo in terms of side effects (diarrhoea, headache, nausea, and rash).

BROMOCRIPTINE

EFFICACY MEASURES

(1)   Positive urine sample

This measure was available in a single trial (Moscovitz 1993), and no significant results were found.

(2)   Craving

Giannini (1989), a small trial (n=30) which compared amantadine x bromocriptine x placebo, showed a non-statistically significant difference favouring bromocriptine in self-reported craving, when compared to placebo.

ACCEPTABILITY

(1)   Non retention in treatment

Results from three trials (Eiler 1995, Handelsman 1997, Moscovitz 1993) concerning 142 patients did not reveal any difference between bromocriptine and placebo in repect to dropout rates (figure 3.4). Discrepancies in dropout percentages were found among the various studies: in Handelsman (1997), 80% of individuals completed the study, whilst in Moscovitz (1993) only one third were able to do so. With regard to dropouts for side effects, Eiler (1995) described similar results.

(2)   Side effects

Two trials (Giannini 1989, Kranzler 1992) investigated specific side effects but no significant results were obtained. In two trials, the number of patients reporting at least one side effect can be seen in figure 3.5.

Figure 3.2. Retention in treatment: amantadine vs placebo (patients with primary cocaine dependence).

Alterman 1992

Kampman 1996
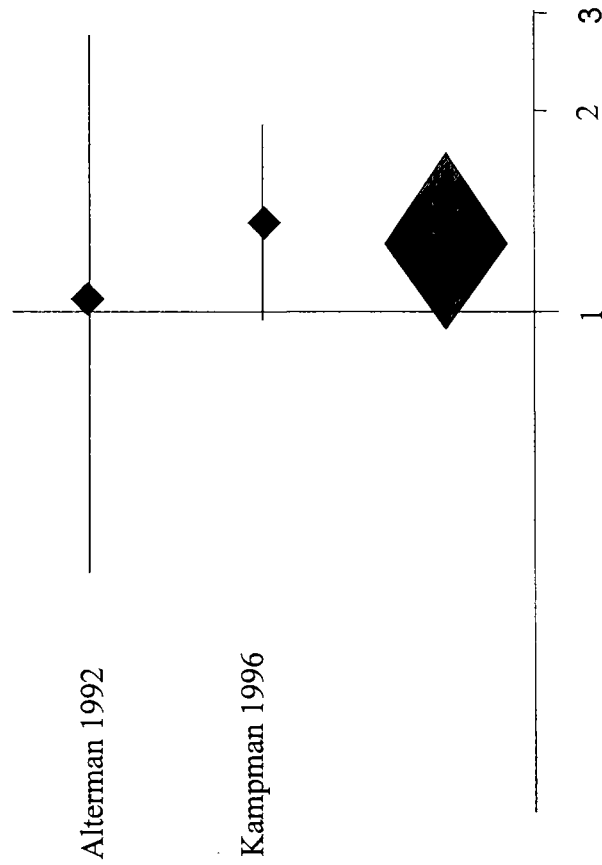
DL pooled relative risk = 1,28 (95,% CI = 0,93 to 1,75)

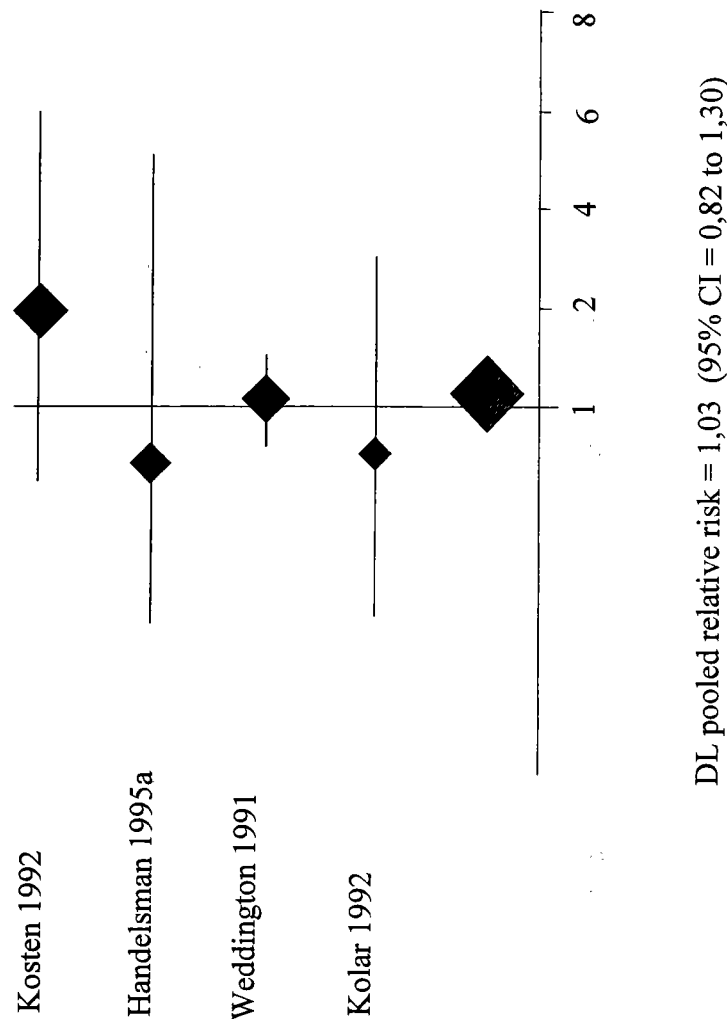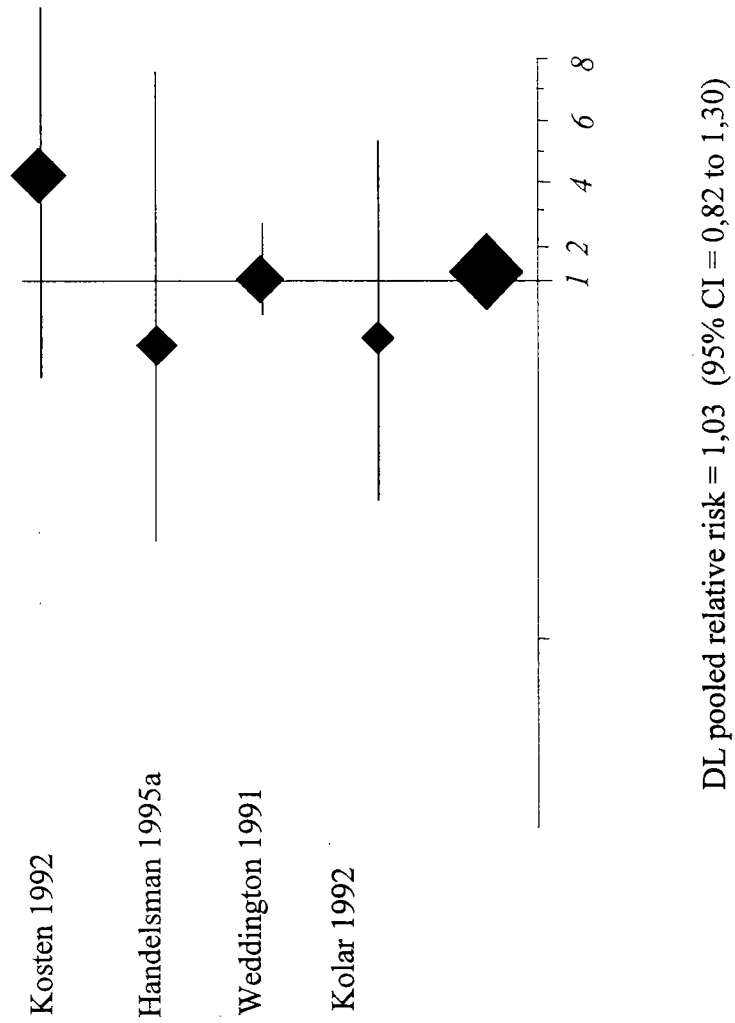Figure 3.3. Retention in treatment: amantadine versus placebo (patients on methadone maintenance.

DL pooled relative risk = 1,03 (95% CI = 0,82 to 1,30)

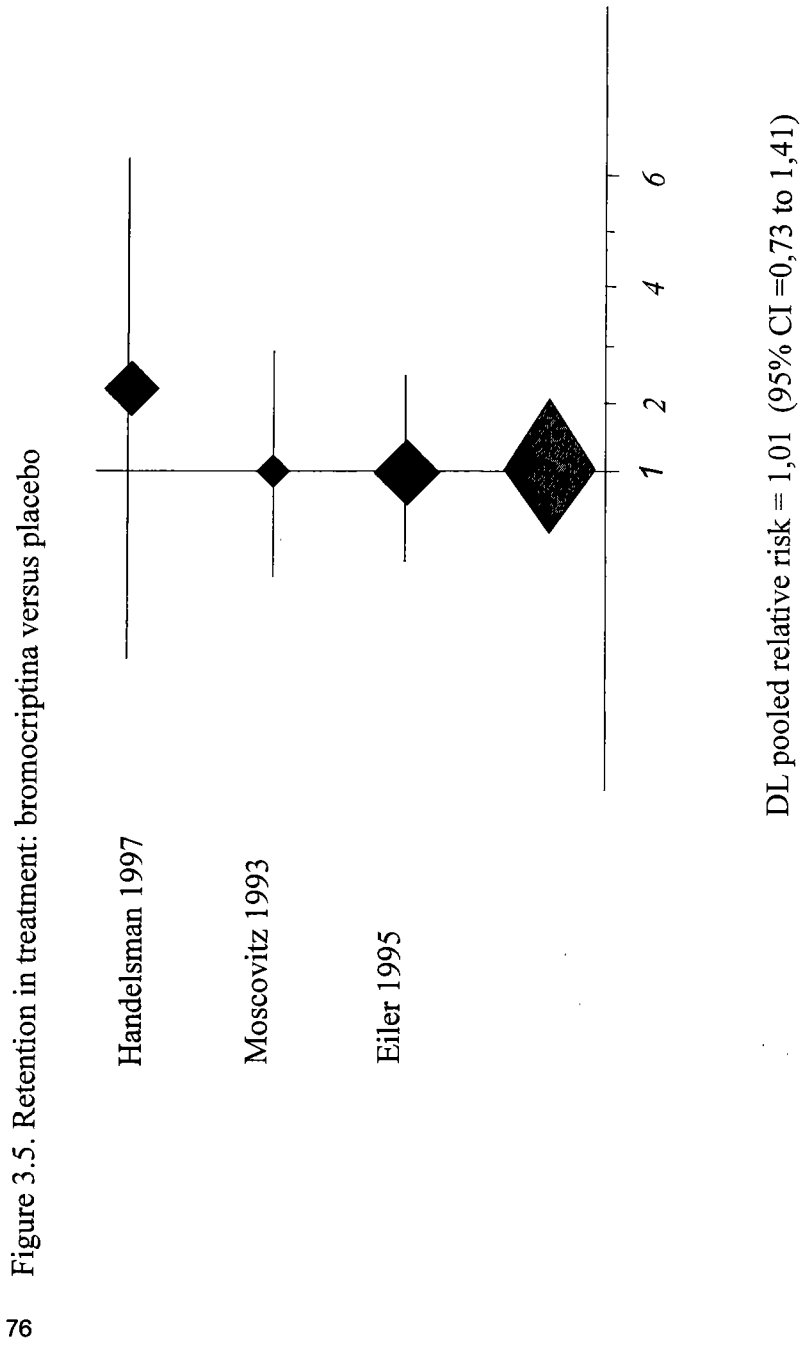Figure 3.4. Retention in treatment: amantadine versus placebo (patients on methadone maintenance

Kosten 1992

Handelsman 1995a

Weddington 1991

Kolar 1992

1 2 4 6 8

DL pooled relative risk = 1,03 (95% CI = 0,82 to 1,30)

Figure 3.5. Retention in treatment: bromocriptina versus placebo

Handelsman 1997

Moscovitz 1993

Eiler 1995

DL pooled relative risk = 1,01 (95% CI =0,73 to 1,41)

DIRECT COMPARISONS

AMANTADINE VS BROMOCRIPTINE

Results from two trials (Giannini 1989, Tennant 1987) did not find any significant difference between these two dopamine agonist for all efficacy measures, including patients subjective reports. However, a trend was observed favouring amantadine in terms of retention in treatment and the occurrence of side effects. When craving was assessed, a trend favouring bromocriptine was found in Giannini's (1989) trial.

AMANTADINE VS DESIPRAMINE

Three trials compared these products (Kolar 1992, Kosten 1992, Weddington 1991). The first two included methadone maintained subjects. Weddington (1991) evaluated just cocaine dependence. In general, there were no differences when retention in treatment and side effects were evaluated. A non-statistical difference favouring desipramine was found in methadone maintained subjects, as revealed by positive urine samples for cocaine metabolites at the end of the trial (figure 3.6.).

DISCUSSION

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

As seen with other treatments, trials included in this review presented important differences in psychiatric and substance use diagnoses, study quality and design, definitions of outcome variables, and varying amounts of psychotherapy provided in conjunction with medications. These discrepancies have two consequences: an increase in the general legibility of data, but also a clear limitation for pooling data.

Data from the 12 included trials are sometimes contradictory. Most trials did not show differences between active drugs and placebo (Eiler 1995, Handelsman 1995, Handelsman 1997, Kampman 1996, Kosten 1992, Kranzler 1992, Moskovitz 1993, Weddington 1991). Amantadine was considered superior to placebo in Alterman (1992) and to bromocriptine in Tennant (1987). Bromocriptine was considered better than placebo and amantadine in Giannini (1989). These three RCT were described as preliminary studies and suggested further investigation. In Kolar (1992), desipramine was described as superior to the other interventions.

Figure 3.6. Report of at least one side effect: bromocriptine versus placebo.

Moscovitz 1993

Kranzler 1992
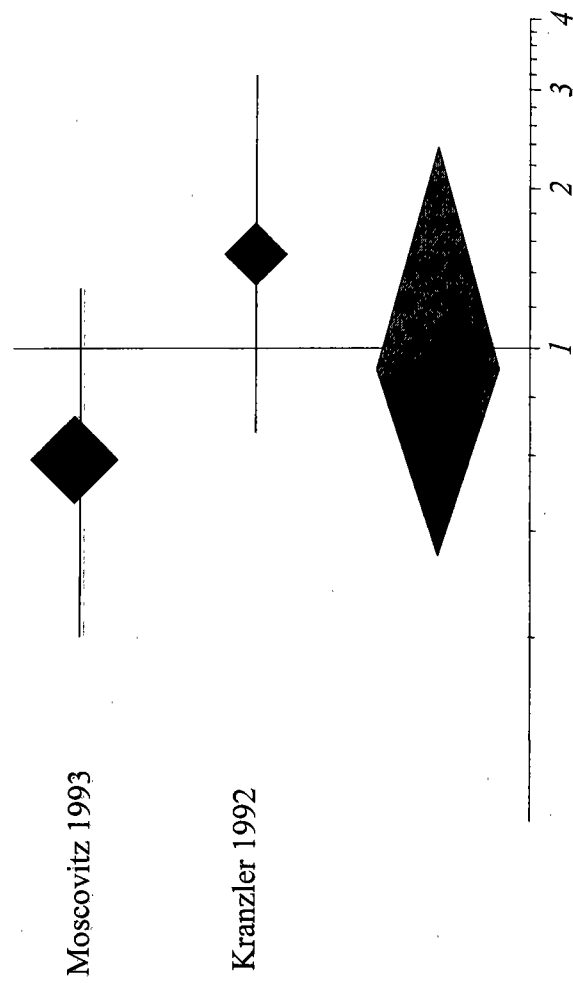
DL pooled relative risk = ,9072 (95,% CI = ,3467 to 2,3741)

EFFICACY FINDINGS: It was thought that dopamine agonist drugs might be a valuable option for cocaine treatment as a result of their action readjusting dopamine receptors' super sensitivity and in alleviating dopamine depletion among long-term cocaine users.

General results from this review do not provide evidence of dopamine agonists being an effective option in treating cocaine dependent patients, whether they are on methadone maintenance treatment or not. In some trials, such as Handelsman (1995)and (1997), Kampman (1996), and Kosten (1992), overall results on compliance and reduction in cocaine use/ craving showed an improvement among patients at the end of the studies, regardless of whether they were on active drugs or placebo. It is suggested that intensive psychosocial therapy, whether in a hospital setting or at the community level, may be the main reason for this finding. Handelsman (1997) even suggests that the effects of cognitive-behavioural therapy may be so great that they overshadow any effect attributable to the drug. This finding could not be replicated in most of the trials included in this review. Besides receiving simultaneous psychosocial interventions, the majority of patients were not able to complete the trial.

Overall, no significant differences were found for any of the efficacy measures. Only a non-significant trend favouring amantadine was seen in Alterman (1992), a trial with a limited number of patients (n=30), when positive urine samples were evaluated. The remaining two trials (Giannini , 1989 and Kampman, 1996) did not report results on urinalysis.

Three trials with opioid dependent patients, comparing amantadine with placebo, provided results on urinalysis. There were no differences between the groups.

DIRECT COMPARISONS

AMANTADINE vs BROMOCRIPTINE

Contradictory results were found in terms of efficacy: while Tennant reported a trend favouring amantadine in urinalysis, in Giannini (1989) it was associated with a higher percentage of self-reported craving than bromocriptine. Retention in treatment and side effects suggested a trend favouring amantadine. However, none of these finding reached levels of statistical significance.

AMANTADINE vs DESIPRAMINE

No significant differences were found for any of the efficacy and acceptability measures. The RRs for urinalysis were higher in trials where patients were on methadone maintenance (Kolar 1992, Kosten

1992) than those found in patients with primary cocaine dependence (Weddington 1991). An outlier result reported by Kolar explains this trend.

ACCEPTABILITY FINDINGS: Consistent with results from our previous systematic review on carbamazepine and anti depressants for cocaine dependence, this review found a high percentage of cocaine dependent patients unable to complete the trial.

There was relevant variation across trials in terms of dropouts. This finding reinforces the fact that very heterogeneous populations have been evaluated in clinical trials, and a set of conditions may be associated with higher percentages of dropouts, including co-morbidity, absence of psychosocial support, and the method of recruitment.

Several pharmacological approaches have been documented for the treatment of this serious condition, even concerning a combination of drugs (Giannini 1989). However, results from this review suggest patients' motivation for behaviour change is necessary if significant improvements are to be expected.

IMPLICATIONS FOR PRACTICE

Current evidence from randomised controlled trials do not support the use of dopamine agonists in the treatment of cocaine dependence. This absence of evidence may place clinicians in a position where they have to balance the possible benefits against the potential adverse effects of the treatment.

High dropout rates for this population suggest that alternative approaches (such as psychosocial interventions) should be considered, aiming at keeping patients in treatment.

IMPLICATIONS FOR RESEARCH

Conclusions regarding potentially useful outcome measures have been described in this series of reviews on cocaine dependence. In light of the evidence assessed in this review, future investigations must avoid the following methodological flaws:

(1) Studies with small sample size - none of the included studies had more than 100 patients;

(2) Poor compliance - there is strong evidence that this population needs specific measures in order to minimise dropouts during trial medication.

Large randomised trials could have the additional advantage of allowing statistical control for the effects of psychosocial interventions, eventually provided in conjunction with medications.

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COCAINE DEPENDENCE:
MISCELLANEOUS TREATMENT

SUMMARY

OBJECTIVES

(1)   To investigate the efficacy and acceptability of drugs such as lithium, mazindol, buprenorphine, haloperidol, and other medications for treating cocaine dependence when compared with placebos;

(2)   Where possible, perform a meta-analytic synthesis of the studies.

TYPES OF INTERVENTIONS

(1)   Treatment with any other drug but carbamazepine, antidepressants, or dopamine agonists;

(2)   Placebo.

MAIN RESULTS: Six randomised placebo controlled trials were included. All studies used a double-blind design. Regardless of the type of drug, participants, length of follow-up, dropout rates, settings, and all the other relevant characteristics, none of the studied compounds showed clinical efficacy for treating cocaine dependent patients. High dropout rates were found.

CONCLUSIONS: Current data is not sufficient to recommend the use of mazindol, phenytoin, nimodipine, lithium, or NeuRecover-SA in clinical practice. In the absence of more convincing evidence, clinicians may consider prescribing alternative medications, where a higher number of studies and patients evaluated are available (for instance, antidepressants).

DESCRIPTION OF STUDIES

EXCLUDED STUDIES: Six studies were excluded from this review. Most of them assessed acute subjective and physiologic responses to the interventions rather than clinical efficacy (challenge studies). Chadwick is a crossover study focusing on withdrawal symptoms.

INCLUDED STUDIES: Substantive descriptions of included studies are shown in table 4. It was possible to extract data from 6 studies. The duration of trials ranged from 5 days to 12 weeks.

SETTING: Most of trials evaluated outpatients (Crosby,1996; Gawin, 1989; Margolin,1995; Stine, 1995). In two trials, participants were inpatients (Cold ,1996; Rosse ,1994).

Table 4. Miscellaneous treatment for cocaine dependence: characteristics of included randomised controlled trials.

AUTHOR/YEAR	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOMES USED	OUTCOMES UNABLE TO USE
Cold 1996	Allocation: randomised, administered by a person not responsible for recruiting patients. Blindness: double Duration: 5 to 21 days Design: two parallel groups Analysis: non ITT	Diagnosis: cocaine abuse and dependence (DSM-III-R) Number: 13 Age: range 25-46 years Sex: 75% male Race: unknown Setting: inpatients History: 10 patients were also treated for alcohol dependence.	1. NeuRecover-SA (tm) 6 capsules daily (n=8) 2. Placebo (n=4)	Abstinence symptoms (ASE modified) Cocaine craving (CCS)	Side effects
Crosby 1996	Allocation: randomised Blindness: double Duration: 12 weeks Design: two parallel groups Analysis: non ITT	Diagnosis: cocaine abuse or dependence (DSM-III-R) Number: 60 Age: ~34 years Sex: 80% male Race: african-american 55% Setting: outpatient History: subjects reported 12 days of cocaine use in the last month.	1. Phenytoin 300mg/day (n=29) 2. Placebo (n=31)	Cocaine use (self report) No retention in treatment Increase in craving Side effects	Positive urine sample for cocaine metabolites Global improvement (DIRS-C, CGI, SGI) Craving (MCCS) Compliance
Gawin 1989	Allocation: randomised Blindness: double Duration: 6 weeks Design: 3 parallel groups Analysis: non ITT	Diagnosis: cocaine dependence (DSM-III-R) Number: 100 Age: ~29 years Sex: male 76% Race: 71% Caucasians Setting: community mental health center History: most patients had other diagnosis such as attention deficit disorder.	1. Desipramine 2,5 mg/kg (n=31) 2. Lithium Carbonate 600 mg (n=37) 3. Placebo-atropine 0.1 mg (n=32)	Positive urine sample for cocaine metabolites Duration of treatment	No retention in treatment Reduction in craving

88

Table 4. Miscellaneous treatment for cocaine dependence: characteristics of included randomised controlled trials.

AUTHOR/ YEAR	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOMES USED	OUTCOMES UNABLE TO USE
Margolin 1995	Allocation: randomised. A staff pharmacist, who didn't have contact with the participants, developed the randomisation code and assigned the interventions. Blindness: double Duration: 12 weeks Design: two parallel groups Analysis: ITT	Diagnosis: cocaine dependence Subjects in methadone-maintenance for heroine treatment Number: 37 Age: mean 34 years Sex: 43% male Race: 68% Caucasian Setting: outpatients History: on average, subjects had been using cocaine for 11 years.	1. Mazindol 1mg/day (n=18) 2. Placebo (n=19)	Positive urine sample for cocaine metabolites No retention in treatment No retention in treatment for side effect Number of participants presenting at least one side effect	BDI Craving (Likert Scale)
Rosse 1994	Allocation: randomised Blindness: double Duration: 3 weeks Design: two parallel groups Analysis: non ITT	Diagnosis: cocaine dependence (DSM-III-R) Number: 70 Age: 33 years Sex: 100% male Race: unclear Setting: inpatient History: average of cocaine use per week was 6.6 grams.	1. Nimodipine 90 mg/day (n=33) 2. Placebo (n=33)	Craving and urges (QCU)	Cocaine craving No retention in treatment Mood state (POMS-BI)

Table 4. Miscellaneous treatment for cocaine dependence: characteristics of included randomised controlled trials.

AUTHOR/ YEAR	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOMES USED	OUTCOMES UNABLE TO USE
Stine 1995	Allocation: randomised Blindness: double Duration: 6 weeks Design: two parallel groups Analysis: ITT	Diagnosis: cocaine dependence (DSM-III-R) Number: 43 Age: ~35 years Sex: 86% male Race: african-american 51% Setting: outpatients History: subjects used at least 12g of cocaine in the 3 months prior to study. Most of participants had primarily alcohol and marijuana abuse. Other psychiatric diagnosis, except major depression, dysthymia, or anxiety disorders, were excluded.	1. Mazindol 2mg/day (n=22) 2. Placebo (n=21)	Positive urine sample for cocaine metabolites No retention in treatment	Craving Depression (BDI)

GLOSSARY:

ASE - Abstinence Symptom Evaluation
BDI - Beck Depression Inventory
CGI - Clinical Global impression
CCS - Minnesota Cocaine Craving Scale
DIRS-C - Drug Impairment Rating Scale
DSM-III-R - Diagnostic and Statistic Manual (American Psychiatric Association), third edition revised
MCCS - Minnesota Cocaine Craving Scale
POMS-BI - Bipolar Profile of Mood States
QCU - Questionnaire of Cocaine Cravings and Urges
SGI - Subjects Global Impression
tm - trade mark

PARTICIPANTS: 323 subjects were randomised for the interventions, most of them with a diagnosis of cocaine dependence. Subjects with a DSM-III-R cocaine abuse diagnosis were also included in two trials (Cold, 1996 and Crosby, 1996). Psychiatric comorbidity was adequately described in Stine (1995). In the other trials, only the use of alcohol was mentioned. Most participants were male. The mean age was of approximately 30-35 years.

INTERVENTIONS: Mazindol, an amidazoline derivate that blocks reuptake of dopamine, was evaluated in two trials (Margolin, 1995; Stine, 1995). In Margolin's study, subjects were also following methadone maintenance treatment. Dose range was 1-2 mg. Crosby (1996) assessed the value of Phenytoin, an anticonvulsant agent, as an anti-craving medication, at doses of 300mg/day. Rosse (1994) compared Nimodipine, a calcium channel blocker, to placebo in, in a daily dose of 90mg. Lithium carbonate, a mood stabiliser widely used in the treatment of bipolar disorders, was studied in Gawin (1989). Daily dosage was of 600mg. Cold (1996) assessed the compound known as 'NeuRecover-SA' (tm), which includes l-tyrosine and various vitamins and minerals for which cocaine users present a deficiency.

OUTCOMES: The following scales were used:

(1) Abstinence Symptom Evaluation (ASE);

(2) Beck Depression Inventory (BDI);

(3) Clinical Global impression (CGI);

(4) Minnesota Cocaine Craving Scale (CCS);

(5) Drug Impairment Rating Scale (DIRS-C);

(6) Bipolar Profile of Mood States (POMS-BI);

(7) Questionnaire of Cocaine Cravings and Urges (CQU);

(8) Subjects Global Impression (SGI).

This review was able to use data related to the ASE, CCS, QCU, and POMS-BI. For the other scales, data were skewed, described in terms of means without corresponding standard deviations, or other means that did not allow extraction.

The most relevant dichotomous outcomes were:

(1) Positive urine samples for cocaine metabolites;

(2) No retention in treatment;

(3) No retention in treatment due to side effects;

(4) Craving;

(5) Side effects.

METHODOLOGICAL QUALITY

RANDOMISATION: All studies were randomised. In two studies (Margolin, 1995; Cold, 1996), the randomisation and assignment of patients was administered by a person who was not responsible for their recruitment. All remaining studies failed to describe the concealment of allocation and were classified as 'B'.

BLINDING: All studies used a double-blind design. Blindness assessment was performed in Margolin (1995).

DESCRIPTION OF RETENTION IN TREATMENT: Three studies (Cold, 1996; Gawin, 1989; Rosse, 1994) did not sufficiently describe dropouts. Variations were seen in terms of dropout rates in the following studies: Crosby (1996) 80%; Margolin (1995) 19%; Stine (1995) 35%.

OUTCOME REPORTING: Many outcomes could not be summarised because they were presented in graphical form or only on statistical tests and p-values. For most of the continuous variables, standard deviation was not provided or data were skewed. Variation was seen regarding trialists' definition of improvement (positive urine samples for cocaine metabolites, self-report of cocaine use, craving, abstinence symptoms).

RESULTS

Independently to the type of drug used, the participants, the length of follow-up, dropout rates, settings, and all the other relevant characteristics, none of the studied compounds showed clinical efficacy for treating cocaine dependent patients. Given the heterogeneity of interventions, results are presented for each drug.

MAZINDOL

Two trials (Margolin, 1995; Stine, 1995) studied the effects of mazindol in the treatment of cocaine dependence. The last trial included patients who had a primary diagnosis of cocaine dependence (without opioid dependence or methadone maintenance treatment). In Margolin (1995), participants were undergoing methadone maintenance treatment.

PRIMARY COCAINE DEPENDENCE: Positive urine sample for cocaine metabolites.

The percentage of patients who had a positive urine samples at the end of the study were high for both mazindol and placebo groups (77% and 71%, respectively) but this difference was not statistically significant. In this 6-weeks study, patients who failed to present at least three consecutive weeks with no cocaine metabolites in the urine samples were considered as positives.

No retention in treatment: No significant differences were found between mazindol (32%) and placebo (38%) in terms of dropouts.

PATIENTS UNDERGOING METHADONE TREATMENT: Positive urine sample for cocaine metabolites.

In Margolin, 56% of patients on mazindol and 68% on placebo had positive urine samples at the end of the trial (12 weeks duration).

Non retention in treatment: Relatively low dropout rates were found in this study (17% for Mazindol, 21% placebo). One patient in the placebo group and two patients on Mazindol failed to complete the trial due to side effects.

PARTICIPANTS PRESENTING AT LEAST ONE SIDE EFFECT: A similar percentage of patients on mazindol and placebo reported at least one side effect during the trial (ten in each group).

The general results, for the mazindol trials, concerning positive urine samples for cocaine metabolites and retention in treatment, are shown in figures 4.1 and 4.2. These include primary cocaine dependence and patients using methadone

PHENYTOIN

In Crosby (1996), assessment of clinical efficacy showed no significant differences between phenytoin and placebo, although more patients on placebo reported use of cocaine (respectively 65% and 55%), and an increase in craving was more frequent among those taking the active drug.

Dropouts were high in both phenytoin and placebo groups, attaining about 80%. Regarding specific side effects, more patients on phenytoin complained having headache, muscle/joint pain and insomnia. However, these results were non-significants.

LITHIUM CARBONATE

In Gawin (1989), there was no significant difference in the percentage of subjects with positive urine samples for cocaine metabolites when comparing lithium and placebo. Duration of treatment was also similar.

NIMODIPINE

In Rosse (1994), it was only possible to extract continuous data, in relation with craving and mood state. Data were skewed for the former outcome and no significant differences were observed in the POMS-B scale in the several items presented.

Figure 4.1. Positive urine samples for cocaine metabolites: mazindol versus placebo
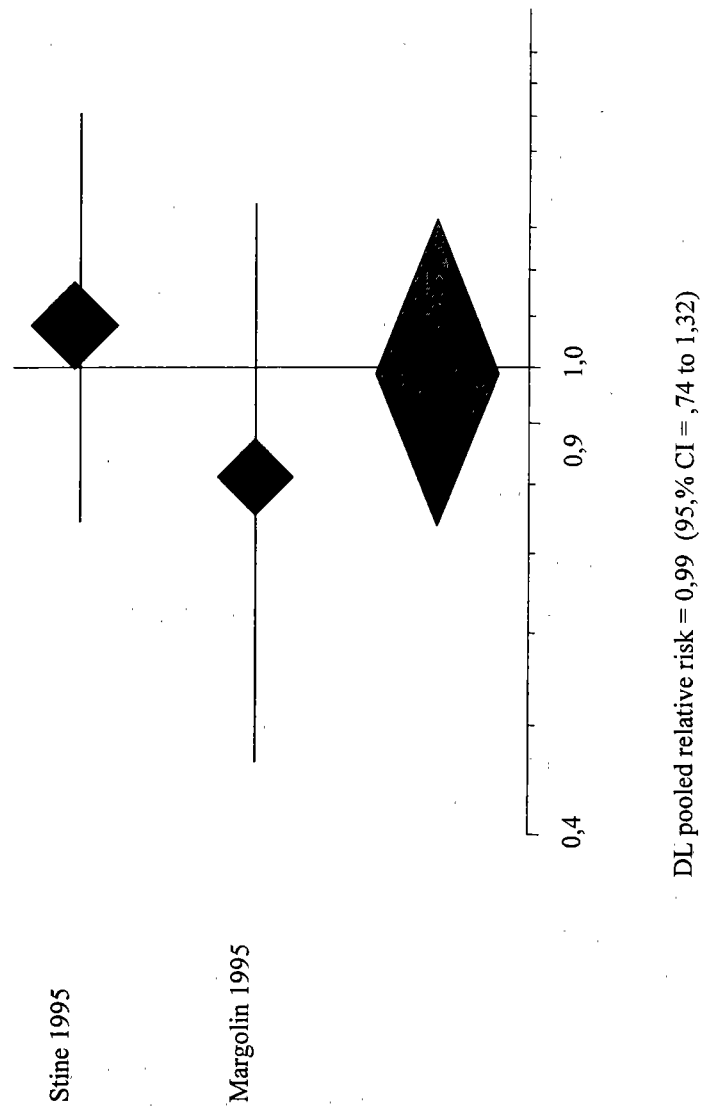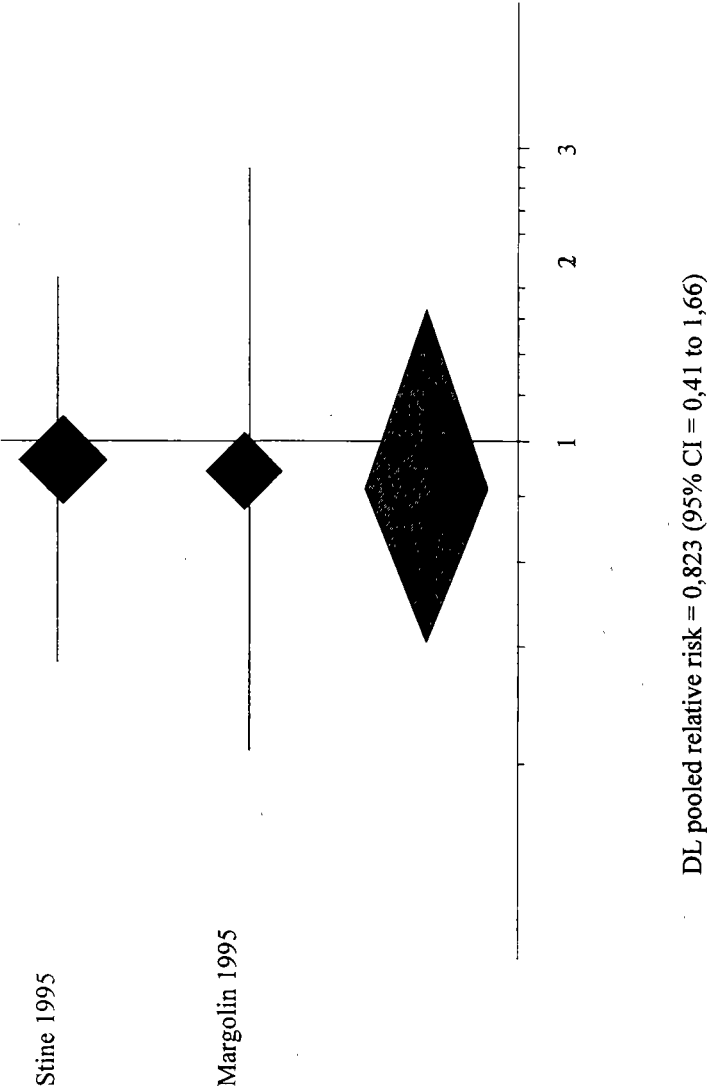
Stine 1995

Margolin 1995

0,4   0,9   1,0

DL pooled relative risk = 0,99 (95,% CI = ,74 to 1,32)

Figure 4.2. Retention in treatment: mazindol versus placebo.

Stine 1995

Margolin 1995

DL pooled relative risk = 0,823 (95% CI = 0,41 to 1,66)

NEURECOVER - SA TM

Results from two scales (ASE and QCU) were similar for both groups (skewed data). It was not possible to obtain further relevant outcomes.

DISCUSSION

This review assessed the efficacy of a number of medications for the treatment of cocaine dependence. As was seen for antidepressants, carbamazepine, and dopamine agonists, positive results obtained from animal studies could not be confirmed in the clinical trials reviewed. Evidence regarding this heterogeneous group of medications is still weak, with a still limited number of trials and patients.

Although conclusions from individual trials included in this review does not differ from those presented here, one pilot study suggested that NeuRecover-SA significantly reduces cocaine craving in various substances abusers. However, these conclusions are based on non-significant differences between the active drug and the placebo.

The hypothesis has been advanced that mazindol would have greater effects in settings, such as day hospitals or case management programs, which provided intensive psychosocial interventions which reinforce compliance with treatment. Results from two RCTs do not support such an assumption. However, this is a complexe issue as all subjects who remained in the study improved over time, and is possible that response to psychosocial treatment could have obscured a response to mazindol, especially if this result was minimal (Margolin 1995).

IMPLICATIONS FOR PRACTICE

In this review, distinct compounds were assessed for treating cocaine dependence, however data is not sufficient to justify recommending that any of these drugs to be incorporated into clinical practice. In the absence of more reliable evidence, clinicians may consider prescribing alternative medications, where a higher number of studies and patients evaluated are available (for instance, antidepressants).

IMPLICATIONS FOR RESEARCH

Given the relative lack of success of drugs assessed in this review, it may be necessary to conduct new clinical studies, characterised by research designs that expressly verify hypotheses concerning possible interactions between treatment and relevant patient characteristics.

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GENERAL CONCLUSIONS

GENERAL CONCLUSIONS

IMPLICATIONS FOR PRACTICE

The urgent demand of clinicians, patients, families, and the community as a whole for an adequate treatment for cocaine dependence may lead to adoption of therapeutic regimes even if the evidence is weak. Although caution is needed when assessing results from a limited number of clinical trials, at the current stage of evidence, there is no data supporting the efficacy of carbamazepine, antidepressants, dopamine agonists or any of the described drugs for cocaine dependence. These drugs are not promising as a mainstay of treatment for unselected cocaine abusers.

Although the efficacy of drugs such as desipramine, fluoxetine have been suggested in individual studies, the results of this review do not support the efficacy of single interventions for cocaine dependence. It seems unlikely that pharmacological agents, with the possible exception of cocaine-specific blocking or maintenance agent, are able to promote a significant improvement on behaviour in the absence of motivation for behaviour change.

The value of drugs when prescribed in conjunction with a more potent psychosocial intervention remains unknown. However, until further efficacy and effectiveness studies are available, clinicians may consider adding psychotherapeutic supportive measures aiming to keep patients in treatment. Such advice does not rely on any direct evidence of efficacy, but does consider the best available evidence, the high dropout rates, and illness behaviour associated with cocaine dependence.

IMPLICATIONS FOR RESEARCH

In general, overall quality of the included studies was reasonable. The unusual dropout rates across studies and drugs, rather than a simple methodological flaw, may suggests that specific compliance promoting approaches are needed to investigate clinical effects of drugs for the treatment of cocaine dependence.

In reviewing RCTs on the treatment of cocaine dependence, some outcome measures seem to be more reliable and useful than others. Trialists can choose to use continuous data from craving or psychiatric scales, mainly those that are widely used and validated. ASI scale seems to be a useful one, given that it is designed to assess problem severity in seven areas commonly affected by addiction. Dichotomous variables can be more easily interpreted by clinicians, and can provide estimations of effect size and number needed to treat/harm, particularly.