A double-blind, placebo-controlled trial of modafinil (200 mg/day) for methamphetamine dependence

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ABSTRACT

Aim To examine the safety and efficacy of modafinil (200 mg/day) compared to placebo in the treatment of methamphetamine dependence and to examine predictors of post-treatment outcome. Participants and design Eighty methamphetamine-dependent subjects in Sydney, Australia were allocated randomly to modafinil (200 mg/day) (n = 38) or placebo (n = 42) under double-blind conditions for 10 weeks with a further 12 weeks post-treatment follow-up. Measures Comprehensive drug use data (urine specimens and self-report) and other health and psychosocial data were collected weekly during treatment and research interviews at baseline, week 10 and week 22. Results Treatment retention and medication adherence were equivalent between groups. There were no differences in methamphetamine abstinence, craving or severity of dependence. Medication-compliant subjects tended to provide more methamphetamine-negative urine samples over the 10-week treatment period (P = 0.07). Outcomes were better for methamphetamine-dependent subjects with no other substance dependence and those who accessed counselling. There were statistically significant reductions in systolic blood pressure (P = 0.03) and weight gain (P = 0.05) in modafinil-compliant subjects compared to placebo. There were no medication-related serious adverse events. Adverse events were generally mild and consistent with known pharmacological effects. Conclusions Modafinil demonstrated promise in reducing methamphetamine use in selected methamphetamine-dependent patients. The study findings support definitive trials of modafinil in larger multi-site trials.

Keywords Abuse liability, counselling, methamphetamine dependence, modafinil, randomised controlled trial, safety, treatment.

INTRODUCTION

Methamphetamine dependence is a major public health issue in many parts of the world [1–3] associated with a wide range of psychological, medical and social problems [4]. Long-term use of high-dose methamphetamine dysregulates monoamine-based neurotransmission, which is hypothesized to form a neurobiological basis of methamphetamine dependence and withdrawal [5–8]. Dysregulation of reward-related glutamate pathways, as observed in cocaine use, represents a further potential neurobiological substrate for methamphetamine dependence [7,9,10]. Despite increasing knowledge of the neurobiological consequences of methamphetamine use, no medications to date have been any more successful than placebo in reducing methamphetamine use in dependent patients [11,12].

Modafinil is a novel non-amphetamine-type stimulant approved in Australia for the treatment of narcolepsy, shift workers syndrome and sleep apnoea-related fatigue. Modafinil acts specifically to promote wakefulness and vigilance, although its precise pharmacological mechanism of action is yet to be delineated [13–16]. The dopamine- and glutamate-enhancing actions of modafinil have been postulated as beneficial in reducing withdrawal severity attributable to psychostimulant-induced neuroadaptation [17,18]. The stimulant properties of modafinil may also attenuate the disturbed sleep
Modafinil for methamphetamine dependence

Modafinil is a well-tolerated drug with a low overdose risk and few side effects [19]. Modafinil does not appear to be behaviourally reinforcing, as use does not produce euphoria and there is no discontinuation effect [20,21]. The effects of modafinil cannot be intensified through high-dose intravenous or intrapulmonary use due to insolubility in water and instability at high temperatures [22]. The safety of modafinil in cocaine users has been investigated in double-blind placebo-controlled interaction studies. Combined cocaine and modafinil (0 mg, 400 mg, 800 mg daily) produced no haemodynamic interactions and significantly reduced subjective drug effect ratings for cocaine [23,24].

Cocaine-dependent patients who received modafinil (400 mg) as a single morning dose provided significantly more cocaine-negative urine samples compared to placebos during an 8-week trial [25]. There were, however, no significant differences on self-reported outcomes, including frequency of cocaine use, spending on cocaine or the severity of cocaine withdrawal and craving. No serious adverse events or overdose of modafinil were reported. The safety and tolerability of modafinil (400 mg/day) during a 10-day in-patient methamphetamine withdrawal programme was examined in an open-label comparison with mirtazapine (60 mg/day) and pericyazine (2.5–10 mg/day) [21]. Modafinil and mirtazapine were found to be safe and well tolerated, with no discernable reinforcing effects. Both were more effective than pericyazine in reducing withdrawal symptoms, with modafinil achieving less severe withdrawal symptoms and less sleep disturbance than mirtazapine. Randomized controlled placebo trials of modafinil in methamphetamine users were recommended.

The aim of the present study was to examine the safety and efficacy of modafinil (200 mg/day) in reducing methamphetamine use and associated harms through a randomized, double-blind, placebo-controlled 10-week trial of modafinil (200 mg/day) in 80 methamphetamine-dependent subjects. Relapse and predictors of methamphetamine use other than group (baseline characteristics, severity of dependence, treatment exposure) were also examined 12 weeks post-treatment.

**METHODS**

**Subjects**

Eighty methamphetamine-dependent subjects were recruited through a primary health care centre (n = 72) and a specialist drug and alcohol service (n = 8) located in the inner city area of Sydney. Subjects met Diagnostic and Statistical Manual (DSM-IV) criteria for methamphetamine dependence operationalized using the Composite International Diagnostic Interview [26] and were current, regular (2–3 days of use per week or more) methamphetamine users confirmed by a methamphetamine-positive urine spot test at baseline interview. Individuals who had an active, serious and uncontrolled medical or psychiatric illness were excluded; however, those with comorbid drug dependence or mental illness were enrolled after consultation with their usual medical attendants. Women of child-bearing age were excluded if they were pregnant, nursing infants or unwilling to avoid pregnancy through abstinence or barrier contraception. The latter requirement was necessary, as modafinil induces metabolism of steroidal contraceptives. Thirty-seven methamphetamine users who presented for treatment were excluded due to incomplete enrolment (n = 10), eligibility (mainly infrequent use/long-term abstinence n = 13) or were eligible but declined either randomization or medication (n = 14). Seven sets of partners were recruited into the trial and randomized together (modafinil n = 4, placebo n = 3); however, data were included from only the presenting index case, as their partners would not constitute independent observations. Subjects provided written informed consent to participate in the trial approved by three institutional human research ethics committees, including that of the University of New South Wales. Subjects were reimbursed $10 for each research interview and urine specimen provided during the trial.

**Design**

Eighty eligible methamphetamine-dependent subjects seeking treatment were randomized equally to receive either modafinil (200 mg/day) (n = 38) or placebo (n = 42) under equivalent conditions for a period of 10 weeks. The sample size of 40 per group was calculated based on an estimated between-group difference of 40% in the proportion of stimulant-positive urine samples at week 10, with missing samples deemed positive and allowing a 25% attrition rate (α = 0.05, 1-β = 0.9). A fixed-dose regimen was selected because modafinil has dose-independent pharmacokinetics between 200 and 600 mg/day [19], and early research in cocaine users found no difference in cocaine suppression or reductions in subjective effects between 200-mg and 400-mg doses. Randomization was conducted independently through Sydney Hospital Pharmacy. Trial medication was dispensed on a weekly basis through Sydney Hospital Pharmacy using medication event monitoring system (MEMS) cap bottles to record unsupervised regimen adherence. All subjects were offered a brief four-session cognitive behavioural intervention developed specifically for methamphetamine users [27]. Data were collected on all drug-
related counselling received by subjects whether within or outside the trial during the 10-week treatment phase. Subjects attended weekly medical reviews for side effects, adverse events, craving, vital observations, renewal of weekly scripts and to provide study urine samples. Subjects were re-interviewed 12 weeks after they completed treatment about their post-treatment progress and drug use. There were no between-group differences in study follow-up at week 10 (modafinil 84%; placebo 88%) and week 22 (modafinil 68%; placebo 62%) (see Fig. 1).

**Measures**

The Opiate Treatment Index (OTI) [28,29] was used to measure self-reported methamphetamine use, other drug use and other treatment outcomes. A ‘cost of habit’ section was added to capture changes in average expenditure on methamphetamine. Additional self-reported methamphetamine use was collected using 28-day drug use diaries. Prospective drug use diaries are acknowledged as an accurate and valid method of collecting drug use data [30]. Psychopathology was assessed using the Brief Symptom Inventory (BSI) [31]. A positive BSI case was defined as a score above the 90th percentile for US non-patient norms on the Global Severity Index or in two or more of the psychiatric domains. Changes in the severity of dependence were measured using the Severity of Dependence Scale (SDS) [32]. Subjects rated their strongest methamphetamine craving in the past week on a 100-mm visual analogue scale (VAS) from ‘none’ to ‘strongest ever’. Urine specimens were collected weekly, while subjects remained in treatment and also at research follow-up interviews. Urine was collected in jars with heat-sensitive strips to confirm that the samples were at body temperature and not substituted or otherwise contaminated. The specimens were analysed by immunoassay for amphetamine and cocaine metabolites using a cut-off of 300 μg/l. High-performance thin-layer chromatography and mass spectrometry were used for unequivocal confirmation of methamphetamine [33] indicative of recent use (within the past 48–72 hours). In order to monitor further adherence with modafinil, all urine samples were tested for the presence of modafinilic acid (urinary metabolite of modafinil) using mass spectrometry.

**Data analysis**

Data were analysed using SPSS for Windows (version 15.0) and SAS (version 9.1) PROC GENMOD. An
intention-to-treat approach was followed. Data were collected at research interviews conducted at baseline, week 10 and week 22, regardless of treatment status. Data for subjects lost to study follow-up were imputed from baseline using a worst-case scenario assumption of no change from baseline. Baseline scores and group variables were entered through the analysis of covariance (ANCOVA) approach as predictors in the relevant analyses [34]. All statistical tests were two-tailed using a 0.05 significance level and 95% confidence (CI) intervals; t-tests were used for normally distributed or transformed continuous variables, the χ² statistic for categorical variables and the Mann–Whitney U-statistic for skewed data. Survival analysis based on the log-rank (Mantel–Cox) statistic was used to examine between-group differences in retention. Outcome predictors other than group (comorbidity, other drug dependence, counselling uptake) were examined by linear regression. Categorical and continuous repeated measures, including vital signs, craving and urine drug screens collected at weekly intervals while subjects remained in treatment, were examined using generalized estimating equations [35,36]. After examination of the within-subject correlation structures, an autoregressive working matrix (which assumes that pairs of measures are correlated more highly than measures that are further apart) was adopted. Missing samples and observations due to varied scheduling, lost, de-identified or testing failures were deemed missing completely at random and results were imputed on a last observation carried forward basis. Missing data due to treatment dropout were not imputed in order not to obscure medication effects, whether positive or negative [37].

### RESULTS

#### Baseline characteristics

The typical subject was male, aged mid-30s, and well educated (Table 1). Most subjects injected methamphetamine on a daily basis, with a third who preferred to smoke crystalline methamphetamine. There tended to be more human immunodeficiency virus (HIV)-positive cases in the modafinil group (all in gay men) and more subjects in the placebo group were employed at baseline.

#### Retention

Eleven modafinil-group subjects (29%) and 15 placebo-group subjects (36%) completed the 10-week course of treatment. There was no difference in retention over the 10-week medication phase [log-rank (Mantel–Cox) χ² = 0.69, P = 0.41] (Fig. 2). Subjects were asked their reasons for ceasing medication. Similar proportions between groups reported medication dropout due to no perceived effect/benefit (modafinil 33%, nine of 27; placebo 30%, eight of 27), unacceptable side effects (modafinil 11%, three of 27; placebo 7%, two of 27) or moving, entering drug rehabilitation or jail (modafinil 11%, three of 27; placebo 33%, seven of 27). Modafinil subjects tended to report ceasing medication early due to achieving abstinence (22%, six of 27) compared to placebo (7%, two of 27) (χ² = 2.7, P = 0.1).

#### Adherence

Subjects who received modafinil remained on medication for a mean of 40 days (±26 days) and were medication-adherent on a mean of 31 days (±21 days) as confirmed.
by MEMS caps and pharmacy records. This represented 78% adherence to daily medication, almost identical to placebo adherence of 77% (mean 34 ± 21 days adherent divided by mean 44 ± 21 days retained). Thus, on an intention-to-treat basis, adherence was 44% in the modafinil group and 49% in the placebo group. The majority of unsupervised doses were taken before 3 p.m. in both groups (modafinil 79%; placebo 84%). Modafinil (as modafinilic acid) was detected in the urine of all modafinil-treated subjects and was not found in any of the placebo group during the medication phase. Medication overuse was measured through the dispensing of 9 days of drug supply for each 7-day period in MEMS containers and tablet returns for both groups. There was no difference in the proportion of subjects who over-used their takeaway medication [modafinil 47%; placebo 51% (P = 0.81)] or in the average number of additional tablets consumed [modafinil 13 ± 10, range 2–32; placebo 22 ± 22, range 2–74 (P = 0.5)]. There was no difference between either the mean total number of internal counselling sessions attended [modafinil 0.6 ± 1.6; placebo 0.5 ± 0.9 (P = 0.7)], external counselling sessions attended [modafinil 1.1 ± 2.4; placebo 1.4 ± 3.3 (P = 0.6)] or the proportions who did not attend any counselling [modafinil 53%; placebo 47% (P = 0.6)].

Stimulant use

Urinalysis results

The chart in Fig. 3 illustrates the proportion of urine samples positive for illicit psychostimulants [cocaine, methamphetamine or 3,4-methylenedioxymethamphetamine (MDMA)] over the 10-week medication period. There was a trend (P < 0.1) in the group × time effect among compliant patients to reduce the proportion of stimulant-positive urine samples over the study period compared to placebo (χ² = 17.10, P = 0.07). When opioid-dependent subjects were excluded post hoc there was no difference (χ² = 14.60, P = 0.15) in the reduced sample (modafinil n = 33; placebo n = 37). There were also no between-group differences in the proportion of negative urine samples collected at the 10-week follow-up (modafinil 26%, 10 of 38; placebo 29%, 12 of 42) or 22-week follow-up (modafinil 18%, seven of 38; placebo 17%, seven of 42) when missing samples were deemed positive.

Self-reported stimulant use

Self-reported illicit psychostimulant use declined in both groups over the study period, with the modafinil group consistently reporting lower rates of stimulant use across
most measures and follow-up points (Table 2). Modafinil subjects provided more stimulant negative weekly urine samples in the 4 weeks matching the 28-day self-report at week 10 (modafinil 1.4 ± 1.4; placebo 0.7 ± 0.9, P = 0.16). When analyses were adjusted post hoc for HIV-positive subjects who were over-represented in the modafinil group, week 10 estimates improved in the direction of treatment [B = 3.59 (95% CI: −0.45, 7.64), P = 0.08] but did not alter appreciably at week 22. When the analysis was limited post hoc to single diagnosis, methamphetamine-dependent subjects with no other drug dependence (i.e. opioid maintenance patients excluded) self-reported days of stimulant use at week 10 were 8.3 ± 8.2 (modafinil) and 13.5 ± 10.2 (placebo) [B = 4.22 (95% CI: 0.08, 8.35), P < 0.05] and at week 22 were 11.6 ± 9.2 (modafinil) and 16.4 ± 10.4 (placebo) [B = 3.82 (95% CI: −0.60, 8.25), P = 0.09].

Study power
A sample size of 58 per group was calculated retrospectively as necessary to detect reliably the observed between-group difference of 20% using a repeated-measures design without imputation for missing data (α = 0.05, 1−β = 0.9, T = 10, p = 0.5) [38]. Alternatively, a sample size of 136 per group would be necessary to detect the between-group difference in frequency of stimulant use at week 10 with missing data imputed from baseline (α = 0.05, 1−β = 0.8, Δ = 3.15/9.2 = 0.34). The effect size estimate (Δ) was calculated using the adjusted between group difference in 28-day stimulant use at week 10 divided by the pooled standard deviation (see Table 2). The difference in sample size estimates reflects the greater statistical power of repeated-measures designs.

Tolerability
There were no medication-related serious adverse events during the study. The most commonly reported adverse events are reported in Table 3. Insomnia was the most common complaint, which did not differ between groups. Headache was the second most common complaint, and did not differ between groups except when severity was taken into account. The modafinil group reported more transient mild/moderate headache consistent with product information. Mood problems were unique to the modafinil group, although all cases were due to an exacerbation of pre-existing symptoms. One subject ceased modafinil due to panic attacks and elevated anxiety, while another managed anxiety symptoms through dose reduction to 100 mg/day. There was a statistically significant reduction in systolic blood pressure over time in the modafinil group compared to placebo (Δ= 19.55, P = 0.03). Differences in weight gain/loss between the groups were due mainly to acute weight loss (>4 kg) observed in four subjects in the placebo group.

Other self-report outcomes
There were no apparent between group differences on a range of secondary outcomes. There was no difference in weekly craving during the medication phase (F = 1.839, P = 0.19) or the SDS score at either treatment follow-up (modafinil 7.3 ± 3.4; placebo 7.3 ± 3.4) or post-treatment follow-up (modafinil 8.1 ± 3.4; placebo 7.7 ± 4.3). Both groups experienced a substantial regression to the mean in terms of the overall proportion of BSI cases (modafinil 95% at baseline to 66% at week 22; placebo 90% at baseline to 60% at week 22). Sixty per cent of modafinil subjects guessed correctly when asked at week 22 if they had received active medication compared to 55% of placebo subjects (χ² = 0.271, P = 0.6).

Predictors of post-treatment outcome other than group
The relationship between potential predictors of post-treatment outcome (other than group) and self-reported

### Table 2 Self-reported stimulant use.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Period</th>
<th>Modafinil (n = 38)</th>
<th>Placebo (n = 42)</th>
<th>Coefficient B (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 28-day drug use</td>
<td>Baseline</td>
<td>18.4 ± 6.8</td>
<td>20.5 ± 6.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week 10*</td>
<td>8.8 ± 8.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week 22*</td>
<td>11.8 ± 9.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change score from baseline</td>
<td>Week 10</td>
<td>−9.6 ± 8.4</td>
<td>−7.3 ± 9.4</td>
<td>U = 650, 0.15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week 22</td>
<td>−6.7 ± 8.8</td>
<td>−4.5 ± 9.9</td>
<td>U = 699, 0.20</td>
<td></td>
</tr>
<tr>
<td>Mean quantity used (OTI)</td>
<td>Baseline</td>
<td>2.3 ± 2.0</td>
<td>2.7 ± 2.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week 10*</td>
<td>0.6 ± 1.0</td>
<td>1.5 ± 2.2</td>
<td>0.78 (0.03, 1.53)</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Week 22*</td>
<td>1.2 ± 1.3</td>
<td>1.8 ± 2.0</td>
<td>0.54 (−0.19, 1.27)</td>
<td>0.20</td>
</tr>
<tr>
<td>Mean spending ($/day)</td>
<td>Baseline</td>
<td>$95 ± 79</td>
<td>$107 ± 90</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week 10*</td>
<td>$41 ± 70</td>
<td>$64 ± 86</td>
<td>17.5 (−17.52)</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>Week 22*</td>
<td>$57 ± 82</td>
<td>$75 ± 95</td>
<td>13 (−12.39)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

CI = confidence interval; OTI = Opiate Treatment Index. *Baseline score included in analysis of covariance; analysis performed after log-transformation.
28-day stimulant use were examined by linear regression (Table 4). The most pronounced effect was from attending counselling. Each session of counselling attended during the 10-week treatment period reduced 28-day stimulant self-report by 1 day (95% CI: -1.7, -0.3) at post-treatment follow-up. Simply attending any form of counselling reduced 28-day self-report by 6 days (95% CI: -10.8, -1.8). HIV-positive subjects who were over-represented in the modafinil group had poorer methamphetamine use outcomes. BSI cases also had poorer methamphetamine use outcomes; however, there were very few non-cases and these were divided equally between the groups [modafinil two subjects (5%); placebo four subjects (10%)]. Opioid maintenance therapy (methadone or buprenorphine) had no significant direct effect on outcome and the small number of opioid maintenance patients were distributed equally between the groups (five in each group). Overall, however, the lack of difference at week 22 between opioid-dependent patients in the modafinil and placebo groups appeared to mask greater between-group effect size for single-diagnosis methamphetamine users (see Self-reported stimulant use). Other baseline and treatment characteristics did not appear to influence post-treatment outcome.

**DISCUSSION**

In this treatment population modafinil showed promise in reducing methamphetamine use in selected methamphetamine-dependent patients. However, there were no differences between modafinil and placebo in retention, methamphetamine abstinence, methamphetamine craving or severity of dependence. Subjects who remained on medication tended to provide more illicit psychostimulant negative urine samples than those who received placebo over the 10-week treatment period. This was consistent with greater declines in the modafinil group in self-reported 28-day stimulant use and the quantity of stimulants used. The between-group differences in favour of modafinil achieved at week 10 persisted at week 22, consistent with a group-related treatment effect. Emergent treatment effects may have been masked by over-representation of HIV-positive subjects in the modafinil group, who had poorer methamphetamine use outcomes.

### Table 3

<table>
<thead>
<tr>
<th>Event</th>
<th>Severity/frequency</th>
<th>Modafinil</th>
<th>Placebo</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>All reports</td>
<td>12/38 (32%)</td>
<td>17/42 (40%)</td>
<td>(\chi^2 = 0.683, P = 0.41)</td>
</tr>
<tr>
<td>Headache</td>
<td>Mild/moderate</td>
<td>7/38 (18%)</td>
<td>2/42 (5%)</td>
<td>(\chi^2 = 3.728, P &lt; 0.05)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>2/38 (5%)</td>
<td>4/42 (10%)</td>
<td>(\chi^2 = 0.522, P = 0.47)</td>
</tr>
<tr>
<td>Nausea</td>
<td>Mild/moderate</td>
<td>2/38 (5%)</td>
<td>5/42 (12%)</td>
<td>(\chi^2 = 1.102, P = 0.29)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>3/38 (11%)</td>
<td>1/42 (2%)</td>
<td>(\chi^2 = 1.277, P = 0.26)</td>
</tr>
<tr>
<td>Gastric pain/discomfort</td>
<td>All reports</td>
<td>5/38 (13%)</td>
<td>3/42 (7%)</td>
<td>(\chi^2 = 0.802, P = 0.37)</td>
</tr>
</tbody>
</table>
| Thought disorder           | All reports        | 2/38 (5%) | –        | Nc
| Anxiety                    | Severe             | 3/38 (8%) | –        | Nc
| Fatigue                    | All reports        | –        | 4/42 (10%)| Nc
| High blood pressure*       | Baseline           | 9/38 (24%)| 10/42 (24%)| \(\chi^2 = 0.234, P = 0.63\) |
| High blood pressure*       | Final observation   | 5/34 (15%)| 5/39 (13%)| \(\chi^2 = 0.054, P = 0.82\) |
| Weight loss                | Between baseline and 10 weeks | 2/11 (18%)| 8/15 (53%)| \(\chi^2 = 3.331, P = 0.07\) |
| Weight change (mean kg)    | Between baseline and 10 weeks | 2.7 ± 2.8| 0.2 ± 3.4 | \(U = 66, P < 0.05\) |

* \(\chi^2 = \) Chi-squared; \(P\) = Probability.

### Table 4

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rationale</th>
<th>Coefficient B (95% CI)</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of counselling sessions</td>
<td>Treatment exposure</td>
<td>-0.99 (-1.73, -0.26)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Any counselling</td>
<td>Treatment exposure</td>
<td>-6.30 (-10.81, -1.79)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HIV-positive</td>
<td>Baseline difference between groups</td>
<td>3.81 (-1.34, 8.95)</td>
<td>0.14</td>
</tr>
<tr>
<td>BSI case</td>
<td>A priori test for comorbidity</td>
<td>6.17 (-2.29, 14.63)</td>
<td>0.15</td>
</tr>
<tr>
<td>Treatment completers</td>
<td>Treatment exposure</td>
<td>-2.45 (-7.24, 2.34)</td>
<td>0.31</td>
</tr>
<tr>
<td>Opioid maintenance patients</td>
<td>A priori test for dual dependence</td>
<td>-1.1 (-7.9, 5.7)</td>
<td>0.75</td>
</tr>
<tr>
<td>SDS</td>
<td>A priori severity of dependence</td>
<td>0.04 (-0.68, 0.76)</td>
<td>0.91</td>
</tr>
</tbody>
</table>

BSI = Brief Symptom Inventory; HIV = human immunodeficiency virus; SDS = Severity of Dependence Scale.
pharmacological outcomes, and the enrolment of subjects in concurrent opioid maintenance treatment. Methamphetamine-dependent subjects with no other substance dependence who received modafinil reported the greatest reductions in methamphetamine use compared to placebo.

Modafinil appeared to be safe and well tolerated. There were no medication-related serious adverse events. The modafinil group reported more transient mild/moderate headaches and also tended to report more nausea/gastric discomfort, all of which resolved after the first week of treatment. Reports of thought disorder and anxiety were unique to the modafinil group and indicate caution in patients with pre-existing psychotic symptoms or anxiety. Modafinil did not appear to be associated with any elevation of blood pressure or heart rate. The clinical significance of a reduction in systolic blood pressure over the 10-week treatment period in medication-adherent subjects receiving modafinil should not be underestimated given the cardiotoxicity of methamphetamine [4]. There was no evidence of excessive use of modafinil, consistent with previous reports of low abuse liability [20]. Significant weight gain in the modafinil group could be interpreted as a positive treatment outcome, as modafinil usually decreases food intake [39]. The measurement of body mass index (BMI) should be considered in future studies. Finally, reports of fatigue were unique to the placebo group and were consistent with the wake-promoting properties of modafinil.

More than one-third of subjects who received modafinil experienced no discernable effects on sleep or attention. The expectation of a rapid, strong stimulating effect may have contributed to disappointment and early treatment dropout for those who believed they were receiving placebo. Another potential factor has been identified in sleep studies, where some patients with previous amphetamine treatment or illicit methamphetamine histories appeared to be less sensitive to the stimulating effects of modafinil [40–42]. Motivational enhancement therapy may improve adherence and treatment retention in future studies, particularly in those where the effect of modafinil was weak or diminishing. The relatively low dose used in this study may not have been optimal. Higher doses in the usual range (up to 200 mg b.i.d.) could improve adherence and treatment retention.

Attendance at any form of counselling although self-selected, was significantly predictive of better post-treatment outcome. Although uptake of the specific cognitive–behavioural treatment (CBT) programme offered to subjects was minimal, many had pre-existing counselling arrangements and study participants accessed a diverse array of counselling services during the course of the trial. The psychosocial platforms on which medications targeted toward psychostimulant use are delivered are critical to their success, and these may vary according to the needs of target populations [43]. Potential strategies to improve the uptake of counselling could include contingent incentives to attend counselling, such as travel reimbursement. Narrative therapy has also shown recent promise in methamphetamine users [44].

There was no group difference in methamphetamine craving. These data suggest that modafinil may not achieve its effects as an anti-craving agent. This finding was consistent with the findings of Dackis and colleagues, who found no reduction in craving in cocaine users measured using a similar visual analogue scale [25]. Lack of effect on craving may simply be evidence for lack of effect on methamphetamine use; however, the analyses that found downward trends in weekly methamphetamine-negative urine samples and self-reported frequency of methamphetamine were not matched by any changes in self-reported craving. It may be more likely that modafinil works as a drug effect agonist and improves cognitive functioning, rather than as an anti-craving agent. Emerging research is drawing attention to the importance of cognitive impairment, impulsivity and stress as critical features of problematic psychostimulant use [45,46]. Chronic psychostimulant use reduces activity in areas of the brain associated with cognitive functioning, regions where modafinil appears to achieve its wake and vigilance-promoting effects. Through restoring cognitive functioning, modafinil may help patients to deal with the life stressors, cravings, cues and compulsive/obsessive drug-seeking behaviour which are common features of relapse among psychostimulant users.

The main limitations affecting interpretation of the results of this study were the absence of an objective quantitative measure, reliance on self-reported outcomes and a sample size which was too small to detect reliably the small differences between modafinil and placebo. Between-group differences based on self-report were not supported by urinalysis of specimens collected at the week 10 and week 22 research follow-up interviews. While prospective self-report is considered valid and reliable in drug and alcohol research, there may be a risk of differential reporting between groups. The substantial placebo effect of 45% and the high proportion of modafinil subjects with no discernable medication effect of 40%, however, mitigated against potential systematic bias in self-report in favour of modafinil. The weekly urine drug screens captured changes in drug use over the 10-week treatment period time, albeit in compliant subjects. Increased dose and motivational enhancement therapy informed by the experience of this trial could improve medication adherence and avoid the treatment disappointment that may have contributed to selective treatment attrition. Alternative biological measures more
sensitive or appropriate to longer-term quantitative changes could be considered, such as hair analysis. Given the predominance of behavioural and psychosocial factors in methamphetamine dependence, it may be unrealistic to expect medication alone to achieve large treatment effect sizes.

Modafinil appeared to be safe, non-reinforcing and moderately beneficial in reducing methamphetamine use in this treatment population. These findings need to be confirmed by larger multi-centre trials. Benefits were selective for medication-adherent patients who engaged in any form of psychosocial therapy or support. Future studies could benefit from the experience in this trial by encouraging completion of the full course of medication and engagement in psychosocial therapies. Future trials could also examine the value of longer maintenance regimens or titration to the higher standard dose of 200 mg b.i.d.

Clinical trial registration
NCT00123370 Clinicaltrials.gov

Declarations of interest
None.

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References


