

Pilot randomized double blind placebo-controlled study of dexamphetamine for cocaine dependence

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ABSTRACT

Aims To establish the feasibility of conducting a placebo-controlled clinical trial of dexamphetamine replacement therapy for cocaine dependence and to obtain preliminary data.

Design Double-blind randomized placebo-controlled trial.

Participants Thirty cocaine-dependent injecting drug users.

Intervention Subjects were assigned randomly to receive 60 mg/day dexamphetamine ($n = 16$) or placebo ($n = 14$) for 14 weeks.

Measurements Immunoassay and mass spectrometric techniques were used to identify cocaine metabolites in urine. Subjects were screened using the Composite International Diagnostic Interview and DSM-IV. The Opiate Treatment Index, Brief Symptom Inventory, Severity of Dependence Scale and visual analogue craving scales were used to collect pre- and post-self-report data.

Findings Treatment retention was equivalent between groups; however, outcomes favoured the treatment group with no improvements observed in the placebo control group. The proportion of cocaine-positive urine samples detected in the treatment group declined from 94% to 56% compared to no change in the placebo group (79% positive). While the improvements were not significant between groups, within-group analysis revealed that the treatment group reduced self-reported cocaine use ($P = 0.02$), reduced criminal activity ($P = 0.04$), reduced cravings ($P < 0.01$) and reduced severity of cocaine dependence ($P < 0.01$) with no within-group improvements found in the placebo group.

Conclusions A definitive evaluation of the utility of dexamphetamine in the management of cocaine dependence is feasible and warranted.

KEYWORDS Cocaine dependence, dexamphetamine, randomized controlled trial, treatment.

INTRODUCTION

Increasing cocaine use has been identified as a serious public health problem in Sydney, Australia, particularly among more marginalized and vulnerable injecting drug users (Darke *et al.* 2002). Harms include compulsive binge behaviour, frequent and frenetic injecting due to the short activity of cocaine, psychosis, HIV risk-taking through unsafe injecting and sexual practices, violence, criminal activity and other antisocial behaviour (van

Beek *et al.* 2001). There are currently no pharmacotherapies recognized as effective in the management of cocaine dependence. A recent systematic review of 45 different studies of pharmacological treatments for cocaine dependence, including many commonly prescribed antidepressants, anticonvulsants and dopamimetics, found no evidence for efficacy as measured by the presence of cocaine metabolites in urine (de Lima *et al.* 2002). The reviewers concluded that, with the exception of cocaine-specific blocking or maintenance agents, it appeared that

currently prescribed pharmacological agents were unlikely to offer significantly improved outcomes for cocaine users.

Agonist therapies aim to replace harmful modes of drug use in terms of dose, route of administration and adverse effects while engaging and retaining cocaine users in treatment. Substitution or agonist therapies are recognized as highly effective for drugs such as nicotine (Jarvik & Henningfield 1993) and heroin (Ward *et al.* 1998) and more recently have been explored for amphetamine users (Shearer *et al.* 2002). Agonist therapies assessed for management of cocaine dependence have included methylphenidate and dexamphetamine. Levin *et al.* (1998) reported significantly reduced cocaine use and cravings in a group of 12 patients dually diagnosed for adult attention deficit hyperactivity disorder (ADHD) and cocaine dependence receiving 40 mg/day sustained release methylphenidate. However, a placebo-controlled trial of 48 cocaine-dependent ADHD adult patients found improvements in reported ADHD symptoms in subjects receiving active methylphenidate, but no between-group differences in cocaine use or cravings (Schubiner *et al.* 2002). Further, in a randomized placebo controlled trial of methylphenidate (20 mg twice daily slow release) in 49 patients without adult ADHD, methylphenidate was ineffective in reducing cocaine intake (Grabowski *et al.* 1998). They suggested consideration of other stimulants that may be more adequate reinforcers. In a three-arm trial ($n=128$) including placebo, 15–30 mg d-amphetamine and 30–60 mg d-amphetamine groups, Grabowski *et al.* (2001) found dose-related changes in retention and cocaine use in favour of dexamphetamine treatment with no serious adverse events or cardiovascular complications.

The aim of the present study was to evaluate the feasibility of prescribed dexamphetamine as substitution therapy for regular, dependent cocaine users and to obtain preliminary data on the safety and efficacy of this intervention in terms of changes in cocaine use and associated harms.

METHODS

Subjects and design

Thirty cocaine-dependent injectors who met study inclusion criteria provided informed consent and agreed to participate in the study. Inclusion criteria included cocaine dependence diagnosis (DSM-IV criteria) and a cocaine-positive urine sample or documented history of cocaine use. Subjects with other significant medical conditions likely to make trial participation hazardous (such as cardiovascular conditions and schizophrenia) were excluded. Subjects were recruited among clients

attending two inner-city drug and alcohol treatment centres: the Kirketon Road Centre and Rankin Court. Ethical approvals were obtained from three institutional ethics committees, including that of the South-eastern Sydney Area Health Service. Subjects were randomized equally to receive either dexamphetamine (60 mg/day) (16 subjects) or placebo (14 subjects) under equivalent conditions for a period of 14 weeks. Randomization was conducted independently through the Sydney Hospital Pharmacy using randomization schedules stratified by gender.

Instruments

Urine samples were collected at baseline and every 2 weeks over the 14-week study period and tested for the presence of cocaine metabolites by immunoassay. Induction commenced at 20 mg, increasing by 5 mg daily until the maximum daily supervised dose of 60 mg was achieved. Adverse events and side-effect data were collected by systematic symptom checklists during standardized medical reviews supplemented by case-note reviews while subjects remained in treatment. The Opiate Treatment Index (OTI) (Darke *et al.* 1992) was used to measure self-reported cocaine use and other treatment outcomes. Severity of cocaine dependence was measured by the Severity of Dependence Scale (SDS) (Gossop *et al.* 1992). Psychopathology was assessed using the Brief Symptom Inventory (BSI) (Derogatis 1993). Cocaine craving was measured using visual analogue scales.

Data analysis

An intention-to-treat approach was used to examine between group differences. The intention-to-treat population was defined as those subjects who were enrolled in the study, randomized and started treatment. Data for included subjects subsequently lost to follow-up were imputed from baseline data using a 'worst case scenario' assumption of no change. Missing urine samples were deemed cocaine-positive. Statistical tests were two-tailed using a 0.05 significance level and 95% confidence intervals; t -tests were used for continuous variables and the χ^2 statistic for categorical variables. Retention data were analysed using the Wilcoxon (Gehan) statistic.

RESULTS

Study sample

The sample of 30 cocaine injectors had an average age of 28 years (± 6 years). Fifty-two per cent were male. Eighty per cent were currently in methadone maintenance treatment for opioid dependence. Forty-five per cent were

involved in sex work. Many subjects had a history of criminal activity; 55% had a history of imprisonment and 42% were facing charges at baseline. Eighty-two per cent reported using cocaine daily or almost daily. Subjects reported injecting cocaine an average of six times a day (± 5) and spent an average of AUD\$227 ($\pm \222) per day on cocaine. Baseline demographic and key outcome data were comparable between groups with no significant between-group differences.

Retention and compliance

Subjects were randomized to treatment ($n = 16$) or placebo ($n = 14$) for a period of 14 weeks. Three treatment-group subjects (19%) and one control-group subject (7%) were lost to follow-up. Six treatment-group subjects (38%) and five control-group subjects (36%) completed the 14-week treatment course. Survival analysis revealed no significant between-group difference (Wilcoxon (Gahen) $\chi^2 = 0.007$, $df = 1$, $P = 0.9$). Treatment subjects who completed induction ($n = 10$) were dispensed dexamphetamine on a mean of 37 days (range 7–76) over a mean attendance period of 72 days (range 19–105) representing compliance to daily dosing of 51% (range 25–78%). Mean average daily dose of dexamphetamine was 41 mg (range 26–52 mg). There was no between-group difference in the proportion of subjects concurrently receiving methadone maintenance treatment at baseline (treatment 75%; control 86%, $P = 0.5$) or at follow-up 69% (treatment) and 71% (control). There was no difference in self-reported heroin use OTI score at week 14 follow-up ($t = 0.3$, $P = 0.8$).

Urinalysis results

The proportion of treatment- and control-group urine samples positive for cocaine metabolites appear in Fig. 1. The proportion of cocaine-positive urine samples declined in the treatment group from 94% at baseline and

remained between 56% and 69% over the study period. In the placebo group, the proportion of cocaine-positive urine samples remained constant at 79% until week 6, when it fell to 57% and then returned to 79% by the end of the study. Between-group difference at the final week 14 follow-up was 22.4% ($\chi^2 = 1.7$, $P = 0.2$). Within-group differences were examined further using a χ^2 test for linear trend (Schlesselman 1982). These were not significant in either group (treatment $\chi^2 = 2.4$, $P = 0.1$; control $\chi^2 = 0.009$, $P = 0.9$).

Adverse events

Three serious adverse events were noted requiring hospitalization. One treatment subject, with an undisclosed history of drug-induced psychotic episodes, was admitted for 24-hour observation for psychotic symptoms. The subject was discharged with no evidence of psychotic symptoms and was withdrawn from treatment. The other two events were not related to study participation or medications. Insomnia and disturbed sleep were the most commonly reported side-effects but did not differ by group (treatment 44%; control 50%).

Other self-report outcomes

Self-reported outcome data appears in Table 1. Higher scores indicate higher levels of dysfunction. There were no significant between-group differences on any self-report outcomes. Within-group changes were in favour of the treatment group and reached significance for cocaine use ($P = 0.02$), cocaine craving ($P < 0.01$), severity of dependence ($P < 0.01$) and crime ($P = 0.04$). There were no positive significant changes identified in the placebo group. The mean social score deteriorated significantly within the placebo group ($P = 0.03$). There were no between-group differences in the proportion of anxiety, depression, paranoia and other personality disorders

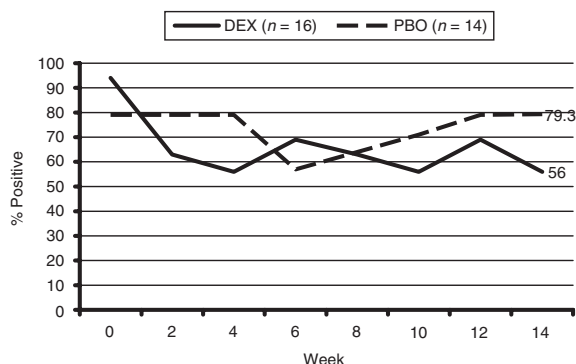


Figure 1 Proportion of study group urine samples positive for cocaine metabolites over study period

Table 1 Mean self-report measures at baseline and follow-up.

	Treatment (n = 16)		Control (n = 14)		(P) ^a
	Baseline	Follow-up	Baseline	Follow-up	
Cocaine use	4.8	2.1	6.6	4.1	(0.3)
HIV risk score	11.0	9.3	13.6	11.8	(0.3)
Expenditure	188	78	280	163	(0.2)
Social	18.3	19.8	19.2	22.4	(0.4)
Crime	2.4	1.9	2.5	2.1	(0.7)
Health	20.2	17.1	17.5	17.8	(0.8)
Craving	77	51	77	67	(0.1)
SDS	9.7	7.6	10.7	9.0	(0.3)

^aIndependent samples t-test for equality of means (two-tailed) between groups at follow-up.

identified in the BSI either at baseline or week 14 follow-up. The study blind was tested after the week 14 follow-up interview. Fifty-six per cent of treated subjects identified their group allocation correctly compared to 36% in the placebo group. Interestingly, 57% of the placebo group believed incorrectly that they had received active dexamphetamine.

DISCUSSION

The study sample represented a specific treatment population, with female sex workers and methadone patients over-represented. However, the demographics of this treatment group were comparable to those found in other surveys of cocaine users in inner-city Sydney (van Beek, Dwyer & Malcolm 2001). Consistent with drug market surveillance, cocaine use was exclusively by injection, with smoked or 'crack' cocaine use extremely rare in Australia (Darke *et al.* 2002). Equivalent between-group treatment retention may have been influenced by the high proportion of methadone clients who were already attending the clinics daily. No adverse interactions in patients concurrently receiving methadone were noted in terms of between-group differences in methadone dose or heroin use. While adverse events and side effects were comparable between groups, the prevalence of mental and physical problems in this study group may have been higher than in less problematic cocaine users. Regular monitoring of psychotic and paranoid symptoms and continuing cocaine use, particularly during the treatment induction phase, was required. Dose reduction or temporary treatment suspension were effective until side effects resolved or adverse events were treated appropriately. Finally, the study sample was too small to evaluate confidently the efficacy of dexamphetamine relative to placebo in reducing cocaine use, cravings and cocaine-related harms.

Despite these limitations, the response to the intervention among a difficult to engage and treat population was encouraging. Outcomes favoured the treatment group in terms of cocaine use measured by urinalysis and self-report, crime, cocaine craving and severity of cocaine dependence, with no improvements observed in the placebo group. As 'proof-of-concept', the results supported the specific efficacy of dexamphetamine in attenuating cocaine craving. These findings in the psychological dimension of dependence were supported further by declines found in the severity of cocaine dependence scores. The intervention and study design also appeared to be acceptable to cocaine users, as evidenced by satisfactory recruitment and retention in an otherwise highly chaotic group. These results support further controlled studies with adequate power to

evaluate the utility of dexamphetamine in the management of cocaine dependence.

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