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Evaluation of modafinil effects on cardiovascular, subjective, and reinforcing effects of methamphetamine in methamphetamine-dependent volunteers

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Abstract

Methamphetamine is a highly addictive stimulant and long-term exposure leads to reductions in dopamine. One therapeutic strategy is to develop and test compounds that normalize dopamine. The primary aim of this study was to determine the safety of modafinil treatment during methamphetamine exposure in a controlled clinical setting. Methamphetamine-dependent volunteers (N=13), who were not seeking treatment, were randomized to receive either modafinil (200 mg, PO) or matching placebo over three days (Days 1-3 or Days 8-10). On Day 1, subjects were randomized to modafinil or placebo in the morning, and then 3 and 6 h later received infusions of methamphetamine (0 and 30 mg, IV), after which cardiovascular and subjective effects were assessed. On Day 3, participants completed IV self-administration sessions during which they made 10 choices for low doses of methamphetamine (3 mg, IV) or saline. Days 4-7 were used as a washout period. On Day 8 participants were assigned to the alternate study medication (placebo or modafinil), and the same testing procedures were repeated through Day 10. The data reveal that modafinil treatment was well-tolerated and not associated with increased incidence of adverse events. In general, modafinil reduced by ~25% ratings of methamphetamine-induced "Any Drug Effect", "High", and "Want Methamphetamine", and reduced total number of choices for methamphetamine and monetary value of methamphetamine, though none of these measures reached statistical significance. Given these encouraging, though non-significant trends, the primary conclusion is that it appears safe to proceed with modafinil in further clinical evaluations of therapeutic efficacy.

Keywords

Modafinil; Methamphetamine; Addiction; Dependence

1.0 Introduction

Methamphetamine is a highly addictive stimulant and acute exposure causes dopamine (DA) release and stimulates midbrain reward centers. Chronic exposure to methamphetamine results in neuroadaptations in presynaptic DA neurons, including changes in the function of the plasmalemmal DA transporter (DAT) and the vesicular monoamine transporter-2 (Chu et al., 2008; Fleckenstein et al., 2009; Volz et al., 2007a,b). In humans, long-term methamphetamine exposure leads to DA reductions (Volkow et al., 2001), which may contribute to drug craving, anhedonia, and other withdrawal symptoms common during methamphetamine abstinence (McGregor et al., 2005; Newton et al., 2004).

One therapeutic strategy is to develop and test compounds that normalize (increase) DA to determine if treatment with these drugs reduces methamphetamine use. A compound of interest is modafinil, and while a precise mechanism of action has not been fully elucidated, modafinil appears to activate orexin-containing neurons with cell bodies in the lateral hypothalamus (Chemelli et al., 1999). Human subjects with narcolepsy are deficient in orexin and activation of these neurons may account for the drug's efficacy in this condition. In addition, modafinil is a relatively weak inhibitor of the DAT with a relatively slow onset of action. Modafinil inhibits the DAT with low affinity between 3.2-6.4 μM (Madras et al., 2006; Mignot et al., 1994), and during chronic treatment the steady-state plasma concentration approaches the affinity for the DAT, indicating that modafinil produces substantial DAT inhibition (Madras et al., 2006). Using rhesus monkeys (*Macaca mulatta*), after treatment with a dose of 2 mg/kg body weight, modafinil occupied $6\pm 2\%$ of striatal DAT sites; after treatment with 5 mg/kg, modafinil occupied $35\pm 11.9\%$ of striatal DAT sites; and after treatment with 8 mg/kg, modafinil occupied $54\pm 3\%$ of DAT sites. Consistent with these findings, modafinil significantly reduced methamphetamine-induced increases in extracellular DA in striatum and significantly reduced methamphetamine-induced hyperactivity in rats (Zolkowska et al., 2009).

There is some debate as to whether modafinil is (Stoops et al., 2005; Gold and Balster, 1996; Vansickel et al., 2008) or is not rewarding or reinforcing (Dackis et al., 2003; Jasinski, 2000; Deroche-Gamonet et al., 2002), though modafinil does not produce cocaine-like subjective effects (Rush et al., 2002). Modafinil inhibits the DAT with a relatively slow onset of action, which probably accounts for its relatively low abuse liability, compared to typical stimulants such as cocaine or methylphenidate.

Modafinil appears to have efficacy as a treatment for stimulant dependence. Modafinil reduced the euphoric effects produced by intravenous cocaine (Dackis et al., 2003), reduced smoked cocaine self-administration and associated subjective effects (Hart et al., 2008), and reduced cocaine use in a double-blind, placebo-controlled clinical trial (Dackis et al., 2005). There has been one case report of successful treatment of amphetamine dependence with modafinil (Camacho and Stein, 2002), and a preliminary study showed that modafinil reduced methamphetamine withdrawal symptoms (McGregor et al., 2005). Most recent, in an outpatient clinical trial conducted in Australia, participants randomized to modafinil (200 mg/day for 10 weeks) provided more methamphetamine-negative urines ($p<0.07$) as compared to those treated with placebo (Shearer et al., 2009).

Taken together, the findings noted above indicate that modafinil may be a promising treatment for methamphetamine dependence. On this basis, we conducted a double-blind, placebo-controlled, within-subjects study to determine the cardiovascular, subjective, and reinforcing effects of methamphetamine in volunteers treated with modafinil and placebo. The primary aim of this study was to determine the safety of modafinil treatment during methamphetamine exposure in a controlled clinical setting.

2.0 Research Design and Methods

2.1 Subjects

A total of 12 subjects completed the entire study. A 13th participant completed one part of the study (modafinil portion), and his data were included in the final analyses, so outcomes are presented as N=12 or N=13.

Participants were recruited using advertisements and paid \$700 in cash for the inpatient stay and an additional \$50 in gift certificates if they completed the entire study. Subjects did not receive the entire payment at once, but received 50% when they were discharged and 50% when they returned for a 2-week follow-up. All participants met DSM-IV-TR criteria for methamphetamine-dependence (as determined using the MINI neuropsychiatric interview) and did not meet criteria for dependence on other drugs, other than nicotine or marijuana. Additional inclusion criteria included being between 18-45 years of age, having a history of using methamphetamine by the smoked or IV route of administration, and being otherwise healthy, as confirmed by a physical examination and safety laboratories. Exclusion criteria included having a history of seizure disorder or head trauma, having a history of prior adverse event associated with methamphetamine abuse (e.g., loss of consciousness), or the presence of any axis I psychiatric disorder other than those noted above. Current serious medical conditions, such as symptomatic HIV disease, heart disease, or neurologic disease, were also exclusionary.

2.2 Study Design

This double-blind, placebo-controlled, within-subjects study was conducted in the UCLA General Clinical Research Center (GCRC). The institutional review board at UCLA approved the study. All participants give informed consent after having the potential risks fully explained to them.

On the day following admission, blood for hematology studies was collected in anticoagulant-containing Vacutainer tubes for analysis of complete blood count, chemistry, liver function tests, renal function tests, and Hepatitis B and C. In females, a urine-based pregnancy test measured human chorionic gonadotropin.

The study schema is provided in Table 1. On Day 1, subjects were randomized to modafinil or placebo in the morning then 3 and 6 h later received infusions of methamphetamine (0 and 30 mg, IV), and cardiovascular and subjective effects were assessed. On Day 3, participants completed IV self-administration sessions during which they made 10 choices for low doses of methamphetamine (3 mg, IV) or saline or a money alternative. Days 4-7 were used as a washout period and on Day 8 participants were assigned to the alternate study medication (placebo or modafinil) and the same testing procedures were repeated through Day 10. Subjects remained in the GCRC for the duration of the study (i.e., all 10 days).

A physician was present during all methamphetamine infusion sessions and carefully monitored participant's heart rate (HR), blood pressure (BP), and ECG wave form. Stopping rules were in place to halt dosing if cardiovascular indices exceeded preset values. These included 1) systolic BP > 185 mm Hg, 2) diastolic BP > 100 mm Hg, 3) heart rate > 130 bpm, 4) behavioral manifestation of methamphetamine toxicity (e.g., agitation, psychosis, inability to comply with study procedures), and/or 5) an uncorrected QT of 470 msec or a rate-corrected QTc of 500 msec on ECG reading.

2.3 Cardiovascular and Subjective Measures

Cardiovascular data (automated heart rate (HR) and blood pressure (BP)) were collected 15 min before, and at several time points (5, 10, 15, 20, 30, 45, 60, 90, and 120 min) following the methamphetamine (0 and 30 mg, IV) infusions.

Subjective effects data were collected at the same time points using visual analog scales (VAS). For VAS scales, subjects reported the degree to which they feel 'Any Drug Effect', 'High', 'Good effects', 'Bad effects', 'Like methamphetamine', 'Want methamphetamine', 'Desire methamphetamine', 'Crave methamphetamine', 'Depressed', 'Anxious', 'Stimulated', and 'Likely to Use' on a continuous scale digitized between 0 and 100 and reported as change from baseline (described below).

Participants also completed the Monetary Value questionnaire 15 min after each infusion. The two questions include 'How much would you pay (in dollars) for what was just administered to you?', and 'How much do you normally pay (in dollars) for a gram of methamphetamine on the street?'

The Addiction Research Center Inventory (ARCI) short form (Martin et al., 1971) was administered 15 min prior to and 60 min following each injection of methamphetamine or saline. The ARCI consists of 49 statements in a true/false format. Scores were calculated for the morphine-benzedrine group (MBG; a measure of euphoria; generally used to assess abuse liability), the pentobarbital, chlorpromazine, alcohol group (PCAG; a measure of sedation), the lysergic acid diethylamide group (LSD; a measure of dysphoria), and stimulant-sensitive scales, including the benzedrine group (BG) and amphetamine (A) scales.

All scales used have been shown to be sensitive to the effects of methamphetamine in previous studies, and timing of all assessments was based on our previously published reports (De La Garza et al., 2008a,b; Newton et al., 2005a, 2006, 2008).

2.4 Sample Sessions and IV Self-Administration

During the sample sessions, on Days 1 and 8, participants received methamphetamine 0 mg (saline) and 30 mg under double-blind conditions at either 11:30 a.m. or 2:30 p.m. A 120 min time period between infusions was selected on the basis of our previous data, which indicates that peak subjective and cardiovascular responses have passed by this time (Newton et al., 2005b). Concerns about potential "carryover effects" from one infusion period to another were also mitigated by using a subtraction from baseline to determine actual effects (see Data Analysis). Participants were made aware that the 30 mg dose reflected the maximum effects the participants could anticipate feeling if they selected all 10 infusions during choice sessions to be held on Days 3 and 10.

Sample infusions were coded as either "red" or "green". Participants were instructed to write down any positive or negative subjective effects produced by the infusion, and encouraged to reference these notes prior to and during subsequent choice sessions. Participants and investigators were blinded as to the coding of methamphetamine or saline as the red or green infusion. This coding was counterbalanced among participants, but kept constant throughout the duration of the study for each individual.

Choice sessions were held twice per day on Days 3 and 10. On these days, one session was held at 11:30 a.m. and involved choices for methamphetamine or saline, and the other session was held at 2:30 p.m. and involved choices for the alternate condition (saline or methamphetamine). On Days 3 and 10, participants made a series of choices between money options of increasing value or 1/10 of the red or green infusion from the day before (i.e. 3 mg methamphetamine or saline). The ten monetary options included \$0.05, \$0.05, \$0.05, \$0.05,

\$1, \$4, \$7, \$10, \$14, and \$16 (presented in that ascending sequence). The dollar choices made available (\$0.05 - \$16) were selected on the basis of our prior work (De La Garza et al., 2008a) and others (Walsh, 2000). All choices were separated by 15 min. The research assistant did not approach the participant every 15 min, rather the participant was told at the beginning of the experiment that they would have to make a choice on a computer tablet every 15 min. If the participant chose money, the cash was immediately placed into an envelope within the participants view. If the participant chose an infusion, he/she actuated the patient-controlled analgesia (PCA) pump him/herself. The PCA pump had a 13 min lockout following a 2 min infusion, thus preventing repeated dosing prior to the completion of the 13 min lockout.

Self-administration sessions were held on Days 3 and 10. On these days, methamphetamine infusions (0 or 3 mg, IV) were administered over 2 min using a PCA pump activated by the participant. One button push, equivalent to a fixed ratio 1 schedule, was sufficient to activate the pump. The 3 mg dosage for methamphetamine was selected as a safe increment that could be self-administered repeatedly, and has been used with success by our laboratory (De La Garza et al., 2008a). Given this information, the dosages and timing of drug administration were deemed appropriate for this study.

For safety purposes, participants were monitored for 4 additional hours after the last infusion on each of the infusion days (1, 3, 8 and 10).

2.5 Drugs

A NIDA contractor provided sterile methamphetamine solution for human use and a saline solution of equal volume and appearance was used as the control. Modafinil was obtained from Cephalon, and re-packaged by the UCLA Research Pharmacy to de-identify the tablets. An IND was obtained from the FDA for the use of modafinil and methamphetamine in this study.

The dose of modafinil (200 mg) was selected on the basis of several published reports showing efficacy for blocking cocaine's effects (Hart et al., 2007) and for enhancing cognition (Turner et al., 2003, 2004a,b), and is a dose that has been shown to be well-tolerated in several distinct patient populations. Peak plasma concentrations of modafinil are obtained 2–3 h after oral administration with an elimination half-life of 10–12 h (Wong et al., 1998). The half-life of methamphetamine is ~11–12 h. On Days 1 and 8, methamphetamine (0 and 30 mg, IV) was administered over 2-min using an infusion pump activated by a physician. A single bolus of 30 mg methamphetamine was used in the sample session since it has been associated with significant increases in positive subjective effects as well as increases in blood pressure and heart rate (Newton et al., 2005a,b, 2006, 2008; De La Garza et al., 2008b), though these changes are not accompanied by adverse events greater than observed after saline administration. The participants were made aware that the 30 mg dose reflected the maximum effects the participants could anticipate feeling if they selected all 10 infusions during choice sessions to be held on Days 3 and 10.

Self-administration sessions were held on Days 3 and 10. On these days, methamphetamine infusions (0 or 3 mg, IV) were administered over 2-min using a PCA pump activated by the participant.

2.6 Data Analyses

Data were analyzed using StatView 5.0 (SAS Institute Inc., Cary, NC, USA). Descriptive statistics were compiled for demographic variables and analyzed using appropriate parametric or non-parametric tests. For all measures, statistical significance was set at $p < 0.05$. All data are presented as mean $\pm$ standard error.

Sample size was calculated on the basis of the work of Hart and colleagues (2007). Given those findings, a sample of 10 would allow detection of medium to large effects (approximately $d = .70$) when comparing groups, with power = .80 and one-tailed $\alpha = .05$. Use of one-tailed tests of significance is appropriate for pilot studies in which the major goal is to determine if there is a signal indicating therapeutic efficacy. On the basis of this information, the sample of $N=12-13$ reported here appears adequate to detect significant effects.

2.7 Across-study measures

The total number of adverse events (AEs) was summed from Days 1-3 and Days 8-10 separately and analyzed using an ANOVA as a function of modafinil dose (0 or 200 mg). Other aspects of AE data reporting (type, severity and duration) were not analyzed since the overall number of AEs was low and not different between treatment conditions.

For across-study measures, all data except time were analyzed as between-subjects factors. Time (in days) was analyzed as a within-subjects factor.

2.8 Post-randomization measures

Heart rate, systolic blood pressure, diastolic blood pressure, and VAS data were analyzed using repeated measures ANOVA as a function of modafinil dose (0 or 200mg) and Time (in min). Time-courses reflect within-session change from baseline (value at a given time-point minus the value at $T=-15$ min). These data were also analyzed with respect to peak effects (occurring at any time point) using a one-way ANOVA as a function of modafinil dose (0 or 200 mg).

For total infusions self-administered, a one-way ANOVA was used to assess differences as a function of modafinil dose (0 and 200 mg) and methamphetamine dose (0 and 3 mg). This analytic approach was based upon one described previously (Walsh et al., 2001), and as previously published by our research group (De La Garza et al., 2008a).

For post-randomization measures, all data except Time were analyzed as between-subjects factors. Time (in min) was analyzed as a within-subjects factor.

3.0 Results

3.1 Demographics and Drug Use

Detailed demographic information and drug-use data are provided in Table 2. The majority of participants were male and Caucasian, who smoked cigarettes regularly and also used alcohol and marijuana on occasion.

3.2 Adverse events

There were no serious adverse events recorded during this trial. The total number of adverse events (most commonly insomnia and headache) was similar during treatment with placebo (1.5 ± 0.45) and modafinil (1.9 ± 0.51) ($F_{1,23}=0.38$, $p=0.5446$), and none were judged to be drug-related.

3.3 Cardiovascular Effects

Acute methamphetamine exposure increased heart rate and blood pressure, and there was a general trend for modafinil to attenuate methamphetamine-induced increases in systolic BP and heart rate (Figure 1), though these did not reach statistical significance. A summary of p values for time course and peak effects outcomes are presented in Table 3. A summary of actual peak values recorded for heart rate and blood pressure is provided in Table 4.

3.4 Subjective Effects

Acute methamphetamine exposure increased several positive subjective effects and there was a general trend for modafinil to attenuate methamphetamine-induced increases in these responses (Figure 2), though these did not reach statistical significance. Time course analyses were also performed on all other positive and negative subjective effects recorded by the VAS instrument (*data not shown*). The visually evident trends in these graphs are representative of the overall outcomes for other positive subjective effects. In general, methamphetamine did not alter negative subjective effects and modafinil did not alter these responses. A summary of *p* values for time course and peak effects for “Any Drug Effect”, “High”, and “Want Meth” outcomes are presented in Table 5. Acute methamphetamine exposure increased ratings on ARCI subscales. A summary of *p* values for ARCI outcomes are presented in Table 5. A final self-report measure obtained after each methamphetamine infusion on Day 10 (0 and 30 mg) was Monetary Value, which was assessed 15 min after each infusion. The two questions include ‘How much would you pay (in dollars) for what was just administered to you?’ (Figure 2), and ‘How much do you normally pay (in dollars) for a gram of methamphetamine on the street?’ A summary of *p* values for Monetary Value outcomes are presented in Table 5.

3.5 Reinforcing Effects

Participants chose methamphetamine more often than saline, and there was a trend for modafinil treatment to attenuate this behavior (Figure 3), though this did not reach statistical significance.

4.0 Discussion

The primary aim of this study was to determine the safety of modafinil treatment during methamphetamine exposure in a controlled clinical setting. The number, type, severity and duration of all AEs were comparable during placebo and modafinil treatment, indicating that modafinil was safe and well-tolerated in these methamphetamine-addicted individuals.

In the current report, and as demonstrated previously (De La Garza et al., 2008b; Newton et al., 2005a,b, 2006, 2008), an acute methamphetamine infusion increased heart rate and blood pressure. There was a general trend for modafinil treatment to attenuate methamphetamine-induced increases in systolic BP and heart rate, though these did not reach statistical significance. There have been concerns voiced about potential “stimulant-like” effects of modafinil (Taneja et al., 2005), yet the cardiovascular data presented here reveal no concern for additive effects when methamphetamine is simultaneously administered. Indeed, we suspect that the inhibitory effects of modafinil on the DAT may slow the entry of methamphetamine into presynaptic neurons, damping the cardiovascular effects of monoamine releasers such as methamphetamine.

Also, in the current report, and as demonstrated previously (De La Garza et al., 2008b; Newton et al., 2005a,b, 2006, 2008), acute methamphetamine exposure increased self-reports of positive subjective effects, including Any Drug Effect, High, and Want Methamphetamine. In general, modafinil treatment was associated with ~25% reduction in positive subjective effects, though these did not reach statistical significance. In earlier research we found that bupropion reduced the positive subjective effects produced by methamphetamine (Newton et al., 2006) and also reduced methamphetamine use in an outpatient clinical trial (Elkashef et al., 2008). This observation suggests that treatment with modafinil, which was associated with modest reductions in the subjective effects produced by methamphetamine, might be similarly effective for the treatment of methamphetamine dependence.

In the current report, and as demonstrated previously (De La Garza et al., 2008b; Newton et al., 2008), acute methamphetamine exposure increased ratings on ARCI subscales. Modafinil treatment did not increase these effects, especially on the MBG and A scales, which are often used to assess potential abuse liability of compounds (Jasinski et al., 2000). As described above, while there have been concerns voiced about potential “stimulant-like” effects of modafinil, the ARCI (and VAS) data obtained in this report reveal no concern for additive effects when methamphetamine is simultaneously administered. Also of interest, the monetary value assigned to the methamphetamine infusion was predictably larger than that of saline, but was also noted to be reduced by approximately 25% when participants were being treated with modafinil. Finally, the reinforcing effects of methamphetamine were measured using a choice paradigm, with money being the alternative choice. As demonstrated previously (De La Garza et al., 2008a), participants made choices for methamphetamine significantly more often than for saline. In fact, the mean number of choices out of 10 (3.2) was identical to that we reported previously. As observed with subjective effects, choices for methamphetamine were reduced by approximately 25% when participants were being treated with modafinil versus placebo, though this did not reach statistical significance.

Limitations of the current study include a short treatment regimen, testing of single doses of modafinil (200 mg) and methamphetamine (30 mg), and the lack of females enrolled. Given the encouraging, though non-significant trends, the primary conclusion is that it appears safe to proceed with modafinil in further clinical evaluations of therapeutic efficacy. In fact, a recent outpatient clinical trial, showed that participants randomized to modafinil provided more methamphetamine-negative urines as compared to those treated with placebo (Shearer et al., 2009). In addition, in a single blind trial, modafinil was administered for 12 weeks, followed by a 4-week placebo phase, and cognitive behavioral therapy was conducted for 18 sessions over the 16-week study. These data reveal that six of the ten study completers reduced their methamphetamine use by >50% (McElhiney et al., 2009). Though the mechanism of action responsible for these effects is unknown, we suspect that the effects of modafinil on the DAT may contribute.

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Figure 1.

Change in heart rate (upper panel) and systolic blood pressure (lower panel) following infusions of methamphetamine (0 and 30 mg, i.v.) as a function of drug (modafinil; N=13 or placebo; N=13) and time (in min). Values represent change from baseline (given time-point minus $t = -15$ min). Data represent the mean $\pm$ S.E.M. from methamphetamine-dependent participants on Days 1 and 8 of the protocol.

Figure 2.

Change in “High” (upper panel) and “Want Methamphetamine” (middle panel) following infusions of methamphetamine (0 and 30 mg, i.v.) as a function of drug (modafinil; N=13 or placebo; N=13) and time (in min). Values represent change from baseline (given time-point minus $t=-15$ min). The lower panel represents monetary value following infusions of methamphetamine (0 and 30 mg, i.v.) as a function of drug (modafinil; N=13 or placebo; N=13). All data represent the mean $\pm$ S.E.M. from methamphetamine-dependent participants on Days 1 and 8 of the protocol.

Figure 3. Self-administration of methamphetamine (0 and 3 mg, i.v.) as a function of drug (modafinil; N=13 or placebo; N=12). Data represent the mean $\pm$ S.E.M. from methamphetamine-dependent participants on Days 3 and 10 of the protocol.

Table 1

Study Design

Study Day	Time	Activity
0		Admission to CRC
1*	7:00 AM 11:30 AM 2:30 PM	Randomization to Placebo <i>or</i> Modafinil (200 mg, PO) METH (30 mg) or Saline infusion administered IV Saline or METH (30 mg) infusion (<i>opposite of 11:30 AM</i>)
2	7:00 AM	Dosing Placebo or Modafinil 200mg
3^	7:00 AM 11:30AM 2:30 PM	Dosing Placebo or Modafinil 200 mg Choice Session 1 METH (3 mg) or Saline administered IV by PCA pump Choice Session 2 (<i>opposite of 11:30 AM</i>) METH (3 mg) or Saline administered IV by PCA pump
4-7		WASHOUT
8*	7:00 AM 11:30 AM 2:30 PM	Assignment to Placebo or Modafinil (200 mg, PO) (<i>opposite condition of Days 1-3</i>) METH (30 mg) or Saline infusion administered IV Saline or METH (30 mg) infusion (<i>opposite of 11:30 AM</i>)
9	7:00 AM	Dosing Placebo or Modafinil 200mg
10^	7:00 AM 11:30AM 2:30 PM	Dosing Placebo or Modafinil 200 mg Choice Session 1 METH (3 mg) or Saline administered IV by PCA pump Choice Session 2 (<i>opposite of 11:30 AM</i>) METH (3 mg) or Saline administered IV by PCA pump

* Sample sessions;

^ Self-administration sessions

Table 2

Demographics and Drug Use. Entries represent N's or means $\pm$ S.E.M. Last 30 days use indicates number of days of use of that drug in the 30 days preceding entry into this study.

	(N=13)
Gender (N)	
Male	10
Female	3
Ethnicity (N)	
Caucasian	7
Hispanic	5
African American	1
Age (years)	36.2 $\pm$ 3.3
Education (years)	12.1 $\pm$ 0.3
Methamphetamine Use	
Years of use	14.2 $\pm$ 2.5
*Last 30 days use	16.4 $\pm$ 2.3
Meth Route of Admin (N)	
Smoke	9
IV	3
Oral	1
Nicotine Use (N)	11/13
Years of use	17.0 $\pm$ 3.8
Last 30 days use	27.6 $\pm$ 2.4
Alcohol Use (N)	8/13
Years of use	17.4 $\pm$ 3.7
Last 30 days use	9.5 $\pm$ 3.3
Marijuana Use (N)	8/11
Years of use	10.6 $\pm$ 3.7
Last 30 days use	11.8 $\pm$ 3.9

Table 3

Summary of *p* values from cardiovascular measures. The measures include those for which significant main effects of modafinil (Mo), methamphetamine (Me), time (T) and significant interactions [Mo * Me (MoMe), Mo * T (MoT), Me * T (MeT), or Mo * Me * T (MoMeT)] as determined by repeated measures ANOVA. Peak effects were analyzed by one-way ANOVA. *P* values are given if they are less or equal to 0.10, and bolded if *p*<0.05. The main effect of Meth was an increase in each cardiovascular measure. For Mod, the main effect was to reduce Meth-induced systolic blood pressure and heart rate.

CV Measures	Time Course Analysis						
	Mo	Me	MoMe	T	MoT	MeT	MoMeT
Heart Rate	--	<0.0001	0.066	<0.0001	--	<0.0001	--
Systolic BP	--	<0.0001	0.047	<0.0001	--	<0.0001	--
Diastolic BP	--	0.0011	--	0.0574	--	0.0004	--
	Peak Effect Analysis						
	Mo	Me	MoMe				
Heart Rate	--	<0.0001	0.082				
Systolic BP	--	<0.0001	0.025				
Diastolic BP	--	<0.0001	--				

Table 4

Summary of peak actual values for cardiovascular measures. Entries represent group means $\pm$ S.E.M. Modafinil 0 is also known as placebo and methamphetamine 0 is also known as the saline infusion.

Modafinil; Methamphetamine Dose	Systolic BP (mmHg)	Diastolic BP (mmHg)	Heart Rate (bpm)
Modafinil 200; Methamphetamine 0	136.6 $\pm$ 4.2	79.3 $\pm$ 2.9	87.2 $\pm$ 4.7
Modafinil 200; Methamphetamine 30	151.4 $\pm$ 4.9	87.9 $\pm$ 2.4	102.1 $\pm$ 4.2
Modafinil 0; Methamphetamine 0	136.3 $\pm$ 4.1	78.8 $\pm$ 2.4	90.1 $\pm$ 2.9
Modafinil 0; Methamphetamine 30	157.6 $\pm$ 5.5	90.5 $\pm$ 1.9	110.6 $\pm$ 4.4

Table 5

Summary of *p* values from VAS, ARCI and Monetary Value. For VAS, the measures include those for which significant main effects of modafinil (Mo), methamphetamine (Me), time (T) and significant interactions [Mo * Me (MoMe), Mo * T (MoT), Me * T (MeT), or Mo * Me * T (MoMeT)] as determined by repeated measures ANOVA. VAS peak effects were analyzed by one-way ANOVA. ARCI and monetary value (Mon Val) data were analyzed by one-way ANOVA. *P* values are given if they are less or equal to 0.10, and bolded if *p*<0.05. The main effect of Meth was an increase in each VAS measure. For Mod, the main effect was to reduce Meth-induced subjective effects.

VAS	Time Course Analysis					
	Mo	Me	MoMe	T	MoT	MeT
Any Drug Effect	--	<0.0001	--	<0.0001	--	<0.0001
High	--	<0.0001	--	<0.0001	--	<0.0001
Want Meth	--	<0.0001	--	<0.0001	--	--
	Peak Effect Analysis					
	Mo	Me	MoMe			
Any Drug Effect	--	<0.0001	--			
High	--	0.0047	--			
Want Meth	--	<0.0001	--			
ARCI	Mo	Me	MoMe			
	Mo	Me	MoMe			
MBG	--	0.0005	--			
PCAG	--	0.0009	--			
LSD	--	0.0001	--			
BG	--	<0.0001	--			
A	--	0.0001	--			
Mon Val	Mo	Me	MoMe			
	Mo	Me	MoMe			
How Much Willing to Pay?	--	<0.0001	--			
How Much g Meth on Street?	--	--	--			