Pharmacological treatment of cocaine dependence: a systematic review

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ABSTRACT

Aims Cocaine dependence is a common and serious condition, associated with severe medical, psychological and social problems, including the spread of infectious diseases. This systematic review assesses critically the efficacy of pharmacotherapy for treating cocaine dependence.

Methods 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Abstracts and LILACS; scans of reference lists of relevant articles, personal communications, conference abstracts, unpublished trials from the pharmaceutical industry and book chapters on the treatment of cocaine dependence. Randomized controlled trials (RCTs) focusing on the use of antidepressants (ADs), carbamazepine (CBZ), dopamine agonists (DAs) and other drugs used in the treatment of cocaine dependence were included. The reviewers extracted data independently, and relative risks (RR) with 95% confidence interval (CI) were estimated. Qualitative assessments were carried out using a Cochrane validated checklist. Where possible, analysis was carried out according to ‘intention-to-treat’ principles.

Findings The search strategy generated 45 different trials. Most studied drugs were ADs (20 studies), DAs and CBZ. Data were very heterogeneous, with dropout rates within the studies between 0 and 84%. A non-significant trend favoring CBZ was found in terms of dropouts (RR 0.88; 95% CI 0.75–1.03) and results from one trial suggest that fluoxetine patients are less likely to drop out. The main efficacy outcome reported in the studies was the presence of cocaine metabolites in the urine. No significant results were found, regardless the type of drug or dose used for all relevant outcomes assessed.

Conclusions There is no current evidence supporting the clinical use of CBZ, antidepressants, dopamine agonists, disulfiram, mazindol, phenytoin, nimodipine, lithium and NeuRecover-SA in the treatment of cocaine dependence. Larger randomized 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.

KEYWORDS Cocaine dependence, meta-analysis, pharmacotherapy, systematic review.
INTRODUCTION

Cocaine consumption and related problems were epidemic in the 1920s in the United States, 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 United States has again been at epidemic levels. Estimates from a recent National Household Survey on Drug Abuse based on a sample of 28,332 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 problems in Europe have become more common since the early 1990s and now are part of the European drug scene (EMCDDA 2000). It 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 et al. 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. While the administration of cocaine increases intercellular dopamine, serotonin and norepinephrine levels acutely by blocking their presynaptic reuptake (Gold 1997), chronic cocaine abuse leads to downregulation of monoamine systems. Post-cocaine use depression and cocaine craving may be linked to this downregulation.

These preclinical 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, Avants & Kosten 1995b).

There is a clear understanding that any discussion of pharmacotherapy for cocaine dependence should be contextualized within a framework of broader psychosocial interventions which could include therapeutic community, day programme or out-patient drug free treatment. A recent work (Simpson et al. 1999) looking at outcomes from a range of psychosocial treatments indicates that there is substantial positive impact from such treatments. The question of combining and evaluating psychosocial and pharmacotherapeutic interventions to improve overall treatment outcomes will be a major challenge to researchers and clinicians in the drug treatment field over the coming decade.

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 and consistent methods in reviews 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 summarize the results of several independent studies, can provide a more precise estimate of the effects of health care than that which can be derived from the individual studies included in a review. In this paper, we report the main results of a series of Cochrane systematic reviews about pharmacotherapy of cocaine dependence. The various types of pharmacological interventions were grouped as follows: antidepressants (ADs); carbamazepine (CBZ), dopamine agonists (DAs); and miscellaneous, including other drugs such as naltrexone, mazindol and lithium.

METHODS

In order to select all relevant randomized controlled trials (RCTs) in the pharmacological treatment of cocaine use disorders, a wide search strategy was performed. Electronic searches of Cochrane Library (2001 issue 4), EMBASE (from 1980 to October 2000), MEDLINE (from 1966 to October 2000), PsycLIT (from 1974 to July 2000), Biological Abstracts and LILACS (from 1982 to 2000) were completed with scanning of the reference lists of relevant articles and personal contacts with authors and to the pharmaceutical industry.

RCTs focusing on the use of drugs for the treatment of cocaine dependence were included, irrespective of the diagnostic criteria. Trials where patients had an additional diagnosis such as opiate dependence were also eligible. Outcomes of interest were retention in treatment and the number of people reporting adverse events; efficacy as measured by urine samples positive for cocaine metabolites; self-reported craving; severity of dependence; amount of cocaine consumed; and quality of life measures. If assessment was not possible and no other outcomes were provided (such as continuous data, without mean and standard deviation), authors were contacted.

Quality of trials was assessed using a criterion based on the evidence of a strong relationship between the potential for bias in the results and the allocation concealment (Schulz et al. 1995). Trials were considered with a low risk of bias if they had adequate allocation...
concealment, and with a high risk of bias if an inadequate allocation of concealment was performed.

Data were extracted independently by reviewers. For dichotomous data a standard weighted estimate of the typical treatment effect across studies, the relative risk (RR)—that is, the risk of an event occurring among treatment-allocated individuals versus the corresponding risk in the control group—was calculated. If the relative risk equals 1, this indicates no difference between the groups compared. The relative risks and its 95% confidence interval (CI) were calculated with Review Manager 4.1 software, with the use of the DerSimonian–Laird random effects model (DerSimonian & Laird 1986). The random effects model includes both within-study sampling error and between-studies variation in the assessment of the confidence interval of the results, but the fixed effects model takes only within-study variation to influence the confidence interval. Therefore, the random effects model is a rather more conservative approach. Whenever possible, analyses were performed according to ‘intention-to-treat’ principles.

To avoid the pitfall of applying parametric tests to non-parametric continuous outcome data, standard deviations and means were required to be reported in the paper or obtainable from the authors, and the standard deviation, when multiplied by 2, had to be less than the mean (otherwise, the mean is unlikely to be an appropriate measure of the centre of distribution) (Altman & Bland 1996). Data not satisfying these standards were not included in the data analysis.

Heterogeneity in the results of the trials was assessed both by graphical inspection and by calculating a test of heterogeneity. Heterogeneity refers to the variation observed between the results of the individual studies. Statistically significant heterogeneity is said to be present when more variation between the studies occurs than can be explained by the play of chance alone. Possible reasons for heterogeneity were prespecified. Responses differ (Allin et al. 1995): according to the different drugs (Alterman et al. 1992); when psychosocial therapies are provided in conjunction with prescribed drugs (Altman & Bland 1996); according to the characteristics of patients participating in trials; and (Arndt et al. 1992) depending on length of treatment. Heterogeneity was then assessed visually from graphs and by the $\chi^2$ test of heterogeneity. A significance level of less than 0.10 was interpreted as evidence of heterogeneity.

RESULTS

The search

More than 1000 citations were found throughout the search. Forty-nine different studies were identified from these citations and were included in the review: 20 on ADs, five on CBZ, 13 on DAs and 11 on miscellaneous interventions. In four studies ADs were compared to both placebo and DAs or another drug. Disulfiram (antabuse) was compared to placebo in three RCTs, with participants presenting co-morbidity, opioid dependence in two trials (George et al. 2000; Petrakis et al. 2000) and alcohol abuse or dependence in Carrol et al. (1998). Mazindol, an amidazoline derivate that blocks reuptake of dopamine, was evaluated in two trials (Margolin et al. 1995a; Stine et al. 1995). Crosby et al. (1996) assessed the value of phenytoin, an anticonvulsant agent, as an anticraving medication. Rosse et al. (1994) compared nimodipine, a calcium channel blocker, to placebo. Lithium carbonate, a mood stabilizer used widely in the treatment of bipolar disorders, was studied by Gawin et al. (1989). Cold (1996) assessed the compound known as NeuRecover-SATM, which includes l-tyrosine and various vitamins and minerals for which cocaine users present a deficiency. A double-blind placebo controlled trial compared naltrexone with placebo (Somoza et al. 1998). In Grabowsky et al. (2000), two doses of risperidone (2 and 4 mg/day), an atypical antipsychotic, were compared to placebo.

Main features of included studies

The main characteristics of the trials included in this review are displayed in Table 1.

Methodological quality

Different methods of randomization were employed in clinical trials, but only nine author groups (Weddington et al. 1991; Kranzler & Bauer 1992; Covey et al. 1993; Moscovitz, Brookof & Nelson 1993; Kranzler et al. 1995; Margolin et al. 1995b; Nunes et al. 1995; Cold 1996) described adequate concealment of allocation (allocation was performed by a person who was not involved in recruitment of patients). These trials were rated as ‘A’; adequate allocation concealment: all remaining studies did not describe the concealment of allocation and were classified as ‘B’.

Most trials included (90%) used a double-blind design. One study used diphenhydramine as an active placebo (Covell et al. 1993). An external evaluator blind to the interventions was used in Carrol et al. (1998), an open study which evaluated three different psychosocial interventions in addition to the disulfiram or no medication.

Outcome reporting

Many outcomes could not be summarized because they were presented in graphical form or only on statistical
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<td><strong>Carbamazepine studies</strong></td>
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<tr>
<td>Campbell et al. 1994</td>
<td>Random allocation (computer-generated list), double-blind, 6 months’ duration, three parallel groups, non-ITT</td>
<td>61 cocaine-dependent out-patients (DSM-III-R); mean age 32 years; 63% males; 90% black</td>
<td>1. Desipramine (n = 21; dose unknown) 2. Carbamazepine (n = 19; dose unknown) 3. Placebo (n = 25)</td>
<td>Duration of treatment</td>
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<td>Cornish et al. 1995</td>
<td>Random allocation; double-blind; 10 weeks’ duration; two parallel groups; non-ITT; two study sites</td>
<td>95 cocaine-dependent out-patients (DSM-III-R); age range 21–51; 98% males; 98% black</td>
<td>1. Carbamazepine (n = 37)</td>
<td>No retention in treatment; urine samples</td>
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<td>Halikas et al. 1997</td>
<td>Random allocation (block design); double-blind; 12 weeks’ duration; three parallel groups; non-ITT (33 replacements)</td>
<td>183 cocaine-dependent out-patients (DSM-III-R); mean age 32.5; 71% males; 66.1% white, with at least an eighth grade education</td>
<td>1. Carbamazepine 400 mg (n = 62) 2. Carbamazepine 800 mg (n = 58) 3. Placebo (n = 63)</td>
<td>No retention in treatment; urine samples</td>
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<tr>
<td>Kranzler et al. 1995</td>
<td>Random allocation (undertaken by a research pharmacist not involved in the clinical care); double-blind; 12 weeks’ duration; two parallel groups; ITT</td>
<td>40 cocaine-dependent out-patients (DSM-III-R); age range 18–45; 100% males; 32% black. Subjects used at least 4 g of cocaine during the preceding month</td>
<td>1. Carbamazepine 600 mg (n = 20) 2. Placebo (n = 20)</td>
<td>Urine samples; no retention in treatment; people with at least one side effect; ASI, BDI, SAS</td>
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<td>Montoya et al. 1994</td>
<td>Random allocation; double-blind; 8 weeks’ duration; two parallel groups; non-ITT</td>
<td>72 cocaine-dependent out-patients (DSM-III-R); mean age 33.2; 79% males; 68% black. At least 14 g of self-reported cocaine use in the previous 3 months</td>
<td>1. Carbamazepine 800 mg/day (n = 28) 2. Placebo (n = 34)</td>
<td>No retention in treatment</td>
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<td><strong>Antidepressant studies</strong></td>
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<td>Arndt et al. 1992*</td>
<td>Random allocation (2:1 ratio); double-blind; 12 weeks’ duration; two parallel groups; non-ITT</td>
<td>79 cocaine abuser out-patients (DSM-III) in methadone-maintained treatment for heroin dependence Mean age 40.5; 100% males, 90% black; 51% of subjects with APD (DSM-III)</td>
<td>1. Desipramine 250–300 mg/day (n = 36) 2. Placebo (n = 23)</td>
<td>No retention in treatment; no retention in treatment for side effect</td>
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<tr>
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<td>Batki et al. 1996</td>
<td>Random allocation; double-blind; 12 weeks' duration; two parallel groups; non-ITT</td>
<td>32 cocaine-dependent out-patients (DSM-III), Age ~34 years; 66% males, 53% African-American 12 participants with major depressive disorder six with APD, six with alcohol abuse dependence</td>
<td>1. Fluoxetine 40 mg/day (20 mg in the first week) (n = 16) 2. Placebo (n = 16)</td>
<td>No retention in treatment; QCI modified version (days used, craving, quality of high)</td>
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<tr>
<td>Campbell et al. 1994</td>
<td>Random allocation (computer-generated list); double-blind; 6 months' duration; three parallel groups; non-ITT</td>
<td>65 cocaine-dependent out-patients (DSM-III-R), Mean age 32; 63% male, 90% black 16 subjects with alcohol dependence, 11 major depression, two generalized anxiety disorder and 16 APD</td>
<td>1. Desipramine (n = 21; dose unknown) 2. Carbamazepine (n = 19; dose unknown) 3. Placebo (n = 25)</td>
<td>Duration of treatment (no SD)</td>
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<td>Carroll et al. 1994</td>
<td>Random allocation; double-blind; 12 weeks' duration; four parallel groups; non-ITT, Subjects received RP or CM</td>
<td>139 cocaine-dependent out-patients (DSM-III-R), Age ~29 years, 73% males, 46% Caucasians; 49% with APD, 65% any other personality disorder, 48% alcohol dependence, 20% affective disorder, 13% anxiety disorder</td>
<td>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)</td>
<td>No retention in treatment Cocaine use during treatment</td>
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<td>Covi et al. 1993</td>
<td>Random allocation (performed by a person who was not involved in recruitment of patients); double-blind; 12 weeks' duration; four parallel groups; non-ITT</td>
<td>45 cocaine-dependent out-patients (DSM-III-R), Mean age 30; 80% males, 56% white, 67% with tobacco dependence, 22% alcohol dependence, 18% anxiety disorders, 7% APD</td>
<td>1. Fluoxetine 20 mg (n = 10) 2. Fluoxetine 40 mg (n = 11) 3. Fluoxetine 60 mg (n = 10) 4. Active placebo (diphenhydramine) (n = 14)</td>
<td>Urine positive for cocaine metabolites</td>
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<td>Ehrman et al. 1996</td>
<td>Random allocation; double-blind; 4 weeks' duration (medical phase); two parallel groups; non-ITT</td>
<td>80 cocaine-dependent out-patients (DSM-III-R), Mean age 37; 100% males, 95.5% African-American; subjects had regular cocaine use ~6 years</td>
<td>1. Ritalin 10 mg/day (n = 40) 2. Placebo (n = 40)</td>
<td>No retention in treatment</td>
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<td>Gawin et al. 1989</td>
<td>Random allocation; double-blind; 6 weeks' duration; three parallel groups; non-ITT</td>
<td>100 cocaine-dependent out-patients (DSM-III), Mean age 29; 76% males, 71% Caucasians. Most participants had other diagnosis such as ADD</td>
<td>1. Desipramine 2.5 mg/kg (n = 31) 2. Lithium carbonate 600 mg (n = 37) 3. Placebo-atropine 0.1 mg (n = 32)</td>
<td>Urine samples; duration of treatment</td>
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<tr>
<td>Author/year</td>
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<td>Giannini et al. 1986</td>
<td>Random allocation (using Texas Instrument Programmable 58 random selection program); double-blind; 40 days' duration four parallel groups; ITT</td>
<td>40 out-patients, 20 chronic cocaine abusers and 20 chronic phencyclidine abusers; age range 20–34 years, 100% male, 100% Caucasians</td>
<td>1. Desipramine 150 mg/day ($n = 10$) 2. Placebo (diphenhydramine) ($n = 10$)</td>
<td>No retention in treatment</td>
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<td>Giannini et al. 1987</td>
<td>Random allocation (using Texas Instrument Programmable 68 random program); double-blind; 45 days' duration; two parallel groups; ITT</td>
<td>20 patients on private-practice psychiatry group, with space-base (combination of free-base cocaine and phencyclidine) abusers. Age range 21–28 years, 100% male, 100% Caucasians</td>
<td>1. Desipramine 200 mg/day ($n = 10$) 2. Placebo ($n = 10$)</td>
<td>Non-abstinent No retention in treatment</td>
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<td>Hall et al. 1994</td>
<td>Random allocation; double-blind; 12 weeks duration; four parallel groups; ITT</td>
<td>94 in-patients at beginning (~2 weeks), with cocaine dependence (DSM-III-R). Mean age 38 years, 100% males, 85% black. Primary cocaine abusers; patients who abused other drugs were also included</td>
<td>1. Desipramine 200 mg: continuity ($n = 23$) 2. Desipramine 200 mg: standard ($n = 22$) 3. Placebo: continuity ($n = 28$) 4. Placebo: standard ($n = 21$)</td>
<td>Urine samples: non-entrance in out-patient program (not leaving the hospital)</td>
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<tr>
<td>Jenkins et al. 1992</td>
<td>Random allocation; double-blind; 12 weeks' duration; two parallel groups; non-ITT; multi-center (four centers)</td>
<td>60 cocaine-dependent in-patients (DSM-III-R) in the first week of trial, mean age 30.8; 95% males; 66% black. Most subjects were employed living in a moderately stable social situation, with no APD</td>
<td>1. Gepirona: mean dose 16.25 mg/day ($n = 20$) 2. Placebo ($n = 21$)</td>
<td>No retention in treatment; duration of treatment; urine samples; no global improvement (CGI)</td>
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<td>Kolar et al. 1992*</td>
<td>Random allocation; double-blind; 12 weeks for desipramine and placebo; 8 weeks for amantadine followed by 4 weeks of placebo; three parallel groups; non-ITT</td>
<td>24 cocaine-dependent out-patients with methadone-maintained (DSM-III-R). Mean age 34.8; 85% males, 68% black. Average use of cocaine: 10 years. Co-morbidities: attention deficit disorder; affective and anxiety disorders</td>
<td>1. Desipramine 200 mg ($n = 8$) 2. Amantadine 200 mg followed by placebo ($n = 5$) 3. Placebo ($n = 9$)</td>
<td>No retention in treatment; urine samples; participants presenting at least one side-effect</td>
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<tr>
<td>Study</td>
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<td>Kosten et al. 1992*</td>
<td>Random allocation; double-blind; 12 weeks’ duration; three parallel groups; non-ITT</td>
<td>94 out-patients with opioid and cocaine dependence (DSM-III-R) Mean age 32 years, 52% males, 82% Caucasians. Other diagnosis: APD (20%); major depression (5%); dysthymia (22%)</td>
<td>1. Desipramine 150 mg (n = 30) 2. Amantadine 300 mg (n = 33) 3. Placebo (n = 31)</td>
<td>Urine samples; no retention in treatment; no retention in treatment for side effect</td>
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<tr>
<td>Margolin 1995a*</td>
<td>Quasi-randomized (stratification by presence of APD and sequentially randomized); double-blind; 12 weeks duration; two parallel groups; ITT; multicenter study</td>
<td>149 out-patients with cocaine dependence (DSM-III-R), methadone-maintained for heroin dependence. Mean age 37.2 years, 62% males, 45% Caucasians. About 50% met criteria for antisocial personality disorder</td>
<td>1. Bupropion 300 mg/day (n = 74) 2. Placebo (n = 75)</td>
<td>No retention in treatment; no retention in treatment for side-effect; Ham-D; ASI; craving</td>
</tr>
<tr>
<td>McElroy et al. 1989</td>
<td>Random allocation; double-blind; 24 weeks’ duration; cross-over (at 12 weeks); non-ITT</td>
<td>15 in-patients with cocaine dependence (DSM-III-R) and also meeting criteria for current or past abuse of other drugs. Mean age 29.5; 73% males. Average duration of cocaine use 5 years</td>
<td>1. Desipramine 200 mg (n = 9) 2. Placebo (n = 6)</td>
<td>Urine samples; no retention in treatment; no retention in treatment for side effect</td>
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<tr>
<td>Nunes et al. 1995</td>
<td>Random stratified allocation, administered by a nurse not involved in recruitment; double-blind; 12 weeks’ duration; two parallel groups; ITT</td>
<td>113 out-patients with cocaine abuse (DSM-III-R). Mean age 32 years, 73% males, 52% Caucasians. Depressive disorder present in 61% of participants</td>
<td>1. Imipramine 150–300 mg (n = 59) 2. Placebo (n = 54)</td>
<td>No retention in treatment; No retention in treatment for side effect</td>
</tr>
<tr>
<td>O’Brien et al. 1988*</td>
<td>Random allocation; double-blind; assessed at follow-up; 12 weeks’ duration; two parallel groups; non-ITT</td>
<td>47 male subjects with cocaine dependence (DSM III R) in methadone maintenance, using cocaine for 3 or more months. Age range 29–50, those with sedative or alcohol dependence were excluded</td>
<td>1. Desipramine (n = 24) 2. Placebo (n = 14)</td>
<td>No retention in treatment</td>
</tr>
<tr>
<td>Tennant &amp; Tarver 1985</td>
<td>Random allocation; double-blind; 12 days for patients on desipramine, 15 for placebo; two parallel groups; analysis unclear</td>
<td>22 subjects with cocaine dependence. Age, sex, race and setting unknown. Patients with other drug dependence were excluded</td>
<td>1. Desipramine (n = 11) 2. Placebo (n = 11)</td>
<td>Positive urine samples for cocaine metabolites; no retention in treatment</td>
</tr>
<tr>
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| Triffleman et al. 1992 | Random allocation (2 x 2); double-blind; 8 weeks’ duration; two parallel groups; non-ITT | 82 male in-patients (for the first 2 weeks) with crack-cocaine dependence. Age unclear; 85% black, 76% unemployed and 32% homeless | 1. Desipramine 200 mg qD (n = 41)  
2. Placebo (n = 41) | Duration of treatment |
| Weddington 1991     | Random allocation (administered by a person not involved in recruitment, using serially numbered, opaque, envelopes); single-blind; 12 weeks’ duration; three parallel groups; non-ITT | 83 out-patients with cocaine dependence (DSM-III-R). Mean age 30 years; 76% males, 69% white. 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) | Urine samples; no retention in treatment; duration of treatment; participants presenting at least one side-effect |
| Alterman et al. 1992 | Random allocation (completed by a research technician using a constrained block); double-blind; 2 weeks’ duration; TWO parallel groups; ITT | 42 day hospital patients with cocaine dependence (DSM-III-R); mean age 35; 100% males, 90% black; Use of cocaine 15 days in the past 30 days and regularly for about 3 years | 1. Amantadine 200–400 mg (n = 21)  
2. Placebo (n = 21) | No retention in treatment; urine samples; BDI |
| Eiler et al. 1995    | Random allocation; double-blind; 18 days’ duration; two parallel groups; non-ITT | 63 male in-patients with cocaine dependence (DSM-III-R); mean age 35.6; 86% black. Last cocaine use within 6 days before study entrance | 1. Bromocriptine 2.5–10 mg/day  
(n = 32)  
2. Placebo (n = 31) | No retention in treatment; no retention in treatment for side-effect |
| Giannini et al. 1989 | Random allocation (Texas Instrument Programmable 68 random computer program); double-blind; 30 days’ duration; three parallel groups; ITT | 30 male out-patients, cocaine abusers. Age range 24–32; 100% Caucasians. Intranasal use on a daily basis for at least 6 months before study. Four subjects with APD | 1. Amantadine 400 mg/day (n = 10)  
2. Bromocriptine 10 mg/day (n = 10)  
3. Placebo (n = 10) | Craving  
Side effects |
| Handelsman et al. 1995* | Random allocation; placebo washout (1 week); double-blind; 8 weeks’ duration; three parallel groups; non-ITT | 67 male out-patients with cocaine and heroin dependence (DSM-III-R); methadone-maintained; mean age 36 | 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 |
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<td>Handelsman et al. 1997*</td>
<td>Random allocation; double-blind; 5 weeks’ duration; two parallel groups; non-ITT</td>
<td>60 male out-patients with cocaine abuse/dependence (DSM-III-R), methadone-maintained and using cocaine in the last 30 days. Mean age 39; 24% black</td>
<td>1. Bromocriptine 5 mg ($n=24$) 2. Placebo ($n=26$)</td>
<td>No retention in treatment</td>
</tr>
<tr>
<td>Kampman et al. 1996</td>
<td>Random allocation (stratified block procedure); double-blind; 4 weeks’ duration; two parallel groups; ITT for urine samples</td>
<td>61 out-patients with cocaine dependence (DSM-III-R) Mean age 35 years, 80% males; 70% black. Cocaine use within 10 days prior to study. Alcohol and marijuana dependence were included</td>
<td>1. Amantadine 300 mg ($n=30$) 2. Placebo ($n=31$)</td>
<td>No retention in treatment; non-abstinent; ASI, BDI, BAI</td>
</tr>
<tr>
<td>Kolar et al. 1992*</td>
<td>Random allocation; double-blind; 12 weeks for desipramine and placebo; 8 weeks for amantadine followed by 4 weeks of placebo; three parallel groups; non-ITT</td>
<td>24 out-patients with cocaine dependence (DSM-III-R). Mean age 34.8; 85% males, 68% black. Average use of cocaine: 10 years. Co-morbidities: ADD, affective and anxiety disorders</td>
<td>1. Desipramine 200 mg ($n=8$) 2. Amantadine 200 mg followed by placebo ($n=5$) 3. Placebo ($n=9$)</td>
<td>Positive urine sample for cocaine metabolites; no retention in treatment</td>
</tr>
<tr>
<td>Kosten et al. 1992</td>
<td>Random allocation; double-blind; 12 weeks’ duration; three parallel groups; ITT</td>
<td>94 out-patients with opioid and cocaine dependence (DSM-III-R) Mean age 32; 52% males, 82% white. ADD (20%); depression (5%); dysthymia (22%)</td>
<td>1. Desipramine 150 mg ($n=30$) 2. Amantadine 300 mg ($n=33$) 3. Placebo ($n=31$)</td>
<td>Urine samples; no retention in treatment; no retention in treatment for side effect</td>
</tr>
<tr>
<td>Kranzler &amp; Bauer 1992</td>
<td>Random allocation (capsules identical in appearance administered by nursing staff, blind to group assignment); double-blind; 21 days duration; two parallel groups; non-ITT</td>
<td>20 male in-patients with cocaine dependence (DSM-III-R). Mean age 27.7 years, 85% white. Subjects had used an average of 3 g of cocaine during the month prior to the admission</td>
<td>1. Bromocriptine 2.5 mg ($n=10$) 2. Placebo ($n=10$)</td>
<td>Participants presenting at least one side effect Side effects</td>
</tr>
<tr>
<td>Moscovitz et al. 1993</td>
<td>Random allocation (performed by a pharmacist who had no contact with subjects); double-blind; 2 weeks’ duration; two parallel groups; non-ITT</td>
<td>29 male out-patients, cocaine users Mean age 37 years. Participants used cocaine at least four times per week for the previous month</td>
<td>1. Bromocriptine 3.75 mg/day ($n=14$) 2. Placebo ($n=15$)</td>
<td>Urine samples; no retention in treatment; participants presenting at least one side effect</td>
</tr>
<tr>
<td>Author/year</td>
<td>Methods</td>
<td>Participants</td>
<td>Interventions</td>
<td>Outcomes used</td>
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<tr>
<td>Tennant &amp; Tarver 1987</td>
<td>Random allocation (using a coin flip); double-blind; 10 days’ duration; two parallel groups; ITT</td>
<td>14 out-patients with cocaine dependence. Age range 16–38; Sex/race unclear; use of cocaine at least four times per day for the 30 days prior to the admission</td>
<td>1. Amantadine 100 mg/day (n = 7) 2. Bromocriptine 2.5 mg/day (n = 7)</td>
<td>Urine samples; no retention in treatment; side effects; side effects</td>
</tr>
<tr>
<td>Weddington et al. 1991</td>
<td>Random allocation (by a person not involved with recruitment of patients, using serially numbered, opaque, envelopes); single-blind; 12 weeks’ duration; three parallel groups; non-ITT</td>
<td>83 out-patients with cocaine dependence (DSM-III-R). Mean age 30.76% males, 69% white</td>
<td>1. Desipramine 200 mg (n = 32) 2. Amantadine 400 mg followed by placebo (n = 23) 3. Placebo (n = 28)</td>
<td>Urine samples; no retention in treatment; duration of treatment; participants presenting at least one side effect</td>
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<tr>
<td>Miscellaneous drugs studies</td>
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<td>Cold 1996</td>
<td>Random allocation (by a person not responsible for recruiting patients); double-blind; 5–21 days’ duration; two parallel groups; non-ITT</td>
<td>13 in-patients with cocaine abuse or dependence (DSM-III-R). Age range 25–46 years, 75% male; race unclear; 10 patients also treated for alcohol dependence</td>
<td>1. NeuRecover-SA™ six capsules daily (n = 8)</td>
<td>Abstinence symptoms (ASE modified); cocaine craving (CCS)</td>
</tr>
<tr>
<td>Crosby et al. 1996</td>
<td>Random allocation; double-blind; 12 weeks’ duration; two parallel groups; non-ITT</td>
<td>60 out-patients with cocaine abuse or dependence (DSM-III-R). Mean age 34 years, 80% male, 55% African-American</td>
<td>1. Phenytoin 300 mg/day (n = 29) 2. Placebo (n = 31)</td>
<td>Cocaine use (self-report); no retention in treatment; craving; side-effects</td>
</tr>
<tr>
<td>Gawin et al. 1989</td>
<td>Random allocation; double-blind; 6 weeks’ duration; three parallel groups; non-ITT</td>
<td>100 out-patients with cocaine dependence (DSM-III-R) seeking treatment. Mean age 29 years; 76% male; 71% Caucasians. Most participants had other diagnosis such as ADDr</td>
<td>1. Desipramine 2.5 mg/kg (n = 31) 2. Lithium carbonate 600 mg (n = 37) 3. Placebo-atropine 0.1 mg (n = 32)</td>
<td>Urine samples; duration of treatment</td>
</tr>
</tbody>
</table>
Margolin et al. 1995b*  
Random allocation (a staff pharmacist, with no contact to participants, developed the randomization code and assigned the interventions); double-blind; 12 weeks’ duration; two parallel groups; ITT  
37 out-patients with cocaine dependence and in methadone maintenance for heroine treatment. Mean age 34 years, 43% male, 68% Caucasian. On average, subjects had been using cocaine for 11 years  
1. Mazindol 1 mg/day (n = 18)  
2. Placebo (n = 19)  
Urine samples; no retention in treatment; participants presenting at least one side effect

Rosse et al. 1994  
Random allocation; double-blind; 3 weeks’ duration; two parallel groups; non-ITT  
70 male in-patients with cocaine dependence (DSM-III-R). Mean age 33 years; race unclear. Average of cocaine use per week was 6.6 g  
1. Nimodipine 90 mg/day (n = 33)  
2. Placebo (n = 33)  
Craving and urges (QCU); mood state (POMS-BI)

Stine et al. 1995  
Random allocation; double-blind; 6 weeks’ duration; two parallel groups; ITT  
43 out-patients with cocaine dependence (DSM-III-R). Mean age 35 years; 86% male; 51% African-American. 67% and 5.8% of participants had alcohol and marijuana abuse, respectively  
1. Mazindol 2 mg/day (n = 22)  
2. Placebo (n = 21)  
Urine samples; no retention in treatment

Somoza et al. 1998  
Random allocation; double-blind; 3 months’ follow-up after hospitalization; two parallel groups; non-information on analysis  
46 patients in a 28-day substance abuse treatment program enrolled in the study during their first week of in-patient treatment. On day 10 of hospitalization they were randomized to treatment groups. After 3 months’ follow-up only six subjects in the naltrexone group and seven subjects in the placebo group remained active in the study  
1. Naltrexone (n = 24)  
2. Placebo (n = 22)  
Self-reported cocaine use; urine samples; subjective cocaine craving; BSI; no retention in treatment

*Studies including patients in methadone maintenance treatment: ADD, attention deficit disorder; APD, antisocial personality disorder; ASI, Addiction Severity Index; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BPRS, Brief Psychiatric Rating Scale; CCS, Cocaine Craving Scale; CO, cocaine craving intensity; CCS, cocaine craving frequency; CGI, clinical global improvement; CSR, cocaine status report; DSM-III, Diagnostic and Statistic Manual (American Psychiatric Association); DSM-III-R, Diagnostic and Statistic Manual (American Psychiatric Association); 3rd edn; DSM-III-R, Diagnostic and Statistic Manual (American Psychiatric Association); 3rd edn revised; HAM-D, Hamilton Depression Scale; ITT, intention-to-treat analysis; M CCS, Minnesota Cocaine Craving Scale; NIMH DIS, National Institute of Mental Health Diagnostic Interview Schedule PANAS, Positive Affect Negative Affect Scale; POMS, Profile of Mood States; QCI, Quantitative Cocaine Inventory; QCI modified, Yale Quantitative Cocaine Inventory; modified version (Baldé et al. 1991, 1993, 1994); SSA, Spielberg State Anxiety score.
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 efficacy (positive urine samples for cocaine metabolites, self-report of cocaine use, craving, abstinence symptoms).

Efficacy findings

The main efficacy outcome reported in the studies was the presence of cocaine metabolites in the urine. Usually, the cut-off value considered to determine a positive test sample was 300 mg/ml. Figure 1 shows these findings for all drugs. No significant results were found, regardless the type of drug or dose used.

Desipramine was evaluated in 14 trials. Some degree of heterogeneity was found when all studies were considered, regardless of whether or not cocaine dependence was a primary diagnosis. In a preliminary analysis, when all desipramine trials with urinalysis data available were included, significant heterogeneity was present ($\chi^2 = 12.7; \text{d.f.} = 6; P = 0.048$). This result favored desipramine, but it was statistically non-significant (RR = 0.82; 95% CI 0.6–1.13). When trials were analysed separately according to the presence of an additional diagnosis of opioid dependence, the result on heterogeneity held for the studies, including patients on methadone maintenance treatment (Kolar et al., 1992; Kosten et al., 1992; $\chi^2 = 4.24; \text{d.f.} = 1; P = 0.04$). A small RCT ($n = 17$) (Kolar et al., 1992) showed an extremely non-significant positive result favoring 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.
Regarding the pattern of cocaine use and craving, the following outcomes were used: duration of treatment in weeks; amount of grams used per day, days of cocaine use per week; percentage of abstinent days; Addiction Severity Index (ASI) drug scores at the end of the trial; craving intensity and frequency. Most of these data, however, were skewed and were not summarized. In other words, there was such a high level of variation in measures used across these studies that it was not possible to incorporate these data into the meta-analysis.

Other clinical ratings

A number of clinical ratings and scales were used in the studies, including the Beck Depression Inventory (BDI), the Spielberg State Anxiety Inventory (SSA), the Symptom Check List 90–Revised (SCL-90-R) and the Patient Global Improvement (PGI), among others. However, relevant data were provided for a limited number of scales. Many continuous outcomes were described in terms of means without corresponding standard deviations, or actual measure units for baseline point and linear change per visit. Such data could not be summarized or presented in graphical form.

Dropouts—no retention in treatment

In 10 studies, authors did not include descriptions of those who dropped out before the end of the trial protocol (Gawin et al. 1989; Giannini et al. 1989; Kranzler & Bauer 1992; Triffleman et al. 1992; Covi et al. 1993; Campbell et al. 1994; Hall et al. 1994; Rosse et al. 1994; Cold 1996; Carrol et al. 1998).

A huge variation was seen in terms of dropout rates in the following studies, ranging from 0% (Giannini & Billet 1987—patients from a private practice psychiatric group) to 84% (Weddington et al. 1991), suggesting that a very heterogeneous set of populations were compared. However, for most of studies a high number of patients who were not able to complete the protocol study was found. In general, the rate of patients remaining in treatment was similar for those taking medications or placebo.

A non-significant trend favoring CBZ was found in terms of dropouts (RR 0.88 95%CI 0.75–1.03), with four studies and 313 individuals included in the meta-analysis.

No significant differences on retention in treatment were obtained for desipramine, gepirone, ritanserin and imipramine trials compared with placebo. Similar results were found for dropout rates due to side effects. One significant result was found by Batki et al. (1996): a higher percentage of patients on fluoxetine completed the study, in comparison with placebo (RR = 0.53; 95% CI 0.32–0.88, n = 32).

In a large RCT on pergolide (n = 464), a dopamine agonist, with 40% of participants presenting co-morbid alcohol and cocaine dependence (Malcolm et al. 2000), dropout rates favored placebo, without reaching statistical significance. Figure 2 shows the dropout rates across different types of drugs.

Side effects

In general, trials did not show significant results in terms of specific side effects between medications and placebo, which can be due to the small number of trials for some drugs and different methods of collecting information on this outcome.

In CBZ studies, several side effects were described, including dermatological hypersensitivity reaction, dizziness, drowsiness, dry mouth, headache, nausea and vomiting, but there were no statistically significant differences between CBZ and placebo. Only two ADs trials (McElroy 1989; Weddington et al. 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 than those on placebo (RR = 1.65; 95% CI 0.98–2.79). Giannini et al. (1989) did not find statistically significant differences between amantadine and placebo in terms of side effects (diarrhoea, headache, nausea and rash). No significant results were found regarding bromocriptine in terms of side effects and placebo.

Direct comparisons

Amantadine versus bromocriptine

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

Amantadine versus desipramine

Three trials compared these products (Weddington et al. 1991; Kolar et al. 1992; Kosten et al. 1992). The first two included methadone-maintained subjects while Weddington evaluated cocaine dependence only. In general, there were no differences when retention in treatment and side effects were evaluated. A non-statistically significant difference favoring desipramine was found in methadone-maintained subjects, as revealed by positive urine samples for cocaine metabolites at the end of the trial.
### Figure 2 Dropout rates

**Subgroup analysis**

Given the heterogeneity of patients, diagnoses and settings, subgroup analysis was performed separately for two groups. Trials where patients had a primary diagnosis of cocaine dependence were compared to those where patients had diagnoses for both cocaine and opioid dependence or were in methadone maintenance treat-
ment. Results were very similar to those obtained for the main analysis, regardless type of drug, suggesting that there is no current evidence to support distinctions among patients with primary cocaine dependence or in methadone maintenance as far the pharmacological treatment of cocaine dependence is concerned. A number of miscellaneous trials are summarized in the figures. None of these trials were of substantial size and none of the results suggested any significant differences. Available data in the original reports did not allow further subgroup analysis.

**DISCUSSION**

Although in this review a large number of RCTs on the pharmacological treatment of cocaine dependence has been identified, no evidence of efficacy was found, regardless of the type of drug or dose used for all relevant outcomes assessed.

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, varying amounts of psychotherapy provided in conjunction with medications and the limitations of meta-analysis per se. Meta-analysis may be affected by biases of original studies and it may often not be the best method for studying the diversity of fields for which it has been used; this could be the case as far the addiction field is concerned. Typical problems related to the use of meta-analytical approaches include: regressions are often non-linear; effects are often multivariate rather than univariate; coverage can be restricted; faulty studies may be included; the data summarized may not be homogeneous; grouping different causal factors may lead to meaningless effect sizes estimates; and the failure to relate data to theories may obscure discrepancies (Eysenck 1995).

In this review, every effort was made to reduce biases, although the generally poor quality of reporting regarding both trial performance and outcome may have limited this aim. For example, the method of random assignment to treatment was seldom described and so 37 of the 46 studies were classified as having a moderate risk of selection bias, thus being more likely to favor the experimental treatment (Schulz et al. 1995).

The key part of this discussion will focus on ADs including desipramine, and CBZ because the largest number of studies have been conducted on these medications. The other drugs reviewed included DAs and miscellaneous drugs but, overall, size of studies was limited, and there was little evidence to suggest benefit from these medications.

**Antidepressants**

**Methodological considerations**

A meta-analysis of desipramine for the treatment of cocaine addiction (Levin & Lehman 1991), including seven randomized 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-analytical 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.

These 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. 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 & Lehman (1991) 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 randomized evidence has since become available: this review includes 14 RCTs (eight 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 analyses and the use of the random effects model, which takes into account heterogeneity between trials.

**Efficacy findings**

Data from 18 RCTs involving 1379 subjects suggest lack of efficacy of ADs compared to placebo. Only three trials (Giannini et al. 1986; Giannini, Loiselle & Giannini 1987; Gawin et al. 1989) showed statistically significant differences favoring the intervention (desipramine) in efficacy measures when compared to placebo. Most of the trials showed a similar decrease in cocaine use and craving in both the placebo and the active drug groups. When
relapse in cocaine-free patients was evaluated, the same pattern of response was found (McElroy et al. 1989). It was suggested that patients who had a history of opioid use were more likely to relapse when treated with ADs (Arndt et al. 1992), but current results were unable to confirm any relevant differences for any of the efficacy measures.

There is still a limited number of RCTs assessing other agents such as fluoxetine, ritanserin, gepirone, 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 et al. 1992; Covi et al. 1993) gepirone and fluoxetine performances were very similar to those found for desipramine trials.

**Dropouts—no retention in treatment**

Although results from single trials suggest that patients on medications such as fluoxetine are less likely to drop out, these results are from single trials and involve a limited number of patients. SSRIs are thought to have better acceptability, but this finding needs replication.

Giannini et al. (1986) found the lowest dropout rate (10%). In this small study \( n = 20 \), participants had a history of cocaine abuse of at least 1 year, and received supportive counselling at 5-day intervals. Batki et al. (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 were paid to participate in the study: $10 for the intake and each of the weekly assessments.

This finding is biased, possibly because of the very heterogeneous populations 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. It is plausible that the best results can be expected in highly motivated populations or associated with highly structured psychosocial interventions aimed at promoting and modulating motivation.

**Carbamazepine**

**Methodological considerations**

The efficacy of CBZ for the treatment of cocaine-dependent patients was first suggested by an open trial with 35 participants (Halikas et al. 1989). These same authors conducted a cross-over randomized controlled study 2 years later confirming this finding \( n = 32 \). Such promising results, however, were based on limited methods, the effects were modest, and the studies performed by a single group. Despite this rationale and the absence of a solid research base, the unfortunate consequence of the early publicity was that carbamazepine made its way into physicians’ practices (Johanson 1995).

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

**Dropouts—no retention in treatment**

Pooled results from five RCTs involving 455 subjects suggest a lack of evidence regarding the efficacy of carbamazepine. Type II error could be an explanation for such findings but other factors such as illness behavior must also be considered. However, the most prominent finding for these studies concern the high dropout rates. Although slightly favoring 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 urgent demand by clinicians, patients, families and the community as a whole for an adequate treatment for cocaine dependence may lead to the 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 preclinical studies to clinical effects in adults, which are not necessarily related to demonstrated and significant clinical effects.

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 et al. patients may be motivated and are not representative of cocaine-dependent patients in the general population. Cocaine-dependent subjects who participated in clinical trials may manifest vastly differing degrees of motivation for change. Such motivation may improve overall outcome significantly 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 anticraving medication (Halikas et al. 1991). Motivation may also be influenced significantly by the overall quality of the program but this is equal for both active drugs and placebo subjects.
Implications for practice

With the evidence currently available, there are no data supporting the efficacy of antidepressants, carbamazepine, dopamine agonists, or other drugs such as disulfiram, naltrexone and mazindol for the treatment of cocaine dependence. 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, ADs). Pharmacological treatments that affect the consumption of other substances such as alcohol may also have a role to play. Disulfiram as a treatment agent requires further exploration; however, given the difficulty in determining its role in alcohol dependence, further studies are required before any conclusions can be drawn on its impact in cocaine dependence.

It seems unlikely that, in the absence of motivation for behavior change, pharmacological agents, with the possible exception of cocaine-specific blocking or maintenance agents, are able to promote a significant improvement in behavior.

The value of medications such as ADs, prescribed in conjunction with a more potent psychosocial intervention, remains unknown. However, until further efficacy and effectiveness studies are available, clinicians may consider adding psychosocial and psychotherapeutic supportive measures aiming to keep patients in treatment. Such advice does not rely on any direct evidence from RCTs, but does consider the best available evidence, the high dropout rates and illness behavior associated with cocaine use. The use of ADs in the absence of depression is not supported by current evidence of impact. This does not preclude the use of ADs to treat major depressive illness that is associated with cocaine abuse and dependence but would clarify that the antidepressant does not have any specific anticraving effect.

Implications for research

There is a need for further exploration of other medications but there is also a need to clarify the current available evidence for psychosocial interventions and to ensure that current psychosocial treatment programs are organized to deliver the greatest possible treatment impact (Carroll et al. 1994). Further studies need also to take account of the organization of the treatment setting when planning trials.

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. If compliance can be improved through psychosocial interven-

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Pharmacological treatment of cocaine dependence


