

Randomized controlled trial of dexamphetamine maintenance for the treatment of methamphetamine dependence

Marie Longo¹, Wendy Wickes¹, Matthew Smout¹, Sonia Harrison¹, Sharon Cahill¹ & Jason M. White^{1,2}

Pharmacotherapies Research Unit, Drug and Alcohol Services South Australia, Norwood, South Australia, Australia¹ and Discipline of Pharmacology, University of Adelaide, Adelaide, South Australia, Australia²

ABSTRACT

Aim To investigate the safety and efficacy of once-daily supervised oral administration of sustained-release dexamphetamine in people dependent on methamphetamine. **Design** Randomized, double-blind, placebo-controlled trial. **Participants** Forty-nine methamphetamine-dependent drug users from Drug and Alcohol Services South Australia (DASSA) clinics. **Intervention** Participants were assigned randomly to receive up to 110 mg/day sustained-release dexamphetamine ($n = 23$) or placebo ($n = 26$) for a maximum of 12 weeks, with gradual reduction of the study medication over an additional 4 weeks. Medication was taken daily under pharmacist supervision. **Measurements** Primary outcome measures included treatment retention, measures of methamphetamine consumption (self-report and hair analysis), degree of methamphetamine dependence and severity of methamphetamine withdrawal. Hair samples were analysed for methamphetamine using liquid chromatography-mass spectrometry. **Findings** Treatment retention was significantly different between groups, with those who received dexamphetamine remaining in treatment for an average of 86.3 days compared with 48.6 days for those receiving placebo ($P = 0.014$). There were significant reductions in self-reported methamphetamine use between baseline and follow-up within each group ($P < 0.0001$), with a trend to a greater reduction among the dexamphetamine group ($P = 0.086$). Based on hair analysis, there was a significant decrease in methamphetamine concentration for both groups ($P < 0.0001$). At follow-up, degree of methamphetamine dependence was significantly lower in the dexamphetamine group ($P = 0.042$). Dexamphetamine maintenance was not associated with serious adverse events. **Conclusions** The results of this preliminary study have demonstrated that a maintenance pharmacotherapy programme of daily sustained-release amphetamine dispensing under pharmacist supervision is both feasible and safe. The increased retention in the dexamphetamine group, together with the general decreases in methamphetamine use, degree of dependence and withdrawal symptom severity, provide preliminary evidence that this may be an efficacious treatment option for methamphetamine dependence.

Keywords Dependence, dexamphetamine, maintenance, methamphetamine, pharmacotherapy, randomized controlled trial, treatment.

Correspondence to: Jason White, Discipline of Pharmacology, University of Adelaide, Adelaide 5005, South Australia, Australia.

E-mail: jason.white@adelaide.edu.au

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INTRODUCTION

Global estimates indicate that amphetamines are second only to cannabis as the most commonly consumed illicit drugs, with 24.9 million people (0.6%) in 2007 reporting use in the previous 12 months [1]. Compared with many other countries, Australia has a

high prevalence of methamphetamine use: in 2005 it was estimated that there were 72 700 dependent methamphetamine users in Australia, with a further 102 600 (1%) using on a more occasional basis [2]. High-level consumption is associated with a variety of harms, ranging from insomnia and irritability to increased aggression, depression and psychosis [3–5].

and there are concerns surrounding potential neurotoxicity [6,7]. However, there are few evidence-based treatments available that focus specifically on methamphetamine use. Maintenance agonist approaches that have proved very effective for opioid dependence have been adopted in the United Kingdom. Evaluations, while positive, are based predominantly on retrospective reviews of case-notes [8–13] and are limited by factors such as small sample sizes, absence of control groups and reliance on self-report measures of illicit amphetamine use.

To date, there have been five randomized controlled trials of dexamphetamine maintenance: two with amphetamine users [14,15] and three with cocaine users [16–18]. Although the two trials with amphetamine users involved supervised daily dosing, these were open-label with no placebo controls. Moreover, one study relied solely on self-report measures of illicit amphetamine use [15]. There has been one placebo-controlled trial with supervised daily dosing of participants who were concurrent heroin/cocaine users, 80% of whom were maintained on methadone [18]. Two placebo-controlled studies in the United States [16,17] used a sustained-release formulation of dexamphetamine in cocaine users and twice-daily dosing to a maximum of 60 mg/day. No study found statistically significant differences between groups in treatment retention, and only one found differences in illicit cocaine use, which favoured the dexamphetamine group [16]. Studies have reported improvements in physical health [15], craving and dependence [14] and self-reported illicit drug use [15,18] among those given dexamphetamine, and in all studies, the incidence of side effects, including psychotic symptoms, was low.

The present preliminary study was a randomized, double-blind, placebo-controlled trial with flexible dosing and daily supervised administration of the maintenance drug. A sustained-release formulation of dexamphetamine was used, enabling once-daily dosing, with the maximum dose set at 110 mg/day. This drug is used therapeutically for the treatment of narcolepsy and attention deficit/hyperactivity disorder (ADHD) in both children [19,20] and adults [21], without evidence of long-term harm [22].

The primary hypotheses were that dexamphetamine would produce greater reductions in illicit methamphetamine use and degree of dependence than placebo, as well as increase treatment retention. Methamphetamine use was monitored by self-report, with hair analysis as an objective biomarker. In addition to measures of efficacy, safety was assessed by routine monitoring of heart rate, blood pressure, body weight and psychotic symptoms.

METHODS

Participants

Forty-nine participants recruited from specialist drug and alcohol treatment services in South Australia between July 2004 and December 2007 provided informed consent and underwent a two-phase screening process before commencing treatment. Inclusion criteria included DSM-IV diagnosis of methamphetamine dependence, a positive urine sample and use of methamphetamine on 3 or more days per week over the previous 12 months. Participants were excluded if they were dependent on other drugs (excluding nicotine), had insufficient hair length for hair analysis or had significant psychiatric or medical conditions. Pregnant females were excluded, as well as participants on antidepressant or antipsychotic medications. Of those who underwent formal screening ($n = 95$), 46 (48%) were ineligible. Reasons included failure to attend appointments, insufficient hair length, inability to attend for daily dosing, urine sample negative for sympathomimetic amines (indicating no recent use of methamphetamine), dependence on other drugs and significant medical or psychiatric diagnoses. See Fig. 1 for information on the flow of participants through the trial.

Design

Ethical approval was obtained from the Royal Adelaide Hospital Research Ethics Committee. Following screening and enrolment, participants were randomized to receive either dexamphetamine ($n = 23$) or placebo ($n = 26$) and baseline research assessments were administered. A simple randomization schedule was used, and allocation was performed according to a computer-generated randomization list to select random permuted blocks of six by the pharmacy assistant who prepared the medication. Participants, all clinicians involved in their care, pharmacists and researchers were blinded as to treatment allocation. The study period comprised an initial stabilization period of up to 14 days, with an initial dose of 20 mg/day increased by 10 mg daily as required until stabilized or to a maximum of 110 mg/day. All participants underwent stabilization, with the placebo group receiving increasing numbers of placebo capsules. Pulse and blood pressure measurements were taken each day during this period, and participants were assessed daily for withdrawal symptoms using the Amphetamine Withdrawal Questionnaire (AWQ), and for adverse effects. The initial screening assessment was performed by a senior medical officer with subsequent daily examinations by experienced nurses, as well as medical assessments if required.

Following stabilization, participants continued maintenance treatment for a maximum of 3 months. Medication was administered once-daily 7 days a week, initially

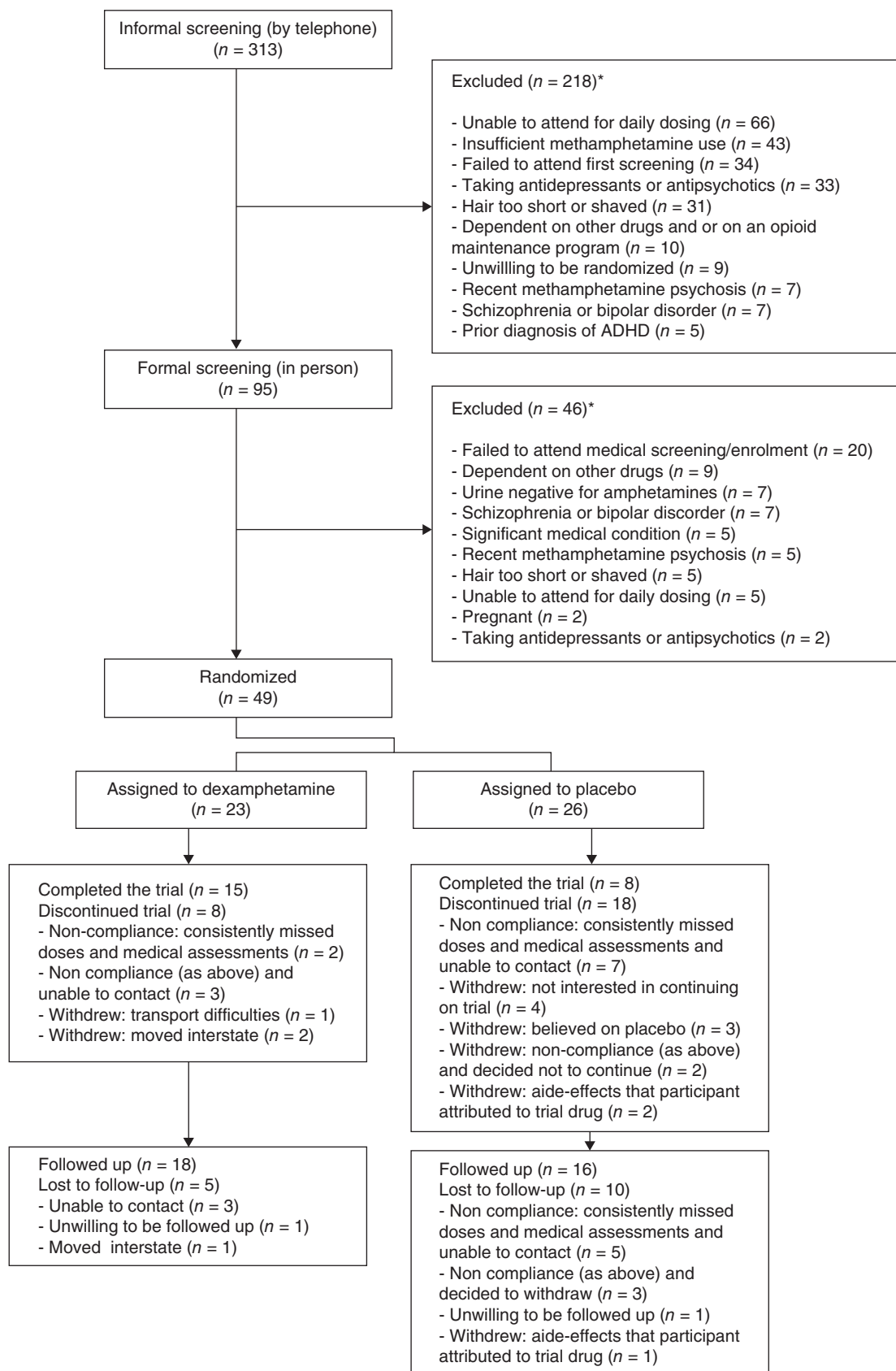


Figure 1 Participant flow in a randomized, placebo-controlled trial of dexamphetamine for the treatment of methamphetamine dependence. ADHD: attention deficit hyperactivity disorder

at clinic pharmacies, with participants dosed at community pharmacies within 4–6 weeks of commencing treatment. No take-away doses were given, and dosing was supervised throughout the trial to minimize the risk of diversion. Participants were monitored throughout treatment, with assessments by research staff each month and medical reviews by a senior medical officer at least fortnightly. Standard psychotherapeutic care was provided, consisting of an introductory appointment followed by a four-session cognitive behavioural model developed for amphetamine users [23]. At the end of the maintenance period, participants were tapered off the medication over 1 month in order to minimize any withdrawal symptoms experienced. Participants were followed-up 2 months after completing treatment. A questionnaire used to evaluate participant blinding showed that, in the dexamphetamine group, 71% identified correctly that they had received dexamphetamine, with 55% of the placebo group identifying correctly that they had received placebo.

Measures

Three primary outcomes were measured in this study: methamphetamine use and degree of dependence over time, and treatment retention. Methamphetamine use was recorded using both self-report and hair analysis. Hair samples were taken at three time-points (baseline, the end of maintenance and follow-up) and analysed using liquid chromatography-mass spectrometry (LC/MS). Self-reported methamphetamine use was measured by asking participants to record the number of days methamphetamine was used on a week-by-week basis in the 30 days prior to the interview, as well as the amount used on each occasion. A measure of total use was then calculated by multiplying the number of days used by the amount used on each day. Other outcome measures included the AWQ [24] and the Leeds Dependence Questionnaire (LDQ) [25]. Side effects and adverse reactions were recorded using standardized medical assessments, which also included monitoring of participants' pulse, blood pressure, weight and psychotic symptoms.

Data analysis

Differences between conditions were analysed using linear mixed effect models with SAS version 9.1 (SAS Institute Inc., Cary, NC, USA), except those involving hair analyses for which data were right-skewed, and consequently did not satisfy the assumptions of a mixed model. These data were dichotomized (positive/negative) and analysed using a logistic generalized estimating equation (GEE) regression model. Separate models for each self-report outcome variable were tested with drug condition, time and the interaction between drug and time fitted as

main effects and a random effect to account for the correlation in the data due to the repeated measurements on each participant. Age and gender were included as covariates in the model. Mixed effects models were employed to use all of the collected information and produce unbiased results for missing data. Available data for each participant were used to adjust the estimates for missing values. To compare time to dropout between the two groups, the Kaplan–Meier or product-limit estimate of the survivor function was calculated for each group, with failure defined as the event of a participant dropping out of the study. Descriptive data were analysed using SPSS for Windows (version 16.0). Medication safety was evaluated by systematic monitoring of adverse reactions and side effects. This was an intention-to-treat analysis, as all participants were included in the analysis in the groups to which they were assigned originally, irrespective of whether they completed treatment. Attempts were made to follow-up all participants who dropped out at two predetermined time-points: the end of maintenance and 2 months post-treatment (see Fig. 1 for more information). Power analysis was not conducted prior to the study, as insufficient published or pilot data were available to support sample size determination.

RESULTS

Participant characteristics

The majority of participants (61%) were male, with a mean age of 31.9 years (± 5.1 years). Participants started using methamphetamine at a mean age of 20.4 years (± 5.7 years). Just over half the participants in the sample (51%) were unemployed, 27% had tertiary or trade qualifications and 47% had received previous treatment for methamphetamine dependence. Most (86%) were intravenous users and reported an average use at baseline of 5 days per week. There were no significant differences between groups on these measures (see Table 1).

Treatment retention

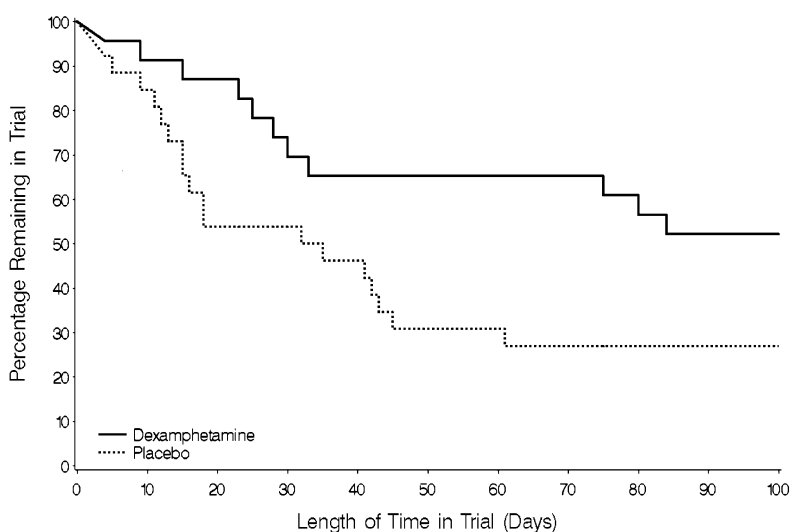
The maximum possible length of time in treatment was 104 days: 14 days of stabilization and 90 days of maintenance. There was a statistically significant difference between groups in the amount of time spent in treatment ($P = 0.014$), with those given dexamphetamine retained for an average of 86.3 days (± 52.2 days) compared with only 48.6 days (± 45.4 days) for the placebo group.

Time to dropout was also compared between groups (Fig. 2). The survival curves illustrate that participants in the dexamphetamine group were less likely to drop out of the study than those in the placebo group. The difference was statistically significant, according to a log-rank test ($P = 0.040$).

Table 1 Baseline socio-demographic characteristics according to treatment group.

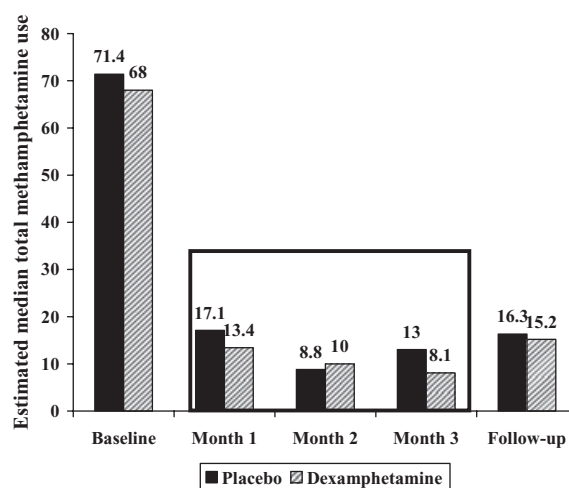
	Dexamphetamine (<i>n</i> = 23)	Placebo (<i>n</i> = 26)	(<i>P</i>) ^b
% Male	65	58	0.806
Mean age (years) ^a	31.9 (4.5; 25–41)	31.9 (5.6; 20–41)	0.989
Mean age first use (years) ^a	20.9 (6.7; 13–36)	19.9 (4.8; 12–30)	0.566
% Tertiary or trade qualifications	30	23	0.796
% Currently unemployed	48	54	0.893
% Had previous treatment for methamphetamine dependence	39	54	0.457
% Injectors	78	92	0.321

^aStandard deviation and range in brackets. ^bIndependent samples *t*-test for equality of means (two-tailed) between groups at baseline; χ^2 test for differences between the two proportions (two-tailed) at baseline.

**Figure 2** Kaplan–Mfeier estimate of the survivor function for retention in treatment

Self-reported methamphetamine use

Participants were asked at each research assessment on how many days they had used methamphetamine in the previous month, and the amount used on each day. Figure 3 compares total methamphetamine use for each group over time, with the treatment phase (3 months of maintenance) highlighted within the rectangle. It can be seen that the biggest reduction in use occurred during the first month, with further reductions during months 2 and 3. Overall, both groups demonstrated statistically significant reductions in use over time ($P < 0.0001$), and *post-hoc* tests revealed that the total amount of methamphetamine used was significantly higher at baseline than at all subsequent time-periods, including follow-up ($P < 0.0001$). However, there were no significant differences between groups. Comparisons were also made between groups in total methamphetamine use during the treatment period only. Again, there were statistically significant reductions in use within each group ($P = 0.046$). Although there was a trend towards a greater reduction

**Figure 3** Estimated median total self-reported methamphetamine use in the previous month based on log-transformed data. Rectangle indicates treatment period

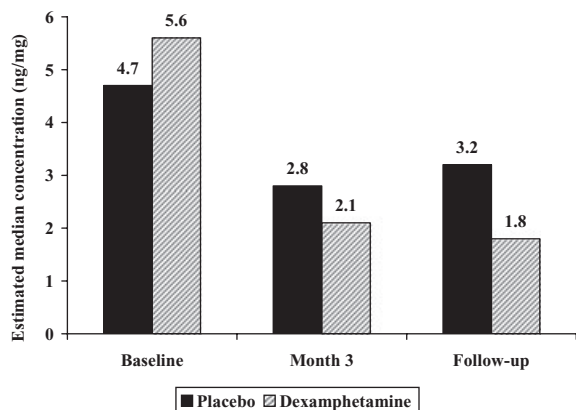


Figure 4 Estimated median concentration of methamphetamine in hair in the previous month based on log-transformed data

in the dexamphetamine group, the results only approached statistical significance ($P = 0.086$).

Objective measure of methamphetamine use

Figure 4 shows the concentrations of methamphetamine in hair samples for each group from baseline to follow-up. Although the median concentration of methamphetamine was higher for the dexamphetamine group at baseline, it was not significantly different from that of the placebo group. Within each group, there was a decrease in concentration between baseline and follow-up that was statistically significant ($P < 0.0001$). Although there was a greater decline in the dexamphetamine group, differences between groups did not reach statistical significance.

Dependence

The degree of dependence on methamphetamine was measured throughout the study period using the LDQ, with higher scores associated with greater levels of dependence. Although there are no normative data on this instrument, participants in both groups reported an average baseline score of 20 from a possible 30, reflecting high levels of dependence. There were statistically significant differences within each group over time ($P < 0.0001$), indicating reductions in the degree of methamphetamine dependence throughout the course of the study (Fig. 5). Moreover, a *post-hoc* test performed at follow-up revealed a significantly lower level of dependence in the dexamphetamine group, with mean scores of 11.5 compared with 15.5 ($P = 0.042$).

Withdrawal symptom severity

Figure 6 shows self-report data on the severity of symptoms experienced from baseline to the end of the treatment period, measured using the AWQ. Possible scores

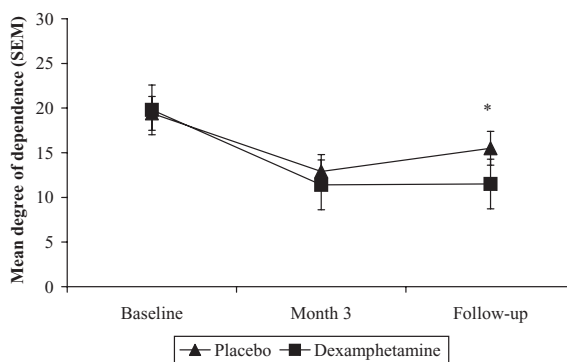


Figure 5 Mean degree of methamphetamine dependence over time. *Denotes a statistically significant difference between dexamphetamine and placebo groups. SEM: standard error of the mean

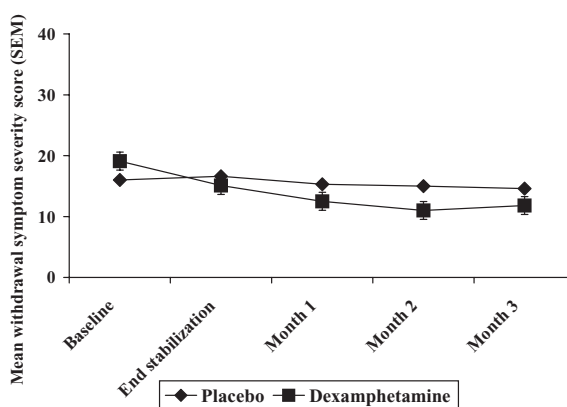


Figure 6 Mean methamphetamine withdrawal symptom severity over time. SEM: standard error of the mean

range from 0 to 40, with higher scores indicating greater severity. During the initial 14-day stabilization phase, it was expected that participants would experience withdrawal as a result of reduction or cessation of methamphetamine use, but that this would be attenuated among those who received dexamphetamine. This was supported by the finding that participants in the dexamphetamine group showed a greater reduction in withdrawal symptom severity during stabilization, a difference which was statistically significant ($P = 0.050$).

For the treatment period as a whole, there was a significant difference in scores over time within each group ($P = 0.009$), and the group \times time interaction showed a trend suggesting greater improvement in withdrawal symptom severity in the dexamphetamine group over the course of treatment ($P = 0.089$).

Psychotherapy

All participants were offered a four-session programme of cognitive-behavioural therapy. The proportions of participants attending at least one session were 61% in

the dexamphetamine group and 54% in the placebo group. Of those who attended at least one session, the mean number of sessions attended was 3.4 ± 3.4 for the dexamphetamine group and 3.4 ± 3.2 for the placebo group. This difference was not statistically significant.

Adverse reactions

Of the seven adverse events that were recorded during the study, only one (hypertension requiring dose reduction from 70 to 60 mg/day) occurred in the dexamphetamine group. Mean systolic blood pressure in the dexamphetamine group decreased consistently from a baseline of 130 mm/Hg to 122 mm/Hg at the end of maintenance. Mean diastolic blood pressure remained steady, ranging from 81 to 85 mm/Hg over the four assessment periods. Baseline mean pulse rate was 86, and this varied from 83 to 87 during maintenance. Mean body mass index (BMI) remained stable in the placebo group (24–25) and decreased from 23 to 21 in the dexamphetamine group.

There were no reports of psychotic symptoms. There were some side effects associated with dexamphetamine use, such as irritability, mood swings and headaches, but these were mild and none required discontinuation of treatment.

DISCUSSION

The primary objectives of this study were to engage users in treatment and reduce methamphetamine use and dependence. Participants in both groups demonstrated significant reductions in self-reported and objective measures of methamphetamine use, degree of dependence and severity of withdrawal symptoms. Importantly, outcomes favouring the dexamphetamine group were found on two of the three primary outcome measures investigated in this study, namely significantly better retention in treatment and a lower degree of methamphetamine dependence, compared with the placebo group at follow-up. On the third primary outcome measure, while there were trends to greater reductions in both self-reported and objective measures of methamphetamine use in the dexamphetamine group, these did not reach statistical significance.

These results indicate that maintenance treatment with sustained-release dexamphetamine can engage and maintain methamphetamine users in treatment. Retrospective studies have reported that the availability of dexamphetamine prescription both increased the number of users presenting to services [9,11] and the duration of contact with the service [11,26]. However, given the *ad hoc* nature of such programmes, as well as the absence of control groups, it is difficult to evaluate accurately the effects of prescription on treatment retention. The

present study is the first placebo-controlled trial with methamphetamine users to show significant differences in treatment retention between dexamphetamine and placebo groups [16–18]. Although one study found a trend to improved retention among cocaine users prescribed dexamphetamine, this was not sustained following more detailed analyses [16].

Study attrition was high, particularly among those in the placebo group. Overall, 39% of participants completed the 12-week maintenance programme. Studies examining predictors of treatment response and treatment outcomes among methamphetamine users have identified that intravenous use is associated significantly with poor treatment outcomes when compared with other routes of administration [27,28]. Intravenous users in these studies had lower rates of treatment engagement and retention, and a higher proportion continued to use methamphetamine during the study period. They were also found to exhibit more severe physical and psychiatric sequelae associated with drug use [27], making them a challenging group to treat. These findings are consistent with the present study, in which the majority ($n = 42$; 86%) of participants were intravenous users.

Reductions in self-reported methamphetamine use were marked during the first 2 months of the study, and were maintained beyond the end of the treatment phase, with use at follow-up significantly lower than baseline levels. This is consistent with retrospective studies reporting that the benefits of dexamphetamine prescription occurred early in treatment [10,13]. The two randomized controlled trials examining amphetamine users reported reductions in illicit use among the dexamphetamine group [14] and improvements in physical health [15], but differences were not significant, and these were open-label trials that were not placebo-controlled. In the present study differences between groups in self-reported methamphetamine use favoured the dexamphetamine group, but results only approached statistical significance. However, the failure to identify differences between groups must be evaluated in the context of the treatment as a whole. Dexamphetamine prescription was one component of a comprehensive programme that included psychotherapy, medical and research appointments, as well as daily monitoring by pharmacy staff. Participants reported that the framework of ongoing assistance and support helped them greatly in reducing their methamphetamine use. It is not surprising, therefore, that there was a considerable reduction in use among the placebo group. It is notable that 43% of the sample did not attend any psychotherapy sessions. This suggests that counselling alone may not be sufficient to engage a high proportion of intravenous users in treatment.

The use of hair analysis as an objective biomarker of methamphetamine use rather than urine sampling, as in

previous studies, was designed to enable an evaluation of maintenance treatment as it would be implemented in a community treatment setting. Urine sampling would have required regular visits to the clinic, and this would have altered the nature of the treatment. Hair analysis allowed us to evaluate the feasibility of implementing the programme using community pharmacies for the daily dispensing of medication to participants. In addition, analysis of the hair samples by LC/MS gives the concentration of the drug accumulated.

The present study differs from the majority of past research in its use of a sustained-release formulation of dexamphetamine. With the exception of two studies [16–17], all others prescribed immediate-release dexamphetamine tablets. The sustained-release formulation has a slower onset of action, the effects persist throughout the afternoon and evening and it has been shown to last 3–6 hours longer than the immediate-release tablet [29]. It also has a lower average maximal dexamphetamine concentration in plasma, and the time to reach this concentration is delayed compared with the immediate-release tablet: 8 hours compared with 3 [30]. These characteristics make it particularly suited to supervised once-daily maintenance treatment, as the slower onset of action and longer half-life serve to diminish the reinforcing effects of the drug [31]. While these very properties may potentially decrease treatment retention compared with the immediate-release tablets due to attenuation of the peak effects experienced by participants, use of the sustained-release formulation is less likely to be associated with dependence.

The doses of sustained-release dexamphetamine used in the present study were also much higher than in past studies, with an average dose of 80 mg/day (maximum 110 mg/day) at the end of stabilization, compared with fixed doses of 30 and 60 mg per day in divided doses [16,17]. Moreover, in contrast to all retrospective studies and two of the randomized controlled trials, dosing was supervised and no take-away doses were allowed, thus providing accurate information on dosing as well as minimizing the potential for diversion.

The number of subjects in each group was a limitation of the present study. In part this was due to the restrictive inclusion and exclusion criteria required for ethical conduct of an experimental treatment of this nature. However, the present results justify further study of the effectiveness of amphetamine maintenance in a larger, multi-site trial.

CONCLUSIONS

This preliminary study evaluated the efficacy and safety of once-daily sustained-release dexamphetamine administered under supervision using a double-blind, placebo-

controlled design. Participants in the dexamphetamine group remained in treatment significantly longer and had a significantly lower degree of methamphetamine dependence at follow-up. A significant difference in methamphetamine use between groups was not demonstrated. This trial has shown the feasibility of implementing a supervised maintenance pharmacotherapy programme for methamphetamine users that is acceptable to both clients and clinicians. The results of this study support further investigation of maintenance pharmacotherapy as an intervention for methamphetamine dependence.

Declarations of interest

None.

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