Protocol

Division of Pharmacotherapies and Medical Consequences of Drug Abuse

Double-Blind, Placebo-Controlled Assessment of Interactions Between Intravenous Methamphetamine and Modafinil

(Study No. 04-01)

Compound	Modafinil
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PROTOCOL SYNOPSIS

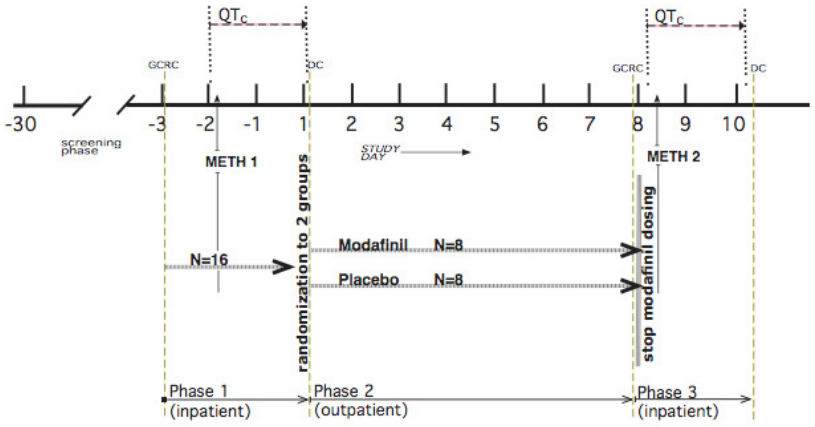
Background	Modafinil, possibly by its glutamate enhancing actions, may be a pharmacotherapy for methamphetamine abuse. Before initiating clinical trials, cardiovascular and psychopharmacological interactions between methamphetamine and modafinil need to be assessed.
Number of Subjects	16 healthy volunteers
Primary Aims	To determine interactions between 400 mg oral doses of modafinil and 30 mg of intravenously administered methamphetamine (MA) on cardiovascular function.
Secondary Aims	To determine pharmacokinetic and psychological interactions between modafinil and methamphetamine.
Primary Outcome Measures	Heart rate, blood pressure, QTc interval and stroke volume (by impedance cardiography).
Secondary Outcome Measures	Subjective effects measured with visual analog self-reports (VAS) and Brief Substance Craving Scale (BSCS) and the Profile of Mood States (POMS), MA pharmacokinetics.
Design	16 subject, randomized, parallel group, placebo controlled, single site study. After screening, subjects will be admitted to the UCSF General Clinical Research Center (GCRC) for MA dosing. **Phase 1** — Pre modafinil MA dose. Following an overnight fast, hospitalized subjects are given 15 mg d-MA IV over 1 minute. One hour later, a second 15 mg MA dose will be given for a total dose of 30 mg. Subjects remain on the GCRC for 48 hours after the MA challenge. Sequential dosing has several advantages: 1. Safety evaluation after the first 15 mg dose with potential dose holding if stopping rules are approached. 2. Assessment of CV and subjective tolerance to the dose. 3. Inclusion of a wider range of methamphetamine-experienced subjects. 4. Drug administration pattern similar to that used by abusers. 5. Less frequent abusers may not tolerate a single 30 mg dose; and can be eliminated before needlessly experiencing an adverse reaction to the first MA dose. After the first MA dose, subjects will be observed for 48 hours. At 48 hours after the MA, the first dose of modafinil (200 mg or placebo) will be given and the subject will be observed for 4 hours and then discharged. Subjects who tolerate the 200 mg dose adequately will be advanced to phase 2.

	Phase 2 – Supervised Outpatient Modafinil Dosing – Modafinil will be given each morning for 7 more days on the GCRC outpatient facility. The first 400 mg dose will be given 72 hours after MA challenge. Urine for toxicology screen and vital signs will be obtained daily before dosing. **Phase 3** – Modafinil-MA Challenge. After the 7th outpatient dose, subjects will be admitted to the GCRC. The next morning after getting their 8th and final daily modafinil dose, they will be dosed with the same sequence of two 15 mg MA injections used in Phase 1. 48 hours after MA dosing, they will be discharged on study day 10.
Inclusion Criteria	1. MA experienced but not dependent males or females aged 18 to 45 years. 2. Females should be either nonchildbearing (tubal ligation or total hysterectomy) or of childbearing potential using one or more of the following barrier methods of contraception: male or female condoms (with/without spermicide), diaphragm (with spermicide) and/or copper containing intrauterine device (with/without spermicide). No other contraceptives are acceptable; 3. Having a body mass index (BMI) between 18 and 30; 4. Willing and able to give written consent; 5. Not currently a subject still in the follow-up period of a preceding drug research study; 6. Having no medical contraindications determined by the following: an adequate medical history, a physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, and urinalysis; 7. Having a negative drug test for barbiturates, benzodiazepines, opiates, cocaine, amphetamines and ethanol at the time of admission (Day -3); 8. For females, having a negative pregnancy test at screening and prior to each study drug administration.
Exclusion Criteria	*Past medical history* 1. History of hematological, hepatic, respiratory, cardiovascular, renal or CNS disease or any other medical condition that is capable of altering the metabolism or elimination of drugs or of constituting a risk factor when taking the study drug; 2. Recent history of MA or other drug addiction and/or alcoholism; 3. Any medical condition that could relapse during or immediately after the study and, in the investigator's opinion, interferes with study evaluations or affects a subject's safety. *Current status* 4. Significant acute or chronic medical disease; 5. Likely to need concomitant treatment medication during the study perioc 6. Blood donation during the 30 days preceding study entry; 7. Tobacco smoker or nonsmoker for less than 3 months; i.e., no recent change in smoking status; 8. Alcohol consumption averaging > 40 g daily during the past 30 days; 9. Coffee (or tea) consumption > 6 cups (6 x 0.24 L) per day or xanthine containing drinks > 1 liter/day (e.g., cola drinks, etc.); 10. A subject without adequate means of contacting the investigator in

	case of emergency or not able to be contacted readily by the investigator; 11. Female who is pregnant, lactating, or plans to become pregnant during the study period and within one month after study drug administration; *Prior or current medication* 12. Exposure to any investigational new drug within 30 days of screening; 13. Use of any herbal products likely to induce or inhibit hepatic microsomal enzyme CYP 2D6 within one month of the start of the study including St. John's wort (Hypericum perforatum).
Study Medication	MA 15 mg IV injected over 1 minute followed 1 hour later by a second 15 mg IV MA dose. Modafinil 400 mg PO qAM (1st dose 200 mg then 400 mg daily for 8 days) Placebo for modafinil
Pharmacokinetic Measures	Methamphetamine PK pre and post modafinil. Plasma for methamphetamine at 0, 5, 15, 30, 60, 65, 75, 90 minutes and 2, 4, 6, 8, 12, 24, 36 and 48 hours after the first MA dose. Trough modafinil levels on days 4, 6, 7, 8, 9, and 10.
Safety Measures	Heart rate, blood pressure, respiratory rate will be recorded at approximately the same times as plasma samples.
Cardiovascular Measures	Heart rate, blood pressure and respiratory rate at pre dose and at 5, 15, and 30, 60, 65, 75, 90 minutes and 2, 3, 4, 6, 8, 12, 24 and 48 hours after MA. QT interval determined by digitized ECG pre dose and at 1, 2, 8, 24 and 48 hours after MA. 12 lead ECG pre-dose, 24 hours, and 48 hours. Stroke volume determined by impedance cardiography pre dose and at 5, 15, and 30, 60, 65, 75, 90 minutes and 2, 3, 4, 6, 8, 12, 24 and 48 hours after MA dosing.
Behavioral Measures	Visual Analog measures of mood and drug effects and tolerability pre dose and at 10, 15, 30, 60, 70, 75, 90 minutes and 2, 3, 4, 6, and 8 hours after dosing. VAS measures are: 1. Any Drug 2. Good Drug 3. Bad Drug 4. Nervous 5. Tolerable BSCS each morning at about 9 AM (before MA dose) while in hospital and at each visit during Phase 2 before getting Modafinil; POMS (30 item) pre and 4 hours after MA.
Withdrawal from the Study	**Safety Criteria**. Subjects will be closely monitored while on the GCRC before and after drug administration. Vital signs, cardiovascular measures, and adverse symptom reports will be used to determine the safety of modafinil and MA in combination and the appropriateness for administering the next dose. Vital signs must be within acceptable limits before modafinil, MA (or placebo) is administered. Criteria for holding dosing and considering terminating study participation are: 1. Supine heart rate >0.75 age predicted maximum (220-age x 0.75) or <40, systolic blood pressure >180 or <90, diastolic blood pressure

	>120 or <45, respiratory rate >24 or <8. 2. Significant arrhythmia defined as ≥6 beats nonsinus supraventricular tachycardia or ≥3 beats ventricular tachycardia. 3. ECG-QT interval >480 msec in females or >500 msec in males. 4. Reported significant nausea or abdominal pain. 5. Reported significant chest pain or dyspnea. 6. Subject confusion, agitation or inability to cooperate. 7. Any other adverse effect regarded as possibly due to drugs or the experimental procedures. If abnormal vital signs occur, subjects will be closely observed with vital sign measurements every 5 to 15 minutes until the abnormalities abate. If stopping criteria are exceeded, subjects will be closely observed and treated as necessary to assure return to their normal baseline state before being discharged from the GCRC. If more than two subjects show a similar pattern of excessive cardio-vascular or behavioral change or a pattern of change from baseline in biochemical indices after drug administration not readily explainable by other factors, the experiment will be halted and the dose plan reassessed before proceeding.
Statistical Analysis	Data will be analyzed by ANOVA

Figure 1 — Timeline



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List of Abbreviations

AE	Adverse event
ANOVA	Analysis of variance
BMI	Body mass index
BSCS	Brief Substance Craving Scale
CHR	Committee on Human Research (UCSF IRB)
CYP2D6	Cytochrome P450 2D6
CV	Cardiovascular
DBP	Diastolic blood pressure
ECG	electrocardiogram
FDA	Food and Drug Administration
GCRC	General Clinical Research Center
HR	Heart rate
ICG	Impedance cardiology
IRB	Institutional Review Board
LC-MS	Liquid chromatography/tandem mass spectrometry
LTP	Long-term potentiation
LV	Left ventricular
MA	Methamphetamine
NIDA	National Institute on Drug Abuse
PK	Pharmacokinetics
POMS	Profile of Mood Scale
PP	Pulse pressure
QTc	QT interval
SBP	Systolic blood pressure
SVR	Symptomatic vascular resistance
$T_{1/2}$	Terminal half-life
UCSF	University of California at San Francisco
VAS	Visual Analog Scale

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1. Specific Aims

The primary aims of this experiment are to determine if there are significant safety interactions between oral modafinil and intravenous methamphetamine. Safety will be assessed by measuring adverse events and cardiovascular responses of heart rate (HR), blood pressure (BP), and electrocardiogram (ECG) and stroke distance (ICG).

The secondary aims are to determine if:

1. Modafinil alters the pharmacokinetics (PK) of methamphetamine or its metabolites;
2. Modafinil treatment alters the subjective effects of or craving for methamphetamine.

Modafinil is in clinical trials as a pharmacotherapy for cocaine abuse and addiction. It may have efficacy for methamphetamine abuse and addiction. Before pharmacotherapeutic trials can start, to assure patient safety cardiovascular interactions between methamphetamine and modafinil need to be assessed. Even if modafinil is an effective pharmacotherapy for methamphetamine dependence, it is likely that addicts will take some illicit methamphetamine during modafinil therapy. Modafinil has some (albeit minimal) cardiovascular activity. If the effects of acutely administered modafinil and methamphetamine are similar, additive or even synergistic interactions and toxicity could occur. Therefore, it is prudent to assess pharmacologic interactions before exposing patients to modafinil in therapeutic trials.

In a parallel group clinical pharmacology laboratory experiment, we will assess the pharmacodynamic interactions (with a focus on cardiovascular effects) of two sequential 15-mg intravenous methamphetamine doses and 8 days of daily oral modafinil doses of 400 mg or placebo for modafinil.

The primary study aim is to assess safety. Safety of methamphetamine administration in modafinil treated subjects will be assessed by determining the nature of any adverse events (AE), measuring blood pressure, heart rate patterns of change, and by careful ECG monitoring. Secondary aims include characterization of methamphetamine pharmacokinetics with and without exposure to modafinil and self-reports of craving, subjective drug effects, and mood.

Cardiovascular interactions between methamphetamine and modafinil will be assessed using complementary indices:

a) Heart rate, systolic and diastolic blood pressure and pulse pressure (SBP, DBP and PP) to assess basic cardiovascular function;
b) Cardiac conductivity and myocyte repolarization assessed with electrocardiogram (ECG) and ECG heart rate corrected QT interval (QTc);
c) Stroke volume measured by impedance cardiography (IC). From the measured stoke volume and heart rate, we will estimate cardiac output and from stroke volume and blood pressure we will estimate systemic vascular resistance.

Subjective symptom, mood effects and craving will be measured using Visual Analog Scale (VAS) and Profile of Moods Scale self-reports and craving by Brief Substance Craving Scale (BSCS).

2. Hypothesis

Following daily doses of 400 mg of oral modafinil for 8 days, the pharmacological responses to 30 mg of intravenous methamphetamine will not significantly change. We predict that modafinil will not alter methamphetamine-induced changes in:

a) Heart rate and blood pressure response
b) Stroke volume
c) Cardiac conduction and repolarization
d) Cardiac output
e) Craving for methamphetamine
f) Subjective effects and mood

3. Background and Significance

A variety of pharmacological strategies are being pursued in the search for an effective treatment for methamphetamine addiction. One approach has been to target the dopaminergic neurotransmitter system involved in the reward mechanism to interrupt the reinforcing action of methamphetamine and thus reduce its use and prevent relapse (Hyman and Nestler 1996; Mendelson and Mello 1996; Ling and Shoptaw 1997). Methamphetamine is thought to produce its major effects through dopaminergic mechanisms in the midbrain. Methamphetamine causes dopamine release and blocks the reuptake of dopamine; the consequent excess of dopamine stimulates the midbrain reward centers. Both dopamine agonists and antagonists have been tested as pharmacotherapies for methamphetamine addiction with disappointing results.

Dopaminergic signaling is modulated by other neurotransmitters including glutamate. Glutamate transmission is required for the development of behavioral sensitization (Karler et al. 1989) and is associated with the neuroadaptive changes leading to addiction (Wolf 1998; Wolf and Xue 1998). Long-term potentiation (LTP) is a glutamate-dependent cell process associated with learning and memory. LTP probably mediates the processes of neuronal plasticity that are clinically expressed as addiction.

Integration of dopamine and glutamate-coded signals at the cellular and molecular level may be a fundamental event underlying long-term plasticity and reward-related learning in corticostriatal networks. Cells upon which dopaminergic and glutamatergic signals impinge (e.g., medium-sized spiny neurons within striatum, or pyramidal cells within cortex) are thought to act as coincidence detectors in associative learning processes (Sutton and Beninger 1999; Berke and Hyman 2000; Horvitz 2002; Kelley et al. 2003; Kelley 2004). Glutamate signaling is thought to encode relatively specific sensory, motor, and mnemonic information in cortico-cortical, corticostriatal, and thalamocortical systems, while dopamine neurons are thought to respond in a global sense to unpredicted, rewarding, or salient events in the environment (Horvitz 2000; Schultz 2002). The coordinated signaling of both of these systems seems to play an important role in shaping synaptic configurations and in altering the activity of neural ensembles with consequent alterations in behavior.

Modafinil may have efficacy in treating cocaine dependence (Dackis et al. 2004). Modafinil is a wake promoting agent thought to act by enhancing glutamate effects in multiple brain regions. The rationale for testing of glutamate-enhancing agents as pharmacotherapies for stimulant dependence is based on recent findings that cocaine dysregulates reward-related glutamate pathways (Thomas et al. 2001; Dackis and O'Brien 2003; Kalivas et al. 2003). Modafinil's glutamatergic actions (Ferraro et al. 1998; Ferraro et al. 1999) may contribute to its utility for treating cocaine dependence because repeated taking of cocaine depletes extracellular glutamate levels (Keys et al. 1998; Hotsenpiller et al. 2001;

Kalivas et al. 2003), and reduces glutamatergic synaptic strength in the nucleus accumbens (Thomas et al. 2001). Normalizing extracellular glutamate levels with N-acetylcysteine abolishes cocaine-induced reinstatement of drug self administration, an animal model of relapse (Baker et al. 2003).

Modafinil has possible advantages as a stimulant dependence pharmacotherapy when compared to other stimulant drugs. Its distinctive pharmacological mechanism of action results in a drug with a relatively low abuse potential that is well tolerated by patients (Lin et al. 1996; Ferraro et al. 1997; Jasinski and Kovacevic-Ristanovic 2000; Rush et al. 2002; Rush et al. 2002; Becker et al. 2004).

Prior to a randomized outpatient clinical trial, it is necessary to demonstrate that modafinil can be used safely by patients likely to use methamphetamine concurrently with modafinil and to explore whether modafinil might effect methamphetamine pharmacodynamics or metabolism.

Pharmacology of Methamphetamine

Methamphetamine inhibits the reuptake and increases release of norepinephrine, serotonin, and dopamine. The dopaminergic activity is thought to contribute to the reinforcing effects of methamphetamine, and actions at dopamine and norepinephrine terminals may contribute to its sympathomimetic effects. Following i.v. administration, methamphetamine is eliminated with a $t_{1/2}$ of 12 ± 3.2 hours. Methamphetamine is metabolized by N-demethylation to amphetamine (Lin et al. 1997) and by hydroxylation to 4-OH methamphetamine (Lin et al. 1995). Both of these reactions are catalyzed by cytochrome P450 2D6 (CYP2D6). Approximately 38% of the administered dose is excreted in the urine unchanged (Mendelson et al. 1995). Methamphetamine and amphetamine also inhibit CYP2D6 with an apparent K*i* of 25 µM and 26.5 µM, respectively (Wu et al. 1997). This could shift metabolism during chronic administration towards urinary excretion of the parent compound.

We propose using a total dose of 30 mg of intravenous methamphetamine but propose giving it in divided 15 mg doses. Each dose will be injected over 1 minute by constant rate infusion with doses separated by 1 hour. This sequential dosing provide an increased margin of safety and mimics the pattern of drug administration commonly used by addicts. Some methamphetamine abusers have a lower tolerance to intravenous methamphetamine and the sequential doses will allow the investigators to stop further methamphetamine administration if excessive cardiovascular response follows the first 15 mg dose. Additionally, if cardiovascular interactions between methamphetamine and modafinil make for increased cardiovascular effects, sequential dosing will allow safer administration of pharmacologically active doses of methamphetamine.

In our prior studies, a single 30 mg i.v. dose of methamphetamine produced peak plasma concentrations of 140 ng/mL (Mendelson et al. 1995). Logan et al. (1998) quantified methamphetamine levels in the postmortem blood of individuals involved in traffic fatalities that had detectable levels of methamphetamine. Levels ranged from 50 to 2,600 ng/mL (median 350 ng/mL). Thus, the dose of methamphetamine to be used in this study is representative of the levels in blood of methamphetamine users while at the same time likely to be a safe dose to administer in the human laboratory setting.

In a pharmacokinetic interaction study with alcohol, we described the cardiovascular effects in 8 subjects following i.v. administration of 30 mg of methamphetamine (Mendelson et al. 1995). Blood pressure peaked at 2 minutes and heart rate peaked at 10 minutes after methamphetamine. Both measures returned from peak values to a plateau level (20 mm Hg above and about 15 bpm above pre-methamphetamine baseline) 15 minutes following i.v. administration. These plateau levels slowly returned to pre-drug baseline levels over 12 hours. Heart rate and blood pressure increases were substantial in some individuals (50 mm Hg elevations in systolic blood pressure). Occasional subjects exhibited a baro-receptor reflex response with a brief, relative bradycardia with heart rates of 55 to 60. All subjects had

robust, consistant responses to the 30 mg dose with immediate intoxication ratings of about 50 (0=none, 100=max). In the interaction part of this study, methamphetamine (30 mg i.v.) was administered in combination with ethanol (1 gm/kg). Methamphetamine pharmacokinetics were not altered by the concurrent administration of ethanol, with the exception decreased apparent volume of distribution at steady state for methamphetamine.

Methamphetamine is a substrate for CYP2D6 (Lin et al. 1997), so that its inhibition by co-administered drugs may affect the pharmacokinetics of methamphetamine. The biodisposition of modafinil is complex and probably proceeds through both oxidation and hydrolysis.

Pharmacology of Modafinil

The mechanism of action for modafinil is not completely understood. Putative mechanisms include GABA antagonism and as a putative agonist of brain alpha-1bAR (Stone et al. 2001a; Stone et al. 2001b; Stone et al. 2002). Modafinil increases locomotor activity in animals (mice, rats, and cats) (Duteil et al. 1990; Rambert et al. 1990), and this hyperlocomotion is prevented by alpha1 adrenoceptor antagonists, prazosin and phenoxybenzamine (Duteil et al. 1990; Rambert et al. 1990). Likewise, prazosin prevented modafinil-induced nocturnal activity in monkeys (Duteil et al. 1990). The behavioral activation caused by modafinil is markedly attenuated not only by central pharmacological blockade but also by genetic ablation of alpha-1bAR (Stone et al. 2002). Thus, when challenged with modafinil, mice genetically deficient in alpha-1bAR (alpha 1bAR KO) showed a significant attenuation (approximately 66%) of motor activity.

Preclinical data show that modafinil has low affinity to dopamine transporter (DAT) (Mignoet et al. 1994); it increases extracellular dopamine levels but does not stimulate dopamine release in vitro (De Sereville et al. 1994; Simon et al. 1995; 2002). In contrast to amphetamine and other stimulants, modafinil-induced increase in locomotor activity is not accompanied by induction of a stereotyped behavior typical for dopaminergic signaling and is not prevented by antagonists of D1 or D2 dopamine receptors (Duteil et al. 1990; Rambert et al. 1990) Unlike amphetamine, modafinil did not produce peripheral sympathetic effects in experimental animal (no salivation, no contraction of the pilomotor muscles, slight midriasis only at high doses). These observations confirm that the behavioral activation induced by modafinil does not involve direct effects on dopaminergic pathways and that mechanisms underlying the modafinil induced stimulant locomotor effect differ from that of amphetamine (Simon et al. 1995).

Modafinil has demonstrated the ability to inhibit the release of GABA in the medial preoptic area and in the posterior hypothalamus in rats (Ferraro et al. 1996). It decreases GABA release in the rat nucleus accumbens as well, but its effect on dopamine release in nucleus accumbens is weak and most probably indirect (Ferraro et al. 1996; Ferraro et al. 1997). More significant is modafinil's ability to increase excitatory glutamatergic transmission (Ferraro et al. 1997); it appears to increase glutamate release in ventral medial thalamus, ventral lateral thalamus, and hippocampus of the rat which, in turn, reduces local GABAergic transmission, thereby diminishing GABA(A) receptor signaling on the mesolimbic dopamine terminals. Taken together, these studies suggest that traditional stimulants such as amphetamine and methylphenidate act on dopaminergic structures in the cortex and subcortical areas, whereas modafinil may act primarily in subcortical areas to a) activate noradrenergic transmission and that way induce adrenergic excitation of mesolimbic dopamine neurons, and/or b) activate glutamatergic transmission and thus diminish GABA(A) receptor mediated inhibitory signaling on the mesolimbic dopamine terminals.

All in all, biochemical and behavioral studies point to a "non-amphetamine" mechanism of stimulant locomotor effect of modafinil in animals (Simon et al. 1995). Behavioral studies of modafinil

compared to traditional stimulants have indicated both similarities and differences. Modafinil produces vigilance without subsequent rebound hypersomnolence when compared to amphetamine in rats (Edgar and Seidel 1997). In this same study, modafinil increased locomotor activity far less than amphetamine and only in proportion to the increased awake time. Using a differential reinforcement of low rate of responding (DRL30-S), Bizot (1998) demonstrated that modafinil in rats increased DRL30-S response rate and decreased reinforcement rate in a similar manner to the effects of nicotine and d-amphetamine. Discriminative stimulus and reinforcing effects of modafinil were evaluated in comparison to l-ephedrine and d-amphetamine (Gold and Balster 1996). In cocaine discrimination studies conducted in rats, modafinil produced dose-dependent increases in cocaine lever selection but the level of modafinil-induced response (67%) versus 82% and 100% for l-ephedrine and d-amphetamine, respectively, was indicative of modafinil's low selectivity in producing cocaine-like discriminative stimulus effects. Modafinil was reinforcing in rhesus monkeys maintained on intravenous cocaine self-administration but its reinforcing effect was 200-times less potent than that of l-ephedrine and d-amphetamine (Gold and Balster 1996).

Oral modafinil does not cause elation or euphoria in non-drug abusing human volunteers (Warot et al. 1993). A human study that evaluated abuse potential of modafinil using methylphenidate as a reference in polydrug abusers with a history of cocaine abuse found that subjects liked the effects of both modafinil (200 mg, 400 mg or 800 mg given as a single oral dose) and methylphenidate (45 mg or 90 mg given as a single oral dose) and discriminated modafinil and methylphenidate from placebo (Jasinski 2000). However, unlike methylphenidate, modafinil did not induce a significant effect on the Amphetamine Scale of Addiction Research Center Inventory. Another study investigated behavioral and physiological effects of a single oral dose of modafinil (200, 400 and 600 mg) in subjects with recent histories of cocaine abuse (i.e., positive urine for cocaine or BE during the initial screening) and compared to those of oral cocaine (100, 200 and 300 mg) and placebo (Rush et al. 2002). The results of this study indicate that cocaine, but not modafinil, produced stimulant-like self-reported drug effects (e.g. increased ratings of High and Stimulated on Drug-Effect Questionnaire) and thus suggest modafinil has minimal abuse potential. Analysis of the case reports of stimulant abusers given modafinil for clinical purposes (total of 4) is reassuring and in accord with preclinical human studies with modafinil mentioned above (Malcolm et al. 2002). Overall, both animal and human studies indicate that modafinil can serve as a reinforcer but its reinforcing properties are mild compared to classic psychostimulants (Gold and Balster 1996; Jasinski 2000; Rush et al. 2002).

Treatment with modafinil does not lead to development of dependence (US Modafinil in Narcolepsy Multicenter Study Group 2000). During treatment discontinuation, patients receiving modafinil did not experience either physical symptoms associated with psychostimulant withdrawal (feeling sick, stomach cramps, muscle spasms/twitching, cold sensation, heart pounding, muscle tension, aches and pains, yawning, runny eyes, insomnia) or mental symptoms of withdrawal, such as anxiety, agitation, irritability and craving (Lyons and French 1991; US Modafinil in Narcolepsy Multicenter Study Group 2000). Modafinil does not seem to produce tolerance and retains its efficacy over long-term treatment (up to 40 week) (Lyons and French 1991; Besset et al. 1996; Mitler et al. 2000).

4. Methods

a. Study Design

This is a three phase randomized parallel-group, placebo-controlled study of 16 methamphetamine abusing but not dependent healthy volunteer patients. Methamphetamine is administered when they are inpatients (phases 1 and 3) on the GCRC and daily modafinil dosing (phase 2) is done while they are outpatients.

Phase 1 is a three day inpatient period for the screening/baseline methamphetamine injections with methamphetamine dosing on day -2. Subjects who tolerate the first sequence of methamphetamine doses will be randomized to placebo or active modafinil in a 1:1 ratio. Modafinil (or placebo) will be started 48 hours (on study day 1) after the first sequence of methamphetamine challenges has been completed. The subjects will be observed as inpatients for 4 hours after the first 200 mg modafinil dose and then discharged to be followed with daily outpatient visits to the GCRC.

Phase 2 consists of supervised daily outpatient doses of modafinil 400 mg (or matched placebo) for 7 more days (study days 2 to 8). Subjects will report daily to the GCRC outpatient facility between 9 AM and 12 noon for observed dosing. Trough modafinil levels will be determined from a pre-dose blood sample obtained on days 4, 6, 7, 8, 9, and 10.

Phase 3 is a second inpatient phase and starts the evening of study day 7 when subjects are readmitted to the GCRC and then dosed the next morning on study day 8 with their final 400 mg dose of modafinil followed 2 hours later by two sequential, constant rate, one minute duration injections of 15 mg methamphetamine administered 1 hour apart, with hospital discharge 48 hours later (day 10). Subjects will be discharged from the study after a safety follow-up visit 1 to 2 weeks (study days 17-24) following the final GCRC discharge.

To assess pharmacologic interactions a series of non-invasive complementary cardiovascular measures assessing ventricular function (impedance cardiography), cardiac conductance and repolarization (ECG QTC interval) and peripheral vascular dynamics (impedance cardiography) will be obtained frequently following methamphetamine. Data acquisition for the entire non-invasive panel requires about 10 minutes. Only a limited methamphetamine pharmacokinetic profile will be obtained because it is unlikely that alterations in the biodisposition of methamphetamine will be related to any pharmacodynamic effects. Pharmacokinetic interactions between modafinil and d-amphetamine have already been assessed with no interactions noted (Hellriegel et al. 2002). Therefore, only trough modafinil levels during outpatient dosing will be measured (to confirm compliance with the observed dosing procedure). Subjective pharmacodynamic effects will be assessed with symptom reports and measured with visual analog scales, the brief craving scale and POMS.

Cardiac Measures

The long QT syndrome is an acquired or congenital repolarization abnormality (caused by alterations in the transmembrane potassium and sodium currents) characterized by prolongation of the corrected QT (QTc) interval on the surface electrocardiogram. It is associated with precipitation of a polymorphic ventricular tachycardia, torsade de pointes, which may cause sudden death. Acquired causes of the long QT syndrome include drugs, electrolyte imbalance, toxins, marked bradycardia, subarachnoid hemorrhage, stroke, myocardial ischemia, protein-sparing fasting, autonomic neuropathy, and human immunodeficiency virus disease. Clinical symptoms are the result of the precipitation of torsade de pointes and range from such minor symptoms as dizziness to syncope and sudden death (Khan 2002). QT intervals will be measured using digital ECG measures.

Impedance Cardiography. Impedance cardiography will be measured using a computerized system consisting of a personal computer with customized data processing software, a transmitting unit with four pairs of electrodes for analyses of the thoracic impedance field. Two of these four electrodes will be placed above the sternocleidomastoid region of the subject's right and left neck; two more pairs will be placed in the midaxillary line on each side at the lower thoracic aperture at the xiphoid level.

Methamphetamine produces a sustained rise in systolic and diastolic blood pressure, most likely due to peripheral vasoconstriction. Peripheral vasoconstriction increases systemic vascular resistance

(SVR). In the past, accurate measurement of SVR required right heart catheterization with attendant risks and complications. Impedance cardiography measures the volume of blood ejected into the aorta with each cardiac cycle and allow computation of cardiac output and, when combined with simultaneous blood pressure measurement, calculation of SVR, all noninvasively (Nelesen et al. 1999; Arthur and Kaye 2001). We will use impedance cardiography to measure the effects of methamphetamine-induced vasoconstriction on vascular resistance and cardiac work. Methamphetamine increases cardiac output, although the heart rate may be reflexively slowed (Mendelson et al. 1995). Subjects in this study are likely to have some effect on left ventricular (LV) function after exposure to methamphetamine; since clinical assessment cannot detect changes in LV function (Hardman et al. 1996), we will use impedance cardiography to measure LV function after methamphetamine.

Other Measures

Adverse Events (AEs)

AEs will be assessed daily and recorded weekly by research staff beginning at consent. The PI or one of the study physicians will assess subjects for any serious medical or psychiatric side effects.

Drug Effect Visual Analog Scales

Visual Analog Measures of drug effect and tolerability will be obtained pre-dose, 10, 15, 30, 60, 70, 75, 90 minutes and 2, 4, 6 and 8 hours after methamphetamine dosing. Measures are:

1. Any Drug
2. Good Drug
3. Bad Drug
4. Nervous
5. Tolerable

Craving

Although a poorly defined construct, craving for drugs is an important determinant of drug use and relapse to addiction. We will assess craving with the Brief Substance Craving Scale. The BSCS asks the subject to rate craving for methamphetamine. The BSCS used for this study is a modification of the State of Feelings and Cravings Questionnaire (Mezinskis et al. 2001). BSCS will be measured each morning at about 9 AM (before MA dose) while in hospital and at each visit during Phase 2 before getting modafinil.

Mood

Profile of Mood Scale (30 item version) will be completed by subjects pre-drug and approximately 4 hours after methamphetamine dosing.

Pharmacokinetics

The pharmacokinetic profiles of methamphetamine will be determined before and after modafinil. Plasma (~3 mL) for methamphetamine will be obtained at 0, 5, 15, 30, 60, 65, 75, 90 minutes and 2, 4, 6, 8, 12, 24, 36 and 48 hours after dose (in times relative to the first MA dose). Pharmacokinetic parameters, peak concentrations (Cmax), time to peak concentrations (Tmax), area under the plasma concentration-time curve for 0 time to infinity ($AUC_{0\text{-}inf}$), area under the plasma concentration-time curve for 0 time to time of last measurement concentration ($AUC_{0\text{-}t}$), clearance, terminal half-life and terminal disposition rate constant will be determined.

Methamphetamine will be analyzed by LC-MS assay.

Trough modafinil levels will be measured on days 4, 6, 7, 8, 9 and 10 during phase 2, to confirm compliance with supervised dosing.

b. Methods of Data Analysis

Statistical group comparisons will be made with SAS general linear model procedure (SAS Institute Inc., Release 9.1.3 and with multifactor repeated-measures analysis of variance using SAS or SuperANOVA (Macintosh) applications. Physiologic data will be transformed to change scores (post-treatment minus pre) and analyzed by repeated measures analysis of variance (ANOVA). After a significant F test, pairwise comparisons will be performed using the least squares means analysis. Effects will be considered statistically significant at $P \leq 0.05$.

We have computed the power of our main measures from a prior methamphetamine study (Mendelson et al. 1995) similar to those we propose. In that study, 30 mg of intravenous methamphetamine was administered and changes in heart rate (20±17; mean±SD) were the smallest differences between active drug and placebo conditions. Based on Cohen's (Cohen 1988) effect size formula, data from a study with a sample size of 6 would yield a power of 0.80. However, this is a parallel group design and a larger N is needed due to increased variance between individuals. Therefore, correcting for the increased between individual variance, we estimate that a sample size of 8 will be sufficient to achieve a power of .80, using a two-tailed alpha = 0.05.

c. Subject Selection

1) Who and Why

Methamphetamine experienced subjects between the ages of 18 and 45 years, in good physical and mental health, with no cardiovascular pathology.

2) Total Number — 16

3) Inclusion/Exclusion Criteria

Inclusion Criteria

Subjects will be included in the study if they:

1. MA experienced but not dependent males or females aged 18 to 45 years;
2. Females should be either nonchildbearing (tubal ligation or total hysterectomy) or of childbearing potential using one or more of the following barrier methods of contraception: male or female condoms (with/without spermicide), diaphragm (with spermicide) and/or copper containing intrauterine device (with/without spermicide). No other contraceptives are acceptable;
3. Having a body mass index (BMI) between 18 and 30;
4. Willing and able to give written consent;
5. Not currently a subject (including still in the follow-up period) of another drug research study;
6. Having no medical contraindications determined by the following: an adequate medical history, a physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, and urinalysis;
7. Having a negative drug test for barbiturates, benzodiazepines, opiates, cocaine, amphetamines and ethanol at the time of admission (Day -3);
8. For females, having a negative pregnancy test at screening and prior to each study drug administration.

Exclusion Criteria

Subjects will be excluded if:

Past medical history

1. History of hematological, hepatic, respiratory, cardiovascular, renal or CNS disease or any other medical condition that is capable of altering the metabolism or elimination of drugs or of constituting a risk factor when taking the study drug;
2. Recent history of MA or other drug addiction and/or alcoholism;
3. Any medical condition that could relapse during or immediately after the study, and in the investigator's opinion, interferes with study evaluations or affects a subject's safety.

Current status

4. Significant acute or chronic medical disease;
5. Likely to need concomitant treatment medication during the study period;
6. Blood donation during the 30 days preceding study entry;
7. Tobacco smoker or non-smoker for less than 3 months; i.e., no recent change in smoking status;
8. Alcohol consumption averaging > 40 g daily during the past 30 days;
9. Coffee (or tea) consumption > 6 cups (6 x 0.24 L) per day or xanthine containing drinks > 1 liter/day (e.g., cola drinks, etc);
10. A subject without adequate means of contacting the investigator in case of emergency or not able to be contacted readily by the investigator;
11. Female who is pregnant, lactating, or plans to become pregnant during the study period and within one month after study drug administration;

Prior or current medication

12. Exposure to any investigational new drug within 30 days of screening;
13. Use of any herbal products likely to induce or inhibit hepatic microsomal enzyme CYP 2D6 within one month of the start of the study including St. John's wort (Hypericum perforatum).

Subjects will not be allowed to take concomitant medications, whether prescription or over the counter (OTC); subjects needing regular doses of prescription medications will be excluded.

d. Investigational Drugs

Modafinil

Modafinil (Provigil®) is manufactured by Cephalon, Inc. (West Chester, PA) and will be supplied as 200 mg tablets for oral administration. Placebo will be supplied by Cephalon, Inc. (West Chester, PA) as an exact match of modafinil.

Methamphetamine

Sterile human use methamphetamine HCl at 10 mg/mL in 1 mL ampules, manufactured by Murty Pharmaceutical, Inc. (Lexington, KY), will be provided by NIDA. The compound will be stored in the pharmacy vault. Standard narcotics control procedures will govern access to the drug. Aliquots of 0, 15 or 30 mg will be drawn into a syringe for i.v. administration. Methamphetamine will be administered by i.v. infusion over 1 minute by the study physician. Any unused drug will be disposed according to standard practices.

e. Subject Recruitment

1) Sources and 2) Initial Contact Method

Subjects will be recruited through advertisements placed on Craig's list (a community Internet site) and advertisements in Bay Area newspapers.

f. Consent Process and Documentation

Informed consent will be obtained prior to study procedures in all subjects.

g. Procedures

1) Study Procedures

Screening (Study Days -28 to -3)

Non-treatment seeking methamphetamine users who are available for the approximately 28 day study duration and are between the ages of 18 and 45 will be screened and consented for participation. During their first visit to the laboratory, subjects will complete routine screening questionnaires, undergo a 12-lead EKG, and provide blood and urine samples for screening chemistries. Their second visit will involve a detailed history and physical exam by a physician. Screening of subjects to establish eligibility will occur initially before GCRC admission; though some assessments may be completed on admission. Assessments performed before admission include collection of demographic information and completion of a subject intake form, subject locator form, a timeline follow back for methamphetamine use for the prior 8 weeks, drug use and treatment history, urine toxicology screen, medical history, physical exam, laboratory analyses including hematology, blood chemistries, and urinalysis, a 12-lead ECG, and vital signs (HR and BP). For women of reproductive potential, a urine pregnancy test will be performed. The BSCS will be obtained during the screening or on admission to the GCRC. Adverse events will be recorded at each visit starting the day of completion of the informed consent process. Applicants not participating in the study will receive treatment referral information as appropriate.

Phase 1: Baseline Methamphetamine Challenge (Study Days -3 to 1)

Subjects who meet inclusion criteria and complete intake procedures will reside full-time as inpatients during this study phase. To ensure abstinence, qualitative urine toxicology will be performed at hospital admission. Subjects with a positive test for methamphetamine, cocaine or opiate metabolites will be discharged and not readmitted. A positive test for cannabinoids will not preclude admission.

Randomization to Modafinil or Placebo

Subjects who tolerate the sequential methamphetamine infusions, will be randomized on study day -1 to modafinil or placebo in a 1:1 ratio. The UCSF research pharmacist will provide pre-coded envelopes with treatment assignments. The Research Pharmacist will dispense the coded bottles of modafinil or placebo to the GCRC. If a subject does not tolerate the initial methamphetamine infusion session, a replacement subject will be randomized until 16 subjects have completed the study.

Methamphetamine Infusion Sessions (Phases 1 and 3)

Each intravenous dose will be administered by a 1-minute duration, constant rate, pump administered, infusion supervised by a study physician. The methamphetamine infusions will begin approximately at 9 a.m (depending on scheduling conflicts, and modafinil dose time). Vital signs will obtained using a Critikon or Escort II monitor or a similar bedside device. Baseline conditions for all the

cardiovascular measures (heart rate, blood pressure, respiratory rate, QT interval, and stroke volume) will be determined during a baseline recording period just prior to methamphetamine administration.

The screening/baseline infusions are to ensure that volunteers are responsive to and safely tolerate the total 30 mg dose of methamphetamine. They also provide cardiovascular and psychometric response data in the absence of the modafinil and serve for training and adaptation purposes. Only subjects responsive to and safely tolerating both doses of 15 mg methamphetamine doses will continue in the study.

A 10 hour fast will precede the injections and no food will be allowed until at least 2 hours after completion of the infusions. Water will be permitted at any time. Caffeine-containing beverages will not be allowed for 12 hours before each methamphetamine dose. No smoking will be allowed at any time after GCRC admission; nicotine patches will be offered to all smokers.

The pharmacokinetic profiles of methamphetamine will be determined. Plasma (~3 mL) for methamphetamine will be obtained at 0, 5, 15, 30, 60, 65, 75, 90 minutes and 2, 4, 6, 8, 12, 24, 36 and 48 hours after dose (in times relative to the first MA dose).

A profile of cardiovascular responses will be obtained from a series of complementary measures to assess drug-drug interactions. The CV profile will include repeated HR, BP, ICG and ECG derived QT intervals. The CV profile will be obtained using automated non-invasive equipment. The CV profile (except for ECG-QT intervals) will be obtained at -15 minutes before, and 5, 15, 30, 60, 65, 75, 90 minutes and 2, 3, 4, 6, 8, 12, 24 and 48 hours following the methamphetamine administration. ECG-QT intervals will be measured at 15 minutes before and 1, 2, 8, 24 and 48 hours after starting infusions. 12-lead ECG will be obtained before and 24 and 48 hours after methamphetamine. Heart rate will be monitored continuously for 60 minutes after each infusion.

Subjective effects items are “any drug effect,” “good drug effect,” “bad drug effect,” “nervous,” “tolerable”. VAS subjective effects will be measured at -15 minutes before, and 10, 15, 30, 60, 65, 70, 75, 90 minutes and 2, 3, 4, 6, and 8 hours following the methamphetamine administration.

Craving will be measured with the BSCS each morning at about 9 AM (before MA dose) while in hospital and at each visit during Phase 2 before getting modafinil. Mood will be measured with the Profile of Mood Scale (30 item version) pre and approximately 4 hours after methamphetamine dosing.

Phase 3 is an inpatient phase and starts the evening of study day 7 when subjects are readmitted overnight and then dosed on study day 8 with 400 mg of modafinil followed 2 hours later by the sequential 15 mg methamphetamine infusions. Subjects will be discharged from the GCRC 48 hours following the methamphetamine-modafinil challenge session (day 10). Subjects will be discharged from the study after the safety follow-up visit that occurs between 1 and 2 weeks (study days 17-24) following the final GCRC discharge.

Modafinil Dosing – All Phases

The first dose of modafinil (or placebo) will be administered 48 hours after the first meth-amphetamine infusion (day 1). To assess the tolerability of modafinil, the first dose will be 200 mg. Following this dose, the subject will be observed for 4 hours and, if tolerated, subsequent doses will be 400 mg and will be administered daily on the GCRC when the subjects arrive as outpatients between 9AM and noon. The 400 mg daily dose will be administered on study days 2 thru 8. Tolerability will initially be determined 4 hours after the first dose and then daily in Phase 2 at 2 hours after each oral dose by:

1. Asking "Are you willing to continue taking this medication";
2. Asking "Do you now or since your last dose have you had a headache". If the subject has developed a headache, they will be excluded if the headache is:
    a. Usually severe and persistent
    b. Associated with vomiting
    c. Associated with any visual symptoms;
3. Measuring VAS Bad drug rating. To continue the rating must be less than 40;
4. Measuring vital signs while recumbent for at least 10 minutes. Subjects will discontinue if:
    a. Systolic blood pressure >145, <90
    b. Diastolic blood pressure >90, <60
    c. Heart rate >105, <50;
5. Lack of obvious agitation or confusion or other side effects that, in the opinion of the investigators, places the subject at increased risk for a serious adverse event.

Supervised outpatient modafinil dosing will be performed on the GCRC with subjects arriving between 9AM and noon daily. Vital signs and urine toxicology will be performed daily before modafinil administration along with assessment of methamphetamine craving using VAS and the BSCS. A positive urine toxicology consistent with recent methamphetamine, opiate or cocaine use will result in subject termination and replacement. On study days 4, 6, 7, and 8, 5 mL blood samples will be obtained before modafinil dosing for trough modafinil levels and on days 9 and 10 at equivalent times for residual levels after dosing stops.

Safety Precautions

A study physician will supervise the infusions and will be present during the infusion and will remain quickly available until vital signs have returned to baseline. If a subject demonstrates a significant adverse reaction to methamphetamine, the methamphetamine administration will be halted, appropriate medical response will be implemented, and the subject will be discontinued from the remainder of the study.

Stopping Criteria for Methamphetamine Infusion and Study Participation

Subjects will be closely monitored before and immediately after drug administration. Vital signs, cardiovascular measures, and adverse symptom reports will be used to determine the safety of the methamphetamine and the appropriateness for administering the next dose. Vital signs must be within acceptable limits before additional methamphetamine is administered. If the following stopping criteria are exceeded within 1 hour of methamphetamine dosing, further methamphetamine doses will be held:

1. Supine heart rate >0.75 age predicted maximum (220-age x 0.75) or <40 or
2. Systolic blood pressure >180 or <90 mmHg.
3. Diastolic blood pressure >120 or <45 mmHg.
4. Respiratory rate >24 or <8.
5. Significant arrhythmia defined as >6 beats nonsinus supraventricular tachycardia or ≥3 beats ventricular tachycardia.
6. ECG-QT interval >480msec in females or >500 msec in males.
7. Reported significant nausea or abdominal pain.
8. Reported significant chest pain or dyspnea.
9. Subject confusion, agitation or inability to cooperate.
10. Any other severe adverse effect regarded as being due to drugs or the experimental procedures.

If abnormal vital signs occur, subjects will be closely observed with vital sign measurements every 5 to 15 minutes until the abnormalities abate. If stopping criteria are exceeded, subjects will be closely observed and treated as necessary to assure return to their baseline normal state before being discharged from the GCRC.

If more than two subjects show a similar pattern of excessive cardiovascular or behavioral change or a pattern of change from baseline in biochemical indices after drug administration not readily explainable by other factors, the experiment will be halted and the dose plan reassessed before proceeding.

Modafinil Safety Concerns

The most commonly reported AEs associated with the use of modafinil include headache, nervousness, nausea, anxiety, and insomnia. In general, at doses of 400 mg/day, modafinil is well-tolerated, and in many clinical studies, only headache occurs significantly more often in the active treatment group versus placebo. The most frequent AEs reported in an open-label study of cocaine-dependent subjects treated with 100 mg or 200 mg modafinil b.i.d. for 8 weeks were "difficulty with sleeping" and feelings of "racey" (C. Dackis, 2002, personal communication). Mean plasma levels of GGT were found to be higher following administration of modafinil, but not placebo in US phase 1, 2 and 3 studies of modafinil (PDR 2004).

Biological Samples

Blood Samples: Venous blood samples will be obtained from the arm at designated collection times; samples will be obtained through an indwelling venous catheter using sterile technique.

Urine Samples: A drug of abuse screen will be performed upon GCRC admission, before methamphetamine dosing on the GCRC and just before each outpatient modafinil dose.

2) Time (Frequency and duration of each study procedure; total amount of time)

Screening: Subjects will have up to 4 weeks to complete outpatient screening (study days –28 to –3). The first visit to the laboratory will last 1 to 2 hours; subjects will complete routine screening questionnaires, undergo a 12-lead EKG, and provide blood and urine samples for routine labs. If the screening tests are within acceptable limits, subjects will return for a second visit. This visit will involve a detailed history and physical exam by a physician.

Phase 1 begins on admission (day-3) and continues with the screening/baseline methamphetamine infusions (day -2) and the first 200 mg modafinil dose (day 1).

Phase 2 begins with discharge from the GCRC and includes 6 additional outpatient administration days of modafinil 400 mg/day (days 2 to 7).

Phase 3 begins the evening of study day 7 when subjects will be readmitted overnight and then dosed on the morning of study day 8 with 400 mg of modafinil followed 2 hours later by the sequential 15 mg methamphetamine infusions. Subjects will be discharged 48 hours later (on day 10 following the second methamphetamine challenge session (day 8). Final study discharge will occur after a safety follow-up visit that occurs between 1 and 2 weeks (study days 20-27) after the last GCRC discharge.

Hospitalizations: Subjects will be admitted to the UCSF General Clinical Research Center (GCRC) and will remain on the ward until at least 48 hours after the first methamphetamine dose. The duration of each of the two GCRC admissions is 3 nights.

3) Study Sites

Study procedures will be carried out at the UCSF General Clinical Research Center.

h. Risks/Discomforts

The most common side effects with intravenous methamphetamine are palpitations, euphoria, anxiety, panic or dyspnea. These are more common at doses of 30 mg or greater and are unlikely with our sequential 15-mg doses. In multiple prior experiments where similar or larger doses of intravenous methamphetamine have been administered, few adverse effects have been seen or reported. We expect the effects of the proposed sequential 15-mg doses to be moderate in intensity and brief in duration. If modafinil increases methamphetamine effects, the magnitude should still be less than we have seen when larger doses of methamphetamine have been given.

We will administer a single oral 200 mg dose of modafinil followed by 8 days of 400 mg modafinil per day. This dose is safe, has pharmacologic activity, and is generally well tolerated. Adverse reactions are dose related and usually mild with the majority affecting the CNS. Reports of insomnia and feeling 'racy' are common but should be minimized by dosing early in the day.

There is a moderate amount of pain, discomfort, bruising, and a very remote potential for infection associated with the placement of needles and catheters in arm veins for blood sampling and drug administration. Approximately 260 mL of blood will be drawn over the entire study.

There is also likely to be some stress from the fact the subject will be living on a hospital ward, and will be subjected to repeated blood sampling, physiological monitoring, questionnaires, and other study procedures. We will make every effort to minimize such stress.

i. Treatment and Compensation for Injury

This will be according to standard UCSF policy. The following statement is included in the consent form: "If I am injured as a result of being in this study, treatment will be available. The University of California, depending on a number of factors may cover the costs of such treatment. The University does not normally provide any other form of compensation for injury. For further information regarding this, I can either discuss it with the investigators or, if this is not clarified to my satisfaction, I can call the UCSF Committee on Human Research Office at (415) 476-1814."

j. Alternatives

The alternative is not to participate

k. Costs to the Subject

There will be no costs to the subject.

l. Reimbursements of Subjects

Subjects will earn compensation starting with the second screening session. This session involves undergoing a physical examination. This session is expected to require 1 to 2 hours; we propose compensation of $20.00. They will receive $150.00 for each night they stay on the research ward and $30.00 for attendance for outpatient dosing. The follow-up visit is expected to require 1 to 2 hours; compensation of $20.00. A 20% completion bonus will be paid if they finish the experimental

series of multiple sessions. If they successfully complete all of the experimental sessions, the total amount they can earn is approximately $1,380.00

If a subject does not complete the experimental series, they will be paid their earnings up to that time, but will get no bonus. Subjects who actively abuse illicit drugs during Phase 1, 2, or 3 will lose all compensation. Payment will be by University of California check. Subjects must provide a forwarding address and a social security number to receive payment for participating in this study.

m. Confidentiality of Records

Subject confidentiality is always a primary concern. Privacy will not be guaranteed. For hospitalized volunteers, there are many possible confidentiality leaks. Prospective subjects will be told of this clearly. Anyone with strong concerns about being identified as a research subject will be encouraged not to participate. Research forms and files are coded by individual code numbers, kept in secure files or on protected computer disks with any identifying information linking to name only available to very limited research personnel. In any UCSF hospital patient records, sufficient medical information must be included to conform with JCAH and UCSF hospital record requirements but possibly embarrassing information will be mentioned, if at all, in only the most circumspect way.

5. Qualifications of Investigator

Dr. Mendelson is a general internist who has extensive experience in pharmacologic studies similar to the one proposed. He has studied the cardiovascular and neuropsychopharmacologic effects of MDMA, methamphetamine, and cocaine. He has an active clinical practice and is well versed in the diagnosis and treatment of hypertension. Dr. Jones is a psychiatrist and clinical psychopharmacologist who has been doing studies like this for almost 30 years at UCSF. Dr. Lori Karan is an internist who is well trained in addiction medicine.

6. Reference to Special Requirements and Attachments

None.

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Appendix 1-1

Interactions Between Intravenous Methamphetamine and Modafinil (Study No. 04-01) Phase 1 — Days -3 to 1										
Actual TIME	**Relative Time**	**IV MA Dosing**	**Vital Signs**	**ICG Profile**	**PK Samples**	**QT Interval**	**12 lead ECG**	**VAS**	**BSCS, POMS**	**Other**
-24 hr										HCG/ Utox
2300										no food
0845 (Pre)	-15		X	X	X	X	X	X	BSCS, POMS	
0900		**MA 15mg**								
0905	5		X	X	X					
0910	10							X		
0915	15		X	X	X			X		
0930	30		X	X	X			X		
1000	1 hr	**MA 15mg**	X	X	X	X		X		
1005	1 hr 5 min		X	X	X					
1010	1 hr 10 min							X		
1015	1 hr 15 min		X	X	X			X		
1030	1 hr 30 min		X	X	X			X		
1100	2 hr		X	X	X	X		X		food allowed
1200	3 hr		X	X				X		
1300	4 hr		X	X	X			X	POMS	
1500	6 hr		X	X	X			X		
1700	8 hr		X	X	X	X		X		
2160	12 hr		X	X	X					
0900	24 hr		X	X	X	X	X		BSCS	
2100	36 hr				X					
0900	48 hr	Modafinil 200 mg	X	X	X	X	X		BSCS	
Vitals = HR, BP, RR; VAS = Visual analog scale; BSCS = Brief Substance Craving Scale; CV Profile = Vitals and ICG. See Tables 2 and 3 for study phases 2 and 3.										

Appendix 1-2

Interactions Between Intravenous Methamphetamine and Modafinil
(Study No. 04-01)
Phase 2 — Days 1 to 7

(Subjects to report to GCRC between the hours of 8 and 12)

Day #	Time In	Time Out	Modafinil Trough Levels	Time of Utox Predose	Time of BSCS Predose	Time of Vitals Predose	Time of Modafinil Dose	Time of Tolerability Questions	Time of VAS
Day 1 modafinil (4 hr observation)									
Modafinil Day 2									
Modafinil Day 3									
Modafinil Day 4			X						
Modafinil Day 5									
Modafinil Day 6			X						
Modafinil Day 7			X						

Observation period for day 1 is 4 hours. Observation period for day 2 to 7 is 2 to 3 hours. On modafinil day 8, subject is in hospital beginning phase 3.
See phase 3 chart for details on phase 3.

Appendix 1-3

Interactions Between Intravenous Methamphetamine and Modafinil (Study No. 04-01) Phase 3 — Days 7 to 10										
Actual TIME	**Rela-tive Time**	**Dosing Modafinil & MA IV**	**Vital Signs**	**ICG Profile**	**Trough and PK Samples**	**QTc Interval**	**I2 Lead ECG**	**V A S**	**BSCS, POMS**	**Other**
-24 hr										HCG/ Utox
2300										No food
0650					Trough draw					
0700		**Modafinil 400 mg**	X							
0845 (Pre)	-15		X	X	X	X	X	X	BSCS, POMS	
0900		**MA 15mg**								
0905	5		X	X	X			X		
0910	10							X		
0915	15		X	X	X			X		
0930	30		X	X	X			X		
1000	1 hr	**MA 15mg**	X	X	X	X		X		
1005	1 hr 5 min		X	X	X			X		
1010	1 hr 10 min							X		
1015	1 hr 15 min		X	X	X			X		
1030	1 hr 30 min		X	X	X			X		
1100	2 hr		X	X	X	X		X		Food allowed
1200	3 hr		X	X				X		
1300	4 hr		X	X	X			X	POMS	
1500	6 hr		X	X	X			X		
1700	8 hr		X	X	X	X		X		
2160	12 hr		X	X	X					
0900	24 hr		X	X	X	X	X		BSCS	
2100	36 hr				X					
0900	48 hr		X	X	X	X	X		BSCS	
Modafinil trough levels on days 8, 9 and 10										
Vitals = HR, BP, RR/ VAS=Visual analog scale/ BSCS =Brief Substance Craving Scale										

Appendix 2

Brief Substance Craving Scale (BSCS)

Subject _____ Date_____ Scheduled Time_____ Actual Time_____

Please answer the following questions with regard to Craving for Methamphetamine

1. The INTENSITY of my craving, that is, how much I desired methamphetamine in the past 24 hours was:

O None at all O Slight O Moderate O Considerable O Extreme

2. The FREQUENCY of my craving, that is, how often I thought of methamphetamine in the past 24 hours was:

O Never O Almost Never O Several Times O Regularly O Almost Constantly

3. The LENGTH of Time I spent in craving for methamphetamine during the past 24 hours was:

O None at all O Very Short O Short O Somewhat Long O Very Long

4. Write in the NUMBER of times you think you had craving for methamphetamine during the past 24 hours: _____

5. Write in the total TIME spent in craving methamphetamine during the past 24 hours:

	:	
HOURS		MINUTES

Appendix 3

POMS BRIEF FORM

Note: POMS is actually administered on multicopy self scored form with scores for: Tension, Depression, Anxiety, Vigor, Fatigue, Confusion, and Total Mood Score

Name Date Subject Number Time

Below is a list of words that described feeling is that people have. Please read each word carefully. Then circle the number the best describes how you feel right now.

	Not at all	a little	moderately	quite a bit	extremely
1. Tense	0	1	2	3	4
2. Angry	0	1	2	3	4
3. Worn-out	0	1	2	3	4
4. Lively	0	1	2	3	4
5. Confused	0	1	2	3	4
6. Shaky	0	1	2	3	4
7. Sad	0	1	2	3	4
8. Active	0	1	2	3	4
9. Grouchy	0	1	2	3	4
10. Energetic	0	1	2	3	4
11. Unworthy	0	1	2	3	4
12. Uneasy	0	1	2	3	4
13. Fatigued					
14. Annoyed			etc.		
15. Discouraged					
16. Nervous					
17. Lonely					
18. Muddled					
19. Exhausted					
20. Anxious					
21. Gloomy					
22. Sluggish					
23. Weary					
24. Bewildered					
25. Furious					
26. Efficient					
27. Full of Pep					
28. Bad Tempered					
29. Forgetful					
30. Vigorous					