Efficacy of central nervous system stimulant treatment for cocaine dependence: a systematic review and meta-analysis of randomized controlled clinical trials

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Psychiatry Service, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Spain\textsuperscript{1} and Fundació Institut Català de Farmacologia, Clinical Pharmacology Service, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Spain\textsuperscript{2}

ABSTRACT

Aims To evaluate the efficacy of central nervous system (CNS) stimulants compared with placebo for the treatment of cocaine dependence. Methods A systematic review and meta-analysis was carried out. Bibliographic databases were searched, reference lists of retrieved studies were hand-searched and the first authors of each study were contacted. All randomized controlled clinical trials (RCCT) comparing the efficacy of any CNS stimulant with placebo in cocaine-dependent patients were included. Quantitative data synthesis was performed for each single CNS stimulant and for all CNS stimulants. Results Nine RCCT met the inclusion criteria. These RCCT included 640 patients and compared five CNS stimulants: mazindol, dextroamphetamine, methylphenidate, modafinil and bupropion with placebo. No CNS stimulant improved study retention \([RR = 0.94 (0.81–1.09)]\) or cocaine use \([RR = 0.90 (0.79–1.02)]\). An exploratory analysis using indirect estimations of cocaine use showed that the proportion of cocaine-positive urine screens was lower with dexamphetamine than with placebo \([RR = 0.73 (0.60–0.90)]\) and that all CNS stimulants pooled together also suggested a significant decrease of cocaine use \([RR = 0.87 (0.77–0.99)]\). Data on craving could not be meta-analysed due to heterogeneity, but no RCCT found differences in cocaine craving between active drug and placebo except one, whose outcome favoured dexamphetamine. No serious adverse event (AE) was reported. Average of AE-induced dropouts was low and was greater for CNS stimulants than placebo: 4.4\% versus 1.3\% \((P = 0.03)\). Conclusion The main outcomes of this study do not support the use of CNS stimulants for cocaine dependence. Nevertheless, secondary analyses provide some hopeful results that encourage further research with these drugs, mainly with dexamphetamine and modafinil.

Keywords CNS stimulants, cocaine dependence, meta-analysis, placebo, randomized controlled trial.

INTRODUCTION

The prevalence of cocaine dependence has been increasing in recent years and has become a world health problem. During 2000–01, 0.3\% of the population world-wide, aged 15 years or more, had used cocaine [1]. In the European Union countries life-time cocaine use prevalence reached 3\% of the adult population, with the United Kingdom (6.1\%), Spain (5.9\%) and Italy (4.6\%) at the upper end of this range [2]. In the United States in 2004, life-time and past-year cocaine use among people aged 12 or older was 14.7\% and 2.4\%, respectively. Among past-year cocaine users, 27.8\% were classified as having a cocaine dependence or abuse disorder [3].

A large list of drugs, comprising antidepressants, antipsychotics, dopamine agonists or mood stabilizers, has been studied for cocaine dependence, although none has proved clearly to be effective [4]. As a consequence, no drug has a Food and Drugs Administration (FDA) or European Agency for the Evaluation of Medicinal

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Addiction trials with parallel groups assessing the efficacy of CNS stimulants was reported first by Khantzian and colleagues [11,12] in attention deficit hyperactivity disorder (ADHD) patients with comorbid cocaine dependence. Initially, the administration of psychostimulants was based on the self-medication hypothesis. This hypothesis posits that cocaine addicts begin substance use in an attempt to relieve ADHD symptoms. In these studies, methylphenidate improved both ADHD and cocaine dependence. Nevertheless, further research did not reproduce these results completely; stimulants improved ADHD symptoms but their efficacy in reducing cocaine use was heterogeneous [13,14].

Subsequently, several studies with CNS stimulants have been carried out on cocaine-dependent patients with and without comorbid ADHD [5,6,15]. A wide range of CNS stimulants have been or are being studied [16], including methylphenidate, amphetamine derivatives, modafinil or caffeine. Although these drugs have shown promising results, their efficacy is still inconclusive.

The aim of this study was to review all randomized controlled clinical trials (RCCT) that assessed the efficacy of CNS stimulants for the treatment of cocaine dependence. As well as this, two subanalyses were planned. Because ADHD is a risk factor for substance dependence [17,18], and CNS stimulants improve ADHD symptoms [19,20] and prevent alcohol and drug abuse in children and adolescents with ADHD [21], a subanalysis with those studies that had assessed and included patients with comorbid ADHD was performed. In addition, a subanalysis for RCCT quality was carried out, because quality affects RCCT efficacy results [22].

**METHODS**

**Inclusion and exclusion criteria**

Double-blind, randomized, placebo-controlled clinical trials with parallel groups assessing the efficacy of CNS stimulants for cocaine dependence were included. RCCTs that included cocaine abusers were excluded. Only those RCCTs reporting outcomes on study retention, cocaine use assessed with urine analysis (UA) for cocaine metabolites or cocaine craving were considered suitable. There were no publication restrictions.

**Search strategy**

A PubMed (from 1966 to November 2006), Cochrane Library (from 1966 to November 2006) and Iowa Drug Information System (IDIS) (from 1966 to November 2006) database search was performed twice (last search: 1 December 2006). Bibliographic reference lists of retrieved studies and reviews [4–6,15] were hand searched in order to find additional RCCTs. Furthermore, the first author of selected articles was contacted in order to request additional articles.

Because ‘psychostimulant’ or ‘CNS stimulant’ are not terms describing a pharmacological group but a pharmacological effect, there is no single list of drugs with this effect. For this reason CNS stimulants are classified into several groups, according to their main indication, in drug classification systems such as the Anatomical Therapeutic Chemical (ATC) classification [23] and the American Hospital Formulary Service (AHFS) Pharmacologic-Therapeutic Classification System [24]. Consequently, a drug search was performed to obtain a complete list of drugs with psychostimulant effects. For this purpose, all drugs belonging to groups or subgroups suspected of containing potential psychomotor stimulant drugs were extracted. These pharmacological groups were the N06BA (centrally acting sympathomimetics), A08AA (centrally acting anti-obesity products), N06 BC (xanthine derivatives), N06BX (other psychostimulants and nootropics), N07BA (drugs used in nicotine dependence) and R03DA (xanthines) from the ATC classification; and 12:92 (miscellaneous autonomic drugs), 28:16.04.92 (antidepressants, miscellaneous), 28:20.04 (amphetamines), 28:20.92 (anorexigenic agents and respiratory and cerebral stimulants, miscellaneous) and 86:16 (respiratory smooth muscle relaxants) from the AHFS classification. Furthermore, drugs metabolized to a known psychostimulant, such as selegiline [25], were included. The World Anti-Doping Agency (WADA) list [26] and other sources of information in pharmacology and psychopharmacology [27–30] were also reviewed.

From this list of potential CNS stimulants, only those drugs having at least one published study showing a CNS stimulant effect were included in the definitive list of psychostimulants. CNS stimulant effect was defined as an increased CNS activity resulting in fatigue relief, improved performance in simple tasks, increased locomotor activity and anorexia in healthy subjects [31–33].

**Inclusion and exclusion criteria**

Products (EMEA) indication for cocaine dependence treatment. During recent years, replacement therapy with central nervous system (CNS) stimulants has been gaining support [5,6]. Replacement therapy involves substitution of the abused drug, which is often illegal, used parenterally several times a day, by a legal, orally administered one. A substitutive drug has a similar mechanism of action and behavioural effects to the abused drug but with a lower addictive potential, being able to block drug craving and withdrawal, leading to drug abstinence and helping patients to follow medical and psychological assistance [6]. This strategy has proved to be efficacious for heroin [7,8] and nicotine [9] dependence. Substitutive therapy has also been assessed for amphetamine dependence, with encouraging results [10].

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final CNS stimulants list included (an asterisk indicates that this drug was not available alone or in combination in the US pharmaceutical market in 2006): amphetamine, dexamphetamine, pemoline, dexamphetamine*., ephedrine, etamiphylline*, ethylamphetamine*, fenfluramine*, fenfluramine*., benzphetamine, methamphetamine, methylenedioxymethamphetamine*., methamphetamine, modafinil, nicotine, norpseudoephedrine*., pemoline, phentermine, pipradrol*, prolintane*, propentofylline*, proxyphylline*, selegiline, sydnocarb*, theobromine* and theophylline.

Figure 1 shows PubMed search syntax. Search terms for the Cochrane Library were ‘cocaine’ and for IDIS database ‘depend/abuse, cocaine 304.2’ and ‘study randomized adult 135’. 

**Data extraction**

One author (X. C.) selected the included studies and extracted all relevant data with a standardized report form. Another author (R. B.) checked extraction results. Discrepancies were solved by consensus. Authors were not blinded either by authorship or publication journal. For each study, the following data were extracted: authorship, funding, participants’ characteristics, intervention description, study design, sample size, efficacy outcomes definition, assessment methods, retention, efficacy and safety outcomes, dropouts and type of statistical analysis: intention-to-treat (ITT) or per protocol (PP). ITT results were preferred to PP results.

Each RCCT quality was assessed by means of the Jadad scale [35]. This scale assesses the reporting quality of randomized RCCT. It is based upon the description of withdrawals and upon the description and appropriateness of randomization and double-blinding. Its score ranges from 0 to 5, and a score below 3 is imputed as poor quality.

**Data synthesis and statistical analysis**

Data were entered into the Cochrane Collaboration Review Manager version 4.2.9 package [36] and were summarized in meta-analyses. Study retention and cocaine use were coded as dichotomous variables. Study retention was defined as the rate of patients who completed the RCCT and cocaine use as the proportion of positive UA for benzoylecgonine (BE) along the RCCT for each study group. When this information was not available, it was requested from the authors. If the information was not finally available, these studies were not included in the main efficacy analysis on cocaine use.

Statistical analysis was planned a priori for each single drug and for all CNS stimulants. Nevertheless, because it is not clear whether bupropion has CNS stimulant properties in humans, as will be discussed further later, a post hoc analysis of the efficacy of all CNS stimulants without bupropion on cocaine dependence outcomes was carried out. In order to explain differences between studies in efficacy outcomes, a group of subanalyses regarding RCCT quality according to the Jadad scale score and for patients with comorbid adult ADHD were performed.

Weighted averages were reported as relative risks (RR), with 95% confidence intervals (CI) and the random-effects model in the calculation of CI were preferred to the odds ratio and fixed-effects model, respectively, because the chosen ones led to a more conservative estimate of treatment effect. To determine whether the results were influenced unduly by a single comparison, meta-analyses were repeated after withdrawing each CNS stimulant versus placebo comparison once and, later, comparing if the sense, direction and confidence intervals were altered significantly with respect to the main analysis. Statistical heterogeneity between studies was assessed by means of the χ² test for heterogeneity.

**RESULTS**

**Article search**

A total of 582 potential articles were found (Fig. 2) from the initial bibliographic database searches and hand-search. Nine [38–46] RCCT fulfilled the inclusion/exclusion criteria, involving 640 patients (344 treated with a CNS stimulant and 296 with placebo). Four [41,42,44,45] of nine articles were completed with additional author information, leading to a substantial increase in analysed data. Additional information on baseline sample features regarding socio-demographic and clinical data such as comorbidities or type and route of cocaine use was requested. Although all articles reported data on dropouts and cocaine use, authors were also contacted if this information was reported as a figure and not numerically, or if it was not provided as the proportion of positive UA for benzoylecgonine along the study. A more precise description about the additional limitations and caveats is needed.
Cocaine dependence:  
((cocaine OR crack) AND (abstinence* OR dependent* OR addict* OR withdraw* OR "use OR abus"))

AND

CNS stimulants:  
(amphetamine OR acetylne piperazine OR adrafinil OR amfebutamone OR amfepramone OR aminorex OR aminophylline OR bamillyline OR benzphetamine OR bufylline OR bupropion OR caffeine OR cathine OR cathanone OR choline theophyllinate OR clobenzorex OR dexamphetamine OR dexamethylphenidate OR diethylpropion OR diprophyline OR doxofylline OR dyphylline OR ephedrine OR etamiphylline OR ethylampheta mine OR fencamfamine OR fenestyline OR fenozalone OR mazindol OR mfenorex OR mesocarb OR methamphetamine OR methylendioxyamphetamine OR methylphenidate OR modafinil OR nicotine OR norpseudoephedrine OR pemoline OR phentermine OR pipradrol OR prolintane OR propentofylline OR proxphylline OR selegiline OR sydnocarb OR theobromine OR theophylline)

AND

Controlled clinical trials*:  

Figure 1 PubMed search strategy for retrieving controlled clinical trials with central nervous system stimulants for cocaine dependence. *This search strategy was designed by Robinson & Dickersin [34]
information provided by the correspondence can be found in Table 1.

Five CNS stimulants have been studied by means of a RCCT methodology: mazindol [39,40], dexamphetamine [42,44,45], methylphenidate [41,43], modafinil [46] and bupropion [38].

Clinical trial and subject features

RCCT characteristics, outcomes and quality score according to the Jadad scale are shown in Table 1. Sample sizes ranged from 30 to 149 days and planned follow-up from 42 to 182 days. Seven RCCT were two-armed [37–41,43,44] and two [42,45] had three intervention arms, resulting in 11 CNS stimulants versus placebo comparisons. One study [45] consisted of two RCCT. The first study assessed the efficacy of dexamphetamine, whereas the second assessed the efficacy of risperidone. Because risperidone has no CNS stimulant properties, only the dexamphetamine RCCT has been included in this review. All studies were conducted by public institutions or university researchers and are almost entirely publicly funded, principally by the National Institute on Drug Abuse (NIDA), which funded eight of nine trials.

Figure 2 Flow diagram of identified citations and inclusion and exclusion process. AE = adverse events; CNS = central nervous system; RCT = randomized controlled trial; IDIS = Iowa Drug Information System.
<table>
<thead>
<tr>
<th>Reference, author affiliation and study funding</th>
<th>Participants</th>
<th>Methods</th>
<th>Interventions</th>
<th>Measures of interest: assessment method</th>
<th>Outcomes</th>
<th>Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Margolin et al. 1995 [39]</td>
<td>n = 37</td>
<td>Two-group, parallel arms, randomized, placebo-controlled, double-blind clinical trial</td>
<td>Mazindol 1 mg/day</td>
<td>Cocaine use: BE presence in urine three times a week</td>
<td>No difference in dropout rate, cocaine use or craving was found</td>
<td>3</td>
</tr>
<tr>
<td>Authors' affiliation: university Study funding: co-funding public and private (Wyeth)</td>
<td>Cocaine-dependent methadone-maintained patients abstinent from cocaine use for at least 2 weeks Patients dependent on other substances were not excluded Adult ADHD assessment: NS</td>
<td>Randomization: eligible subjects were randomized to placebo or active compound Follow up length: 84 days</td>
<td>Psychotherapy: psychosocial therapy integrated by: case management, behavioural contingency and group psychotherapy</td>
<td>Statistical analysis: NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stine et al. 1995 [40]</td>
<td>n = 43</td>
<td>Two-group, parallel-arms, randomized, placebo-controlled, double-blind multi-centre (2 sites) clinical trial</td>
<td>Mazindol 2 mg/day q.d.</td>
<td>Cocaine use: BE presence in urine once a week</td>
<td>No difference in dropout rate, cocaine use or craving was found</td>
<td>3</td>
</tr>
<tr>
<td>Authors' affiliation: university and medical centres Study funding: co-funding public and private (Wyeth)</td>
<td>Cocaine-dependent patients according to DSM-III-TR criteria, reporting cocaine use of at least 12 g in the 3 months prior to entering the study Patients dependent on substances other than cocaine or nicotine were excluded Adult ADHD assessment: NS</td>
<td>Randomization: eligible subjects were randomized to placebo or active compound Follow up length: 42 days</td>
<td>Psychotherapy: 6 sessions of group therapy with counselling sessions</td>
<td>Statistical analysis: ITT</td>
<td></td>
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<tr>
<td>Grabowski et al. 2001 [42]</td>
<td>n, ITT sample 128; PP sample = 112</td>
<td>Three-group, parallel arms, randomized, placebo-controlled, double-blind clinical trial</td>
<td>Dexamphetamine-SR 15–30 mg/d b.i.d. versus dexamphetamine-SR 30–60 mg/day b.i.d. versus placebo</td>
<td></td>
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<td>3</td>
</tr>
<tr>
<td>Authors' affiliation: university Study funding: entirely public</td>
<td>Cocaine-dependent patients according to DSM-IV criteria Patients dependent on substances other than cocaine and nicotine were excluded Adult ADHD#: excluded</td>
<td>Randomization: eligible subjects were assigned randomly to placebo or one of two active d-amphetamine doses Follow-up length: 101 days Statistical analysis: only those patients with at least 1 urine analysis+ for BE (PP sample) at baseline were compared</td>
<td>Psychotherapy: 13 sessions cognitive behavioural psychosocial therapy</td>
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<tr>
<td></td>
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<td></td>
<td>Cocaine use#: BE presence in urine twice a week AE#: by means of a 33-item checklist</td>
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</tbody>
</table>

**Table 1** Description of the characteristics of the clinical trials included in this systematic review and their quality score according to the Jadad scale [33].
Table 1. Cont.

<table>
<thead>
<tr>
<th>Reference, author affiliation and study funding</th>
<th>Participants</th>
<th>Interventions</th>
<th>Measures of interest: assessment method</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jadad score</td>
<td>Grabowski et al. 2004 [45]</td>
<td>Authors’ affiliation: university, and hospital; Study funding: entirely public</td>
<td>n: ITT sample 94 (PP sample = 62) Cocaine-dependent patients according to DSM-IV criteria and medications-naïve according to DSM-IV criteria Adult ADHD: excluded</td>
<td>Three-group, parallel arms, double-blind clinical trial Randomization: eligible participants were randomly assigned to placebo or one of two active d-amphetamine doses Follow-up length: 182 days Statistical analysis: outcomes on cocaine use are assessed using a so-called ‘evaluable sample’ which consists of those patients who have taken at least one administration of study medication (62/84 = 73.8% of the ITT sample)</td>
</tr>
<tr>
<td>Shearer et al. 2003 [44]</td>
<td>Authors’ affiliation: university, and hospital; Study funding: public grant and pharmaceutical industry help</td>
<td>n = 30# Cocaine-dependent patients according to DSM-IV criteria: self-report and urine BE cocaine use</td>
<td>Two-group, parallel arms, randomized, placebo-controlled, double-blind clinical trial Randomization: performed using independent pharmacy staff following randomization schedules stratified by gender Follow-up length: 98 days Statistical analysis: ITT</td>
<td>Methylphenidate IR 30–90 mg/day t.i.d. versus placebo</td>
</tr>
<tr>
<td>Schubiner et al. 2002 [43]</td>
<td>Authors’ affiliation: university, and hospital; Study funding: public grant and pharmaceutical industry help</td>
<td>n = 48 Cocaine-dependent patients according to DSM-IV criteria: self-report and urine BE cocaine use</td>
<td>Two-group, parallel arms, randomized, placebo-controlled, double-blind clinical trial Randomization: stratified by gender Follow-up length: 84 days Statistical analysis: NS</td>
<td>Caffeine, methylphenidate IR 30–90 mg/day t.i.d. versus placebo, drug and alcohol counseling</td>
</tr>
<tr>
<td>Reference, author affiliation and study funding</td>
<td>Participants</td>
<td>Methods</td>
<td>Interventions</td>
<td>Measures of interest: assessment method</td>
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<tr>
<td>Jadad et al. 1997 [41]</td>
<td>n = 49</td>
<td>Two-group, parallel arms, randomized, placebo-controlled, double-blind clinical trial</td>
<td>Methylphenidate IR + SR 45 mg/day b.i.d. versus placebo, with 2 weeks of medication stabilization, 11 weeks of trial and 2 weeks of post-trial discharge</td>
<td>No difference in dropout rate or in cocaine use was found</td>
</tr>
<tr>
<td>Authors’ affiliation: university</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study funding: entirely public</td>
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<tr>
<td></td>
<td>Cocaine-dependent patients according to DSM-IV</td>
<td>Follow-up length: 91 days</td>
<td>Psychotherapy: 11 sessions of psychosocial therapy</td>
<td></td>
</tr>
<tr>
<td>Patients dependent on substances other than cocaine, nicotine were excluded</td>
<td>Statistical analysis: NS</td>
<td>Modafinil 200–400 mg/day q.d.</td>
<td>Cocaine use: BE presence in urine three times a week</td>
<td>No difference in dropout rate or craving was found</td>
</tr>
<tr>
<td>Adult ADHD: excluded</td>
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<tr>
<td>Authors’ affiliation: university and medical centre</td>
<td></td>
<td>Randomization: after eligibility, patients were allocated randomly to placebo or active medication</td>
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<td></td>
</tr>
<tr>
<td>Study funding: co-funding public and private (Cephalon)</td>
<td>Follow-up length: 56 days</td>
<td></td>
<td>Follow-up length: 56 days</td>
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<tr>
<td></td>
<td></td>
<td>Statistical analysis: ITT</td>
<td>Statistical analysis: NS</td>
<td></td>
</tr>
<tr>
<td>Margolin et al. 1995 [38]</td>
<td>n = 149</td>
<td>Two-group, parallel arms, randomized, placebo-controlled, double-blind clinical trial</td>
<td>Bupropion 200–300 mg/day t.i.d.</td>
<td>Cocaine use: BE presence in urine three times a week</td>
</tr>
<tr>
<td>Authors’ affiliation: university, medical centres and NIDA</td>
<td></td>
<td>Randomization: after eligibility, patients were allocated randomly to placebo or active medication</td>
<td>Psychotherapy: group or individual psychotherapy for patients on MMT</td>
<td>Cocaine craving: VAS</td>
</tr>
<tr>
<td>Study funding: co-funding public and from a private foundation</td>
<td>Follow-up length: 84 days</td>
<td></td>
<td>Follow-up length: 84 days</td>
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<tr>
<td></td>
<td></td>
<td>Statistical analysis: NS</td>
<td>Statistical analysis: NS</td>
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</tbody>
</table>

ADHD = attention deficit hyperactivity disorder; AE = adverse events; APD = antisocial personality disorder; BE = benzoylecgonine; b.i.d. = twice a day; BPD = borderline personality disorder; BSCS = Brief Substance Craving Scale; CBT = cognitive behavioral therapy; ITT = intention-to-treat; IR = immediate release; i.v. = intravenous; MMT = methadone maintenance treatment; NA = not assessed; NS = not specified; PP = per protocol; q.d. = once a day; SR = sustained release; SUD = substance use disorder; t.i.d. = three times a day; VAS = visual analogue scale. Hash (#) indicates that additional information was requested and obtained from the first author.
In Table 2, baseline patient characteristics are presented for those trials reporting this information. Gender, age and the proportion of opioid-dependent patients were available from all RCCT, whereas race from six, length of cocaine use and type of cocaine from five and employment status, the cocaine route of use and the proportion of ADHD from four RCCT. RCCT featured mainly male (89.1%), middle-aged (mean: 34.9 years), unemployed patients (71.4%). With regard to the characteristics of cocaine use, the patients were mainly crack users (65.3%) and intrapulmonary (i.p.) route users (51.4%), and only a minority (12.8%) were intranasal (i.n.) cocaine users. It is noteworthy that almost half the included subjects were also opioid-dependent.

<table>
<thead>
<tr>
<th>Sample size</th>
<th>640</th>
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<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>% female</td>
<td>11.9</td>
</tr>
<tr>
<td>Age:</td>
<td></td>
</tr>
<tr>
<td>Mean age</td>
<td>34.9</td>
</tr>
<tr>
<td>Race</td>
<td></td>
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<tr>
<td>% white</td>
<td>48.3</td>
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<tr>
<td>% black</td>
<td>40.9</td>
</tr>
<tr>
<td>% other races</td>
<td>10.8</td>
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<tr>
<td>Employment status</td>
<td></td>
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<tr>
<td>% currently employed</td>
<td>28.6</td>
</tr>
<tr>
<td>Length of cocaine use:</td>
<td></td>
</tr>
<tr>
<td>Range of mean lifetime cocaine use (years)</td>
<td>7.7–14.0</td>
</tr>
<tr>
<td>Type of cocaine</td>
<td></td>
</tr>
<tr>
<td>% crack</td>
<td>65.3</td>
</tr>
<tr>
<td>Cocaine route of use</td>
<td></td>
</tr>
<tr>
<td>% i.n.</td>
<td>12.8</td>
</tr>
<tr>
<td>% i.p.</td>
<td>51.4</td>
</tr>
<tr>
<td>% i.v.</td>
<td>35.8</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>% opioid dependents</td>
<td>46.9</td>
</tr>
<tr>
<td>ADHD</td>
<td>7.6</td>
</tr>
</tbody>
</table>

RCCT = randomized controlled clinical trials; ADHD = attention deficit hyperactivity disorder; i.n. = intranasal; i.p. = intrapulmonary; i.v. = intravenous.

In Table 2, baseline patient characteristics are presented for those trials reporting this information. Gender, age and the proportion of opioid-dependent patients were available from all RCCT, whereas race from six, length of cocaine use and type of cocaine from five and employment status, the cocaine route of use and the proportion of ADHD from four RCCT. RCCT featured mainly male (89.1%), middle-aged (mean: 34.9 years), unemployed patients (71.4%). With regard to the characteristics of cocaine use, the patients were mainly crack users (65.3%) and intrapulmonary (i.p.) route users (51.4%), and only a minority (12.8%) were intranasal (i.n.) cocaine users. It is noteworthy that almost half the included subjects were also opioid-dependent. Most (88.1%) of these dual cocaine and opioid-dependent patients were included in three studies [38,39,45] for which this condition was an inclusion criterion. Three studies [40,42,43] provided no data on cocaine use along the study and were excluded from the main efficacy analysis on this outcome. Nevertheless, estimates of cocaine use along the study could be assessed from the baseline and the final data on cocaine use and were included in an exploratory analysis.

Efficacy and safety

Two studies with dexamphetamine [42,45] and one study with modafinil [46] showed that these drugs decrease cocaine use (Table 1). Nevertheless, no study showed a decrease in the dropout rate compared with placebo. When all the studies were pooled together, no differences in retention (Fig. 3) or cocaine use (Fig. 4a) were found between any single CNS stimulant or all CNS stimulants and placebo. No significant changes in efficacy outcomes were found after withdrawing each CNS stimulant versus placebo comparison once.

An exploratory analysis (Fig. 4b) including also those RCCT reporting baseline and final cocaine use showed a significant superiority of dexamphetamine over placebo on cocaine use [RR (CI) = 0.73 (0.60–0.90)] and of all CNS stimulants pooled together [RR (CI) = 0.87 (0.77–0.99)] with bupropion and without it [RR (CI) = 0.82 (0.71–0.94)].

In Table 3, a summary of cocaine craving outcomes of those trials reporting this information is shown. Only one trial with dexamphetamine [44] showed a decrease of cocaine craving; the rest found no differences with placebo. Unfortunately, craving outcomes could not be meta-analysed due to great heterogeneity: five RCCT reported data on craving, which was assessed by means of four different instruments.

Secondary analysis showed that those trials with superior reporting quality (Jadad scale score ≥ 3) had no different results than those with lower reporting quality (Jadad scale score < 3). Subanalysis of the impact of comorbid adult ADHD on the efficacy of CNS stimulants on cocaine dependence could not be carried out because only one study [43] reported data on that issue.

Although it was not planned initially, a subanalysis was carried out of those studies for which dual cocaine and opioid dependence was an inclusion criterion [38,39,45]. The results did not differ substantially from the main analysis and showed a RR of 0.85 (0.56–1.30) for the dropout rate and 0.86 (0.68–1.09) for cocaine use.

Regarding safety, the most commonly reported adverse events (AE) were sleeping problems, anxiety or jitteriness. The administration of a CNS stimulant, compared to placebo, was associated with a higher AE-induced dropout rate: 15/344 (4.4%) versus 4/296 (1.3%) (P = 0.03). The specific AE responsible for patients’ dropout were not generally described. No study reported abuse of study medication.

DISCUSSION

The results of this meta-analysis do not support that CNS stimulants are more efficacious than placebo for cocaine use.
dependence. CNS stimulants did not improve study retention or cocaine use in cocaine-dependent patients. Data on craving could not be meta-analysed due to heterogeneity. One trial with dexamphetamine [44] reported favourable outcomes on craving, whereas the rest found no difference with placebo. Nevertheless, promising results exist, mainly with dexamphetamine and modafinil. It is striking that the efficacy of CNS stimulants has been studied mainly in middle-aged men, long-term and i.p. cocaine users, half of them with comorbid opioid dependence.

Information on adverse drug reactions is too limited to draw conclusions about CNS stimulants toxicity. Dose-dependent, reversible, noradrenalin agonism-related AE were the most commonly reported. No study reported abuse of study medication. A higher AE-related dropout rate has been found with CNS stimulants, but of only 4.4%.

Substitution therapy has proved to be efficacious for heroin [7,8] and nicotine dependence [9]. Although the main outcomes of this meta-analysis do not support that this strategy is efficacious for cocaine dependence, there are data suggesting that these drugs could have some therapeutic role in the treatment of cocaine use that deserve further research. On one hand, dexamphetamine and modafinil show a trend toward a higher efficacy over placebo on cocaine use. Also, the original modafinil study [46] showed a statistically significant beneficial effect on cocaine use. None the less, due to meta-analytical constraints, data were transformed in order to homogenize

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>CNS stimulant</th>
<th>Placebo</th>
<th>RR (random)</th>
<th>Weight</th>
<th>RR (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% Cl</td>
<td></td>
<td>95% Cl</td>
</tr>
<tr>
<td>01 Mazindol</td>
<td>Margolin 1995b</td>
<td>3/18</td>
<td>4/19</td>
<td>1.01</td>
<td>0.79 [0.21, 3.06]</td>
</tr>
<tr>
<td></td>
<td>Stine 1995</td>
<td>13/22</td>
<td>13/21</td>
<td>7.92</td>
<td>0.95 [0.59, 1.55]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>40</td>
<td>40</td>
<td>8.93</td>
<td>0.93 [0.59, 1.47]</td>
</tr>
<tr>
<td>02 Dexamphetamine</td>
<td>Grabowski 2001-1</td>
<td>21/35</td>
<td>18/24</td>
<td>14.61</td>
<td>0.80 [0.56, 1.14]</td>
</tr>
<tr>
<td></td>
<td>Grabowski 2001-2</td>
<td>42/46</td>
<td>18/23</td>
<td>34.02</td>
<td>1.17 [0.92, 1.47]</td>
</tr>
<tr>
<td></td>
<td>Shearer 2003</td>
<td>17/28</td>
<td>15/20</td>
<td>12.10</td>
<td>0.67 [0.42, 1.06]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>10/16</td>
<td>9/14</td>
<td>6.24</td>
<td>0.97 [0.56, 1.60]</td>
</tr>
<tr>
<td>03 Methylphenidate</td>
<td>Grabowski 1997</td>
<td>13/24</td>
<td>10/24</td>
<td>5.14</td>
<td>1.30 [0.71, 2.37]</td>
</tr>
<tr>
<td></td>
<td>Schubiner 2002</td>
<td>13/25</td>
<td>15/24</td>
<td>111.27</td>
<td>1.15 [0.77, 1.73]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>49</td>
<td>48</td>
<td>111.27</td>
<td>1.15 [0.77, 1.73]</td>
</tr>
<tr>
<td>04 Modafinil</td>
<td>Dackis 2005</td>
<td>11/30</td>
<td>11/32</td>
<td>4.11</td>
<td>1.07 [0.55, 2.09]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>32</td>
<td>4.11</td>
<td>1.07 [0.55, 2.09]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>270</td>
<td>221</td>
<td>100.00</td>
<td>0.97 [0.85, 1.11]</td>
</tr>
<tr>
<td>05 Bupropion</td>
<td>Margolin 1995a</td>
<td>11/74</td>
<td>13/75</td>
<td>3.30</td>
<td>0.86 [0.41, 1.79]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>74</td>
<td>75</td>
<td>3.30</td>
<td>0.86 [0.41, 1.79]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>344</td>
<td>296</td>
<td>100.00</td>
<td>0.97 [0.85, 1.10]</td>
</tr>
</tbody>
</table>

Figure 3: Efficacy of central nervous system stimulants versus placebo on dropout rate
Figure 4 Efficacy of central nervous system stimulants versus placebo on cocaine use assessed by means of urine analysis (UA). (A) Only studies that provided cocaine use as the proportion of positive UA along the study are included. (B) Studies for which indirect estimates of the proportion of positive UA along the study could be calculated are also included.
with the rest of the pooled studies. As a result of this conversion, the data turned into a statistical trend. Moreover, an exploratory analysis, including the three studies for which cocaine use was estimated from the baseline and final cocaine use, shows a 27% reduction of the proportion of BE-positive UA in the group of patients treated with dexamphetamine in comparison with those treated with placebo, and of 13% or 18% with all CNS stimulants, without or with bupropion, respectively.

On the other hand, methodological flaws of the included studies regarding sample size, concomitant interventions and baseline patient features may have made it difficult to prove that CNS stimulants are efficacious. At first, most RCCTs were pilot studies with a small sample size. If the data obtained from the exploratory analysis were used to assess the sample size for a RCCT with CNS stimulants with a power of 80%, a two-tailed \( P \)-value of 0.05 and a dropout rate of 50% [4], a sample size ranging from 144 to 584 subjects per arm would be necessary. This is higher than the sample size of any included study, thus a lack of power could explain that no efficacy was found. Additionally, some studies included concomitant behavioural therapies which have proved to be efficacious for cocaine dependence [47]. This could have diluted the efficacy of CNS stimulants. This meta-analysis could not assess the impact of these interventions on CNS stimulants efficacy because these interventions were very heterogeneous. Thirdly, baseline patient characteristics (Table 2) show that the sample was biased towards the inclusion of patients with bad prognoses, such as i.v. or i.p. users [48,49], unemployed [50] and patients with comorbid opioid dependence [51]. Also, most studies did not assess the presence of comorbid ADHD, which has been associated with drug use and poor prognosis [52]. Although it was planned initially, the impact of ADHD comorbid disorder could not be studied because ADHD was assessed in only one trial [43]. However, in Grabowski’s studies with dexamphetamine, ADHD was an exclusion criterion and they showed a decrease of cocaine use. This highlights the need for assessing the presence of this disorder in future studies.

Regarding study retention, although no CNS stimulant showed to be superior to placebo, it is also true that studies featuring dual heroin- and cocaine-dependent patients [38,39,45] showed a higher retention than the studies including subjects dependent only on cocaine. The explanation is that all dual participants were treated with methadone, which has been shown clearly to increase study retention [53], and the study intervention focused specifically on the treatment of comorbid cocaine dependence. It should be noted that one [45] of these three RCCT with dual heroin and cocaine dependence, in comparison with studies including heroin-dependent patients, showed a lower than expected retention rate.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Craving scale</th>
<th>Drug craving</th>
<th>Final craving</th>
<th>Final craving</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mazindol</td>
<td>Likert (0–10)</td>
<td>VAS (5 points)</td>
<td>VAS</td>
<td>VAS</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Dexamphetamine</td>
<td>VAS</td>
<td>VAS</td>
<td>VAS</td>
<td>VAS</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Methylphenidate IR</td>
<td>CSSA, CCQ</td>
<td>VAS</td>
<td>VAS</td>
<td>VAS</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Bupropion</td>
<td>VAS</td>
<td>VAS</td>
<td>VAS</td>
<td>VAS</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference</th>
<th>Drug</th>
<th>Craving scale</th>
<th>Drug craving</th>
<th>Final craving</th>
<th>Final craving</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Margolin et al. 1995 [39]</td>
<td>Mazindol</td>
<td>Likert (0–10)</td>
<td>VAS (5 points)</td>
<td>VAS</td>
<td>VAS</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Stine et al. 1995 [40]</td>
<td>Mazindol</td>
<td>VAS</td>
<td>VAS</td>
<td>VAS</td>
<td>VAS</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Shearer et al. 2002 [44]</td>
<td>Dexamphetamine</td>
<td>VAS</td>
<td>VAS</td>
<td>VAS</td>
<td>VAS</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Schubiner et al. 2002 [44]</td>
<td>Methylphenidate IR</td>
<td>CSSA, CCQ</td>
<td>VAS</td>
<td>VAS</td>
<td>VAS</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Dackis et al. 2005 [46]</td>
<td>Bupropion</td>
<td>VAS</td>
<td>VAS</td>
<td>VAS</td>
<td>VAS</td>
<td>&lt; 0.01</td>
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<td>Margolin et al. 1995 [38]</td>
<td>Bupropion</td>
<td>VAS</td>
<td>VAS</td>
<td>VAS</td>
<td>VAS</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

BCSC = Brief Substance Craving Scale; CCQ = cocaine craving questionnaire; CSSA = cocaine selective severity assessment; IR = immediate release; VAS = visual analogue scale; NR = not reported.
highlighting that dual heroin–cocaine dependence is a more complex disorder than heroin dependence. Indeed, cocaine use has been associated with poor outcomes of heroin dependence treatment [54, 55].

Three studies assessed the efficacy of dexamphetamine for cocaine dependence, two of them showing a decrease in cocaine use [42, 45] and one [44] showing no differences with placebo. The use of different dexamphetamine formulations and administration schedule could explain, in part, the difference in their findings. While one study [44] used an immediate release (IR) formulation that was administered once a day in the morning, the other two [42, 45] used a twice-a-day sustained-release (SR) formulation, which has a slower onset of action and longer half-life than the IR formulation [56]. As substitution therapy involves the administration of a drug with the same effects but a slower onset of action and longer half-life than the abused drug, it is not strange that those studies using a SR formulation show improved outcomes on cocaine use. An additional explanation for these differences is that Grabowski et al.’s studies [42, 45] show positive outcomes on cocaine use after withdrawing those participants who dropped out from the study [42] or those who never provided a positive BE urine screen [45], suggesting that dexamphetamine could be efficacious mainly for cocaine-dependent subjects who are using cocaine actively. Finally, differences in baseline sample features could also explain the results of the dexamphetamine RCCT. The study by Shearer et al. [44], using IR dexamphetamine, was conducted in a community clinic and featured a extremely marginalized sample, with 45% of sex workers, 55% of participants with a history of criminal activities and 42% facing penal charges, all in all hampering the possibility of proving the efficacy of this drug in cocaine use.

The fact that we have pooled together drugs with notable differences in their mechanisms of action, behavioural effects and classified into different pharmacological groups deserves an explanation. All these drugs, although dissimilar, share common ground and have some behavioural effects in common. At first, all of them, among other mechanisms of action, block dopamine reuptake (mazindol [57], dexamphetamine [58], methylphenidate [59], modafinil [60] and bupropion [61, 62]), which has been shown to be responsible for cocaine’s reinforcing properties [63, 64]. It should be noted that modafinil’s affinity for dopamine transporter (DAT), considered essential for its stimulating properties [65, 66], seems to be lower than that of other CNS stimulants. Moreover, other mechanisms seem to be involved in its stimulating properties, such as actions on glutamate, gamma-aminobutyric acid, histamine and hypocretin systems [67]. These differences set modafinil into a different group of CNS stimulants from thoseamphetamine-related ones. Secondly, these drugs have substitutive properties for cocaine and for other prototypical CNS stimulants in discriminative stimulus studies [68–77]. Thirdly, these drugs also share some behavioural effects. Human behavioural studies show that dexamphetamine, methylphenidate and modafinil have CNS-stimulating properties [78–82]. It should be stressed that, whereas dexamphetamine and methylphenidate also have euphorigenic effects, thus having abuse potential [83, 84], modafinil does not show this [80–82] and therefore its abuse potential is low [85]. Conversely, there are no behavioural studies in healthy volunteers assessing CNS stimulant properties of mazindol. Nevertheless, in clinical sample studies, mazindol shows an increase in alertness and a decrease in appetite [86, 87]. In contrast, bupropion has several behavioural studies showing contradictory results indicating that it has no, or at most few, CNS stimulant properties in humans [88–93] and has shown stimulant properties only in non-human animal studies [94, 95]. For this reason, bupropion is not a clear CNS stimulant in humans and, consequently, the polled efficacy analysis is presented with and without bupropion in this meta-analysis.

Finally, in accordance with these pharmacological similarities, most of these drugs have been shown to be effective for the treatment of disorders such as ADHD (methylphenidate [96, 97], dexamphetamine [96, 97], bupropion [98] and modafinil [99]), fatigue relief, sleepiness, somnolence or narcolepsy (mazindol [86], methylphenidate, dexamphetamine, modafinil [100] and bupropion [101]) and are or have been used for weight loss (mazindol [102], dexamphetamine [103], bupropion [102] and modafinil [104]). Therefore, from a pharmacological viewpoint all these drugs could substitute cocaine in dependent patients leading to a decrease in cocaine use. The results of this meta-analysis should be interpreted in light of several limitations, some of which are related to the meta-analytical approach. Information bias, leading to an excess of effect because negative studies are not reported, has been controlled by using multiple database sources, hand-searching the bibliographical references of all retrieved RCCT and contacting authors. Heterogeneity among studies is another limitation of meta-analysis. Heterogeneity arises from different sample features and different RCCT designs. The presence or absence of comorbid ADHD and opioid dependence accounts largely for this probable heterogeneity. Although a heterogeneity test found no statistically significant heterogeneity, this test is very specific but not too sensitive. To limit meta-analytical flaws, recommendations from the ‘quality of reporting of meta-analyses’ (QUOROM) statement [105] have been used to carry out this study.
Data about cocaine use of two RCCT [42,45] are PP. Nevertheless, it should be noted that the reported cause for withdrawing patients and carrying out a PP analysis in these studies does not appear to be related to drug effect, thus bias is unlikely.

Limitations regarding patients’ baseline characteristics must be stressed. As stated previously, the sample is over-represented by patients with bad prognoses. The sample consisted of a high rate of i.v. and i.p. users and dual opioid and cocaine addicts. This may have hindered proving the efficacy of CNS stimulants and has limited the external validity of these studies and of this meta-analysis.

Finally, the study variable for cocaine use in this meta-analysis is the proportion of BE-positive UA in each group along the clinical trial. It would have been more powerful to use the mean and standard deviation of the proportion of positive UA for each patient in each group. Nevertheless, cocaine use was reported in this manner in only one study [40]. This highlights the need that future studies should report cocaine use as a continuous variable. If a categorical variable was used, it would be preferable to use a variable such as the proportion of abstinent patients, in order to facilitate understanding and enable comparison across studies [106].

In the context of these limitations, this meta-analysis does not support that CNS stimulants are more efficacious than placebo for the treatment of cocaine dependence. Nevertheless, some promising data, especially with dexamphetamine and modafinil, exist. Hence, it is not surprising that CNS stimulants are currently the group of drugs with most ongoing trials for cocaine dependence [16]. A follow-up meta-analysis with the inclusion of ongoing RCCT is warranted.

CONCLUSION

Many CNS stimulants exist; only five of them have been studied for the treatment of cocaine dependence. This systematic review and meta-analysis does not show that CNS stimulants decrease dropout rate, cocaine use or craving compared to placebo. However, promising results exist for dexamphetamine and modafinil, suggesting the need for further research with this group of drugs.

Acknowledgements

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References


