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PHASE 2, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF MODAFINIL FOR METHAMPHETAMINE DEPENDENCE

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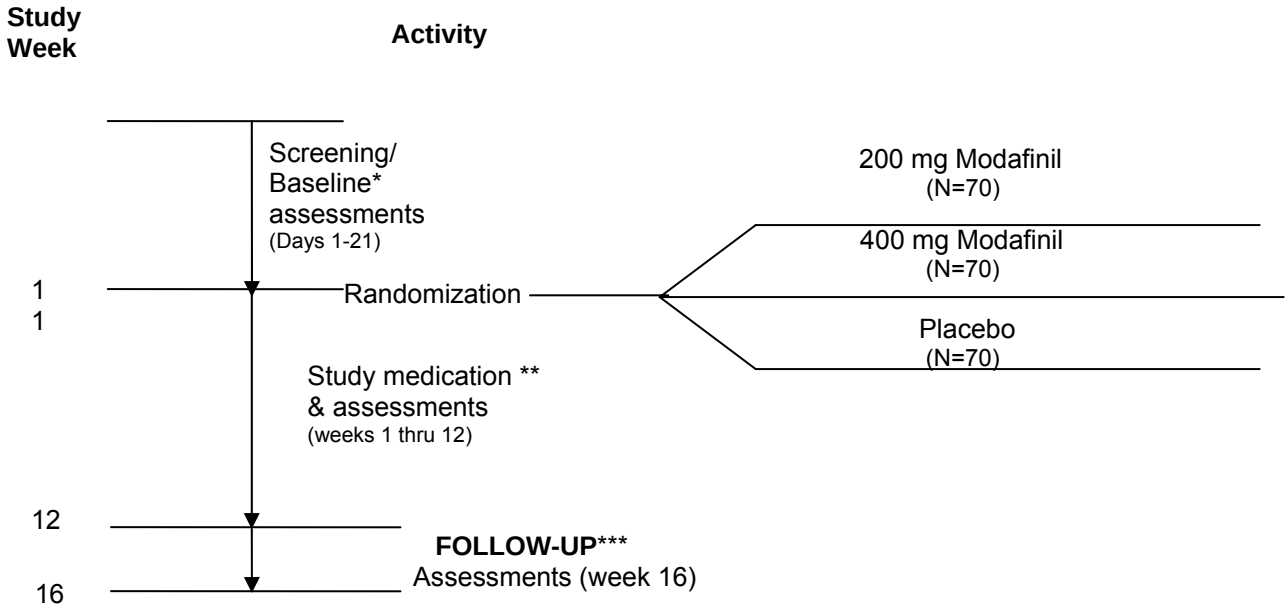
APPENDICES

1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADHD	attention deficit hyperactivity disorder
ADD	attention deficit disorder
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALP	alkaline phosphatase
alpha-1bAR	alpha 1b-adrenergic receptors
alpha-1bAR KO	alpha 1b-adrenergic receptors knock-out
ALT/SGPT	alanine aminotransferase/serum glutamic-pyruvic transaminase
ASI-Lite	Addiction Severity Index-Lite
AST/SGOT	aspartate aminotransferase/serum glutamic-oxaloacetic transaminase
AUC	area-under-the-curve
BE	benzoylecgonine
BP	blood pressure
BSCS	Brief Substance Craving Scale
BUN	blood urea nitrogen
CANTAB	Cambridge Neuropsychological Test Automated Battery
CAP	College of American Pathologists
CBT	Cognitive Behavioral Therapy
CGI-O	Clinical Global Impression Scale – Observer
CGI-S	Clinical Global Impression Scale – Self
CLIA	Clinical Laboratory Improvement Amendment of 1988
CNS	central nervous system
CRF	Case Report Form
CPK	creatine phosphokinase
CYP2C9	cytochrome P450 2C9 isoform
CYP2C19	cytochrome P450 2C19 isoform
CYP2D6	cytochrome P450 2D6 isoform
CYP3A4	cytochrome P450 3A4 isoform
DAT	dopamine transporter
DBP	diastolic blood pressure
DPMC	Division of Pharmacological and Medical Consequences
DSMB	Data and Safety Monitoring Board
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
ECG	electrocardiogram
EDS	excessive daytime sleepiness
FDA	Food and Drug Administration
FTA-abs	fluorescent treponemal antibody absorption
GABA	gamma-aminobutyric acid
GGT	gamma-glutamyl transferase
HAM-D	Hamilton – Depression Rating Scale
HIV	human immunodeficiency virus

Abbreviation	Definition
HR	heart rate
HRBS	HIV Risk-Taking Behavior Scale
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-treat
LAAM	levo-alpha-acetylmethadol
LDH	lactate dehydrogenase
MAO	monoamine oxidase
MHA-TP	microhemagglutination for *Treponema pallidum*
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MUSC	Medical University of South Carolina
NDA	New Drug Application
NET	norepinephrine transporter
NIDA	National Institute on Drug Abuse
OTC	over-the-counter
PDR	Physicians' Desk Reference®
PPD	purified protein derivative (test for tuberculosis)
RPR	rapid plasma reagin (test for syphilis)
RR	respiration rate
SAE	serious adverse event
SBP	systolic blood pressure
SCID	structured clinical interview for DSM-IV
SERT	serotonin transporter
SUR	substance use report
TPPA	*Treponema pallidum* particle agglutination
VAS	Visual Analog Scale

2 STUDY SCHEMA



* Screening and baseline assessments may be conducted concurrently and may be as short as a 14-day period.

** Double-blind period consists of 12 weeks of study medication administration with 200 mg or 400 mg modafinil or placebo administered orally as a single morning dose. All study medication groups will receive psychosocial therapy three times a week.

***Follow-up period consists of a follow-up at week 16.

†Randomization to study medication groups will be done by stratifying by clinical site then using an adaptive randomization procedure based on current ADHD, gender, and frequency of historical self report of methamphetamine use in the 30 days prior to informed consent (≤ 18 *versus* >18).

3 ABSTRACT

STUDY OBJECTIVES: To evaluate the efficacy and safety of modafinil in reducing methamphetamine use in subjects with methamphetamine dependence. It is hypothesized that modafinil, compared to placebo, will be associated with an increase in the number of methamphetamine non-use weeks over time as measured by [redacted] for methamphetamine.

STUDY DESIGN: This is a double-blind, placebo-controlled, parallel-group study in which, after a 14 to 21-day screening/baseline period, subjects will be randomly assigned to one of three study medication groups. Subjects will receive 200 mg modafinil, 400 mg modafinil or matched placebo daily for 12 weeks, with a follow-up assessment 4 weeks after completion/termination of the study medication phase. Randomization to study medication groups will be done by stratifying by clinical site then using an adaptive randomization procedure based on current ADHD, gender, and frequency of historical self report of methamphetamine use in the 30 days prior to informed consent (≤ 18 *versus* >18).

STUDY POPULATION: Two hundred and ten subjects with Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria for methamphetamine dependence, determined by structured clinical interview (SCID), will be randomized into one of three medication arms (70 subjects per arm). The subject population will include those who provide at least one methamphetamine-positive urine during the 14 to 21-day screening/baseline period prior to randomization, and who verbalize the ability to understand and provide written informed consent.

STUDY MEDICATION: During the 12 weeks of study medication administration, subjects will receive 200 mg or 400 mg of modafinil daily, or matched placebo. Modafinil/placebo is administered orally once a day. All subjects will receive standardized psychosocial therapy, which will consist of manual-guided cognitive behavioral therapy (CBT) three times a week during the 12-week study medication administration period.

SAFETY ASSESSMENTS: All potential subjects for study enrollment will have a physical examination, a 12-lead electrocardiogram (ECG), clinical laboratory studies (blood chemistry, hematology, infectious diseases, urinalysis, and pregnancy test, if female), and the Hamilton Depression Rating Scale (HAM-D) completed during screening/baseline. Vital signs are done three times a week during screening/baseline and for the first three weeks of study medication administration and then weekly thereafter. Adverse events and concomitant medication use will be assessed three times per week during screening/baseline and during the study medication administration period. Adverse events (AEs) will be assessed at each study visit and reviewed by a study physician once a week. A HAM-D will be performed during screening/baseline and at weeks 4, 8, and 12. A pregnancy test, if female, will be performed at screening, on study day 1 prior to randomization and at weeks 4, 8, 12 and 16. At week 12 or at the time of study discontinuation, all subjects will have an ECG, vital signs, physical examination, HAM-D, clinical laboratory studies (including pregnancy test, if female) and an AE assessment. A final AE assessment will be performed at follow-up 4 weeks after study completion/termination.

EFFICACY ASSESSMENTS: The primary efficacy outcome measure is methamphetamine use or non-use weeks during the study medication administration period. Secondary assessments include analyses of other measures of success in the reduction of methamphetamine use including the proportion of successful subjects with 21 consecutive days of abstinence in which all [redacted] are negative for methamphetamine, overall proportion of negative methamphetamine use days by self report, the maximum number of consecutive methamphetamine non-use days, reductions in methamphetamine use as compared to baseline, and reduction in scores of HIV risk-taking behavior assessed by the HIV Risk-Taking Behavior Scale (HRBS). Severity of methamphetamine dependence will be assessed by comparing the change in scores of the Addiction Severity Index (ASI and ASI-Lite Follow-up), Brief Substance Craving Scale (BSCS), Clinical Global Impression as assessed by the subject (CGI-S) and an observer (CGI-O), Barratt Impulsiveness Scale (BIS), the Adult ADHD Investigator Symptom Rating Scale (AISRS), and a neuropsychological battery (CANTABelect). The ASI will be performed at screening/baseline and the ASI-Lite will be performed at the first visit of week 6 and at week 12 or early termination. The BIS will be assessed at screening/baseline and at weeks 6 and 12 or early termination. The ASIRS will be gathered at screening/baseline and at weeks 4, 8 and 12 or early termination. The BSCS, CGI-S, and CGI-O will be performed at each week during screening/baseline and at the first visit of each study week during the study medication administration period. The HRBS will be used to characterize the population's HIV risk-taking behavior at screening/baseline and at the end of the study. A set of neuropsychological tests administered by The Cambridge Neuropsychological Test Automated Battery (CANTAB) will be conducted at screening, baseline and at weeks 6 and 12. End-of-study assessments to be performed if a subject completes the protocol or is terminated early for any reason are listed in Section 12.

ANALYSIS: Each primary and secondary outcome variable will be analyzed using appropriate statistical methods for the intent-to-treat (ITT), evaluable and study medication completer populations. The ITT population is defined as the subjects who are randomized to study medication and who receive the first dose of study agent. The evaluable population is defined as the ITT subjects who contribute at least six (6) usable on-study medication urine samples and 21 days of self-report. Study medication completers are the ITT population who take at least one dose of study medication in week 12, provide at least one urine sample in week 12, and provide self reports of substance use through the last day of week 11. The individual effects, if any, of gender, age, race, prior methamphetamine use, usual route of methamphetamine use (oral/nasal inhalation *versus* intravenous/smoked), depression, and clinical site on the primary outcome will be determined. Statistical tests will be two-sided at a 5% Type I error rate.

Summaries of the characteristics of the subject population in all three study medication arms at baseline will be prepared for the ITT, evaluable and study medication completer subjects. A summary will be prepared to show dropouts/retention over time in each study medication arm, along with the reason for early termination. The number of missing observations will be compared between study medication arms. Weekly study medication compliance and behavioral therapy compliance in each study medication arm will be summarized. The types and frequency of other drugs used by self-report of use and by positive urine drug screen will also be reported for each study medication arm. The proportion of subjects in each study medication arm that are abstinent at Week 16 will be summarized (abstinent is defined as no self-reported use since

Week 12 and the Week 16 methamphetamine urine drug screen is negative). All AEs will be reported in tabular form indicating the frequency of each type of event.

4 INTRODUCTION

4.1 Methamphetamine

Methamphetamine (Methedrine, "speed", "ice") is used and misused as a central nervous system stimulant. Methamphetamine (N-methylamphetamine) is a non-cathecholamine phenylisopropanolamine that belongs to the ephedrine family of sympathomimetic drugs. It readily enters the central nervous system and has a marked stimulant effect on mood and alertness and a depressant effect on appetite. Methamphetamine acts primarily by increasing release of stored catecholamines - dopamine, epinephrine and norepinephrine. It is also a weak inhibitor of monoamine oxidase (MAO), an action that would increase cathecholaminergic activity. Its pharmacokinetics are similar to those of ephedrine: it has high bioavailability, a long duration of action, and a significant fraction of methamphetamine is excreted unchanged in the urine. Methamphetamine abuse has a typical pattern of withdrawal manifested by signs and symptoms opposite to those produced by the drug. Users become sleepy, have a ravenous appetite, are exhausted, and may suffer from mental depression. This syndrome may last for several days after the drug is withdrawn. Since the duration of action of methamphetamine is much longer than that of cocaine, intoxication may last for several days after a single smoke. Tolerance develops quickly, so that abusers may take huge doses compared with those used medically, e.g., as anorexants.

4.2 Methamphetamine as a Major Health Problem

Methamphetamine has become a major drug of abuse in this country (NEDTAC, 1998) for nearly a decade. High rates of methamphetamine dependence are also registered in Great Britain (Klee, 1992; 1997a), Japan (Suwaki, 1991; 1997), Australia (Hando and Hall, 1994; 1997; Makkai and McAllister, 1993), and in many other countries (Klee, 1997b). In Great Britain, the methamphetamine problem is considered of greater public health consequence than cocaine, especially in relation to HIV. In Australia, amphetamines are the second most frequently used drugs, after cannabis.

In the United States, methamphetamine abuse is particularly a problem in the western states and it has more recently become a substantial concern in other sections of the country. The National Household Survey on Drug Abuse (1997) reported a 28% increase from 1994 to 1996 in the number of individuals who have tried methamphetamine in their lives (3.8 million in 1994 compared to 4.9 million in 1996). The rate of use among high school seniors was approximately 2.3% in 1996 and 4.4% reporting lifetime use (Monitoring the Future, 1997). Increased methamphetamine availability and production are being reported in diverse areas of the country, particularly rural areas, prompting concern about widespread use (ONDCP, 1998) and the problems associated with its use are also growing.

Methamphetamine-related visits to emergency rooms nationwide remain high (SAMHSA, 1997); methamphetamine-related deaths increased 217% between 1992 and 1995 (DAWN, 1998); and

the amount of methamphetamine seized in California in the past three years increased 518% (ONDCP, 1998). Violence associated with methamphetamine (users under the influence, users who commit violent acts to obtain methamphetamine, and/or distributor-trafficker violence) is also a concern (DEA, 1996). Moreover, a generation of new users is engaging in highly risky sexual activities under the influence of methamphetamine, which raises the possibilities for a new wave of HIV transmission.

The problem is particularly acute in California, where methamphetamine has been a significant concern for 30 years. Methamphetamine-related hospital admissions have increased 366% between 1984 and 1993 (Cunningham and Thielemeir, 1996). Recently, methamphetamine has been the primary drug problem for those admitted for drug treatment in the state; and the increase in admissions has been particularly noticeable among Latino methamphetamine abusers (NEDTAC, 1998). The lack of effective treatment for methamphetamine users has far reaching health ramifications both in terms of the consequences from continued drug use and from the potential for increased HIV transmission. As a result, the development of effective treatments for methamphetamine dependence has become a pressing concern for the national and global drug abuse treatment community.

4.3 Search for Effective Treatments for Methamphetamine Dependence

Despite a decade of intensive research, an effective pharmacotherapy for stimulant dependence remains elusive with a noted lack of controlled clinical trials in pharmacotherapy for methamphetamine abuse in particular (King and Ellinwood, 1995; Ling and Shoptaw, 1997). To date, the bulk of the research in the field is oriented toward treatment of cocaine dependence and much of the suggestions on pharmacotherapies for methamphetamine abuse are based upon clinicians' experiences with treating cocaine abuse. Inherent in this approach is the assumption that what applies to cocaine treatment might also apply to methamphetamine. Although the efficacy of cocaine-focused treatment when applied to methamphetamine users remains largely unknown, the similarities between the two stimulants support using existing cocaine treatment research as a starting point for the development of treatment approaches for methamphetamine users.

The idea of applicability of cocaine treatment strategies for pharmacotherapy of methamphetamine dependence is based on the similarity of their pharmacological actions, i.e. cross-behavioral sensitization and tolerance between these psychostimulants in animal studies (Akimoto *et al*., 1990; Kazahaya *et al*., 1989; Peltier *et al*., 1996). Cocaine is able to cross-sensitize the locomotor responses to other psychostimulants (Elmer *et al*., 1996), and chronic methamphetamine (and amphetamine) produce cross-tolerance to the discriminative and reinforcing stimulus of cocaine (Peltier *et al*., 1996). These data, as well as similarities of biochemical modes of action of cocaine and methamphetamine - both enhance the efflux of striatal dopamine (Kazahaya *et al.*, 1989) and recruit brain nitric oxide system when behaviorally cross-sensitizing (Itzhak, 1997) - implied that effects of cocaine and methamphetamine may converge on a molecular level via induction of specific patterns of gene expression.

The concept of building on knowledge from cocaine dependence studies and applying this knowledge to methamphetamine studies was endorsed by the recent Methamphetamine

Addiction Treatment Think Tank (MATTT) consultants meeting convened at NIDA on 12 January 2000.

One conceptual approach for cocaine pharmacotherapies has been to evaluate medications that have antidepressant properties to treat the anhedonia and depressive symptoms in early withdrawal [e.g., desipramine, and selective serotonin reuptake inhibitors (SSRIs)]. Medications that alleviate anhedonia have a direct effect on improving the patient's depressive mood and are believed to reduce the "fantasy urges" that often trigger use (King and Ellinwood, 1997). Another strategy has been to target dopaminergic neurotransmitter system involved in the reward mechanism to interrupt the reinforcing action of these psychostimulants and thus reduce their use and prevent the relapse (Hyman and Nestler, 1995; Ling and Shoptaw, 1997; Mendelson and Mello, 1996). There is a clear evidence that methamphetamine dependence involves the dopaminergic system (McGregor and Roberts, 1994). Many studies confirm that methamphetamine increases the concentration of dopamine in the synaptic cleft (Zetterstrom *et al*., 1988; Hernandez *et al.,* 1989; Kuczenski and Segal, 1989; Robinson *et al.*, 1990; Yamamoto and Pehek, 1990) and that withdrawal from methamphetamine is associated with decreases in extracellular dopamine (Imperato *et al*., 1992; Rossetti *et al*., 1992). Dopamine antagonists interfere with self-administration of methamphetamine (Risner and Jones, 1976; Davis and Smith, 1974; Yokel and Wise, 1975) but these agents can augment withdrawal symptoms such as anergy, anhedonia and depression (Gawin, 1991). Indeed, aversive effects have been reported for dopamine receptor antagonists, and their usefulness in treating cocaine addiction has been limited (Shippenberg *et al*., 1987, 1991). Conceptually, restoring levels of dopamine (by increasing dopamine release, preventing uptake or slowing degradation after release) to pre-dependence levels will help methamphetamine abusers to initiate and/or maintain abstinence, to alleviate withdrawal symptoms, and prevent relapse (Johnson and Vocci, 1993).

Multiple compounds have been tested in proof of concept trials for stimulant addiction including marketed medications as well as new molecular entities. Five marketed medications have shown positive signal so far these are, modafinil (Dackis *et al*., 2005), topiramate (Kampman *et al*., 2005), disulfiram (Carroll *et al*., 2004), ondansteron (Johnson *et al*., in press), and bupropion (Elkashef *et al*., 2006). These medications are currently being pursued in large confirmatory studies. For a thorough review of the data and a summary of the compounds tested please see review (Vocci and Elkashef, 2005).

Conceptual Support for Noradrenergic Agents as a Methamphetamine Medication. For a long time, cocaine and methamphetamine were generally considered to exert their locomotor and rewarding effects exclusively through an increased dopaminergic transmission in the nucleus accumbens; therefore, much attention has been paid to the alterations in the regulation of DAT and DA receptors as a result of long-term exposure to these stimulants. Far less attention has been paid, however, to the role of noradrenergic systems as mediators of the acute and chronic actions of cocaine and methamphetamine, although cocaine accumulates in high concentrations in NE-rich brain regions of non-human primates, such as locus coeruleus, hippocampus and amygdala (Madras and Kaufman, 1994) and dose dependently increases extracellular NE in the rat hippocampus, prefrontal cortex and nucleus accumbens (Florin *et al.,* 1994; Li *et al.,* 1996) while single administration of amphetamine induces a long-lasting (up to 22 days) increase (up to 165%) of evoked NE release in rats (Schmidt *et al*., 2001). The recently reported interactions

between central noradrenergic and dopaminergic systems (adrenergic excitation of DA neurons or adrenergic potentiation of central dopaminergic neurotransmission) also implicate noradrenergic transmission in the behavioral effects of *d*-amphetamine (Darracq *et al*., 1998; Auclair *et al.,* 2002). This cross-talk between noradrenergic and dopaminergic neurons takes place at the level of alpha 1b-adrenergic receptors (alpha-1bAR). Brain alpha-1bAR are physiologically stimulated by NE and are critically involved in mediation of the noradrenergic influence on active behavior (locomotor activity) (Stone *et al.,* 2001a). They play an important role in cardiac development and/or function, as well as in blood pressure response to alpha(1)-agonists via vasoconstriction, and appear to be involved in CNS processes such as nociceptive responses, modulation of memory consolidation and working memory (Tanoue *et al*., 2002). Central alpha-1bAR are also important for locomotor and rewarding activities of stimulants, and locomotor hyperactivity and rewarding effects induced by *d*-amphetamine (1-3 mg/kg), cocaine (5-20 mg/kg) or morphine (5-10 mg/kg) are dramatically decreased in mice lacking alpha-1bAR (alpha-1bAR KO) (Drouin *et al.,* 2002). Auclair and colleagues convincingly proved the presence of a coupling between noradrenergic and dopaminergic neurons through the stimulation of alpha-1bAR (Auclair *et al.,* 2002). Thus, blunted locomotor responses to *d*-amphetamine in alpha-1bAR KO mice are correlated with an absence of *d*-amphetamine-induced increase in extracellular dopamine in the nucleus accumbens, the fact that a) points to critical role of alpha-1bAR and noradrenergic transmission in the vulnerability to addiction, and b) suggests that alpha-1bAR may be important therapeutic target in addiction (Auclair *et al.*, 2002).

This study will investigate modafinil, a putative agonist of alpha-1bAR (Stone *et al.,* 2001a, b; Stone *et al.,* 2002), as a potential medication to treat methamphetamine dependence.

4.4 Rationale for Studying Modafinil

Modafinil (Provigil®), 2-[(diphenylmethyl)sulfinyl]acetamide, is a novel non-amphetamine psychostimulant approved by the FDA for the treatment of narcolepsy, a sleep disorder characterized by uncontrollable sleepiness and frequent daytime sleep, and idiopathic hypersomnia. Modafinil has been found to increase wakefulness, alertness and vigilance (i.e., the ability to stay on task, thinking clearly and functioning normally) but, unlike prototypic psychostimulants, it has low propensity for euphoria, jitteriness, anxiety, excessive locomotor activity, hypertension and tachycardia at therapeutic doses (Bastuji *et al.,* 1998). Modafinil is a memory improving and mood-brightening psychostimulant, which is currently under study for the treatment of attention deficit hyperactivity disorder (ADHD), cognitive deficits in Alzheimer's disease and negative symptoms in schizophrenia. It is as effective as traditional dopamine-acting stimulants for treatment of narcolepsy (Roth and Roehrs,1996; Fry, 1998; Green and Stillman, 1998), but its pharmacological profile is notably different from the amphetamines, cocaine or methylphenidate.

Modafinil acts as a putative agonist of brain alpha-1bAR (Stone *et al.,* 2001a, b; 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 DAT (Mignoet *et al.,* 1994) and causes an increase in extracellular dopamine levels but does not stimulate dopamine release *in vitro* (DeSereville *et al.,*1994; Simon *et al*.,1995; PDR, 2006). 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 animals (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 the mechanisms underlying the modafinil-induced stimulant locomotor effect differ from those of amphetamine (Simon *et al.,*1995).

Using 2-deoxyglucose autoradiography of the rat brain, Engber and colleagues (1998) compared regional brain metabolic activity induced by amphetamine and modafinil. Both modafinil and amphetamine increase glucose utilization in all subregions of the hippocampus (subiculum, CA1-CA3 and dentate gyrus) and in the centrolateral nucleus of the thalamus; modafinil, but not amphetamine, increased glucose metabolism in the central nucleus of the amygdala. Amphetamine, but not modafinil, increased metabolic activity in the basal ganglia, frontal cortex, nucleus accumbens, ventral tegmental area and pontine reticular field. The same pattern of metabolic activity was found in the cat brain where, at equivalent wake-promoting doses, amphetamine or methylphenidate, but not modafinil activate basal ganglia, nucleus accumbens and cortical regions as measured by increases in *c-fos* expression (Lin *et al*.,1996).

Modafinil has demonstrated the ability to inhibit the release of GABA in the median preoptic area and in the posterior hypothalamus in rats (Ferraro *et al.,* 1996b). 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.,* 1996a,1997a). More significant is modafinil's ability to increase excitatory glutamatergic transmission (Ferraro *et al.,* 1997b); 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 this 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-substance abusing human volunteers (Warot *et al.,* 1993). The results of a human study that evaluated abuse potential of modafinil using methylphenidate as a reference in polysubstance abusers with a history of cocaine abuse indicate 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 response 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 that 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). Thus, in the first case, treatment with modafinil in an outpatient setting to detoxify a male with a history of polysubstance abuse, including psychostimulants, led to a decrease in patient's craving for amphetamine. The patient admitted taking a higher than prescribed dose of modafinil on one occasion, but he felt that this single excessive use did not produce euphoria. The second case was a female nurse with a history of hospitalizations for amphetamine-related psychosis that was treated with modafinil to improve alertness and concentration. Although being on modafinil for several weeks, she denied using it in doses of over 200 mg/day and did not use it with stimulants or alcohol. When asked to classify modafinil in relation to euphoric effects of other stimulants, she replied that 'modafinil is not as good as dextroamphetamine, amphetamine, methylphenidate, phentermine and is not as good as pimoline either'. In the third case, a male with ADHD and a history of abuse of methylphenidate, amphetamine and cocaine, was treated with Wellbutrin with

little success. Modafinil was added and the dose was increased to 200 mg/day over the first 2 weeks. This patient continued to take modafinil for several months without difficulty or abuse reported. The fourth case is that of a male cocaine abuser who was given modafinil for the treatment of ADHD. Modafinil was effective in improving the patient's cognitive problems and blunted the craving for and use of cocaine. Again, there was no indication of use of modafinil with other stimulants or alcohol, or of excessive use of modafinil in this patient. All in all, 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; Malcolm *et al.,* 2002; 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).

Modafinil reduces the neurotoxic effects of excessive glutamate in cultured cortical neurons (Antonelli *et al.,* 1998) and demonstrates a neuroprotective effect in animal studies (Aguirre *et al.,* 1999; Jenner *et al.,* 2000). Thus, co-administration of modafinil with nigrostriatal damage inducing agent 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) restores to normal the number of neurons in mouse substantia nigra (Aguirre *et al.,* 1999). Modafinil is also reported to reverse motor disability in MPTP-treated common marmosets and to prevent MPTP-induced nigral cell death in this species (Jenner *et al.,* 2000).

Modafinil demonstrated working memory-enhancing effect in mice (Beracochea *et al.,* 2001). In healthy human volunteers, modafinil demonstrated cognitive enhancing effects in the tests of digital span, visual pattern recognition memory, spatial planning and stop-signal reaction time (Turner *et al.,* 2002). Modafinil improved cognitive deficits in patients with alcoholic organic brain syndrome (Saletu *et al.,* 1990).

In animal studies, modafinil administration, in contrast to dexamphetamine, is not associated with an increase in anxiety (Simon *et al.,* 1994). Moreover, modafinil may have clinically important antidepressant properties and appears to act as an augmenter of antidepressants, especially in patients with treatment-resistant depression (Menza *et al*., 2000). Thus, in patients with DSM-IV depression (4 with major and 3 with bipolar depression), it augmented a partial response (residual tiredness and fatigue) or non-response to antidepressant (HAM-D assessment) with all 7 patients achieving full or partial remission within 1 to 2 weeks of treatment with modafinil at doses of 100 to 200 mg/day. Modafinil is also reported to enhance mood in patients with myotonic dystrophy (MacDonald *et al.,* 2002). Thus, Profile of Mood States assessment of patients treated with modafinil for 2 weeks indicates a decrease in total mood disturbance scores and enhanced quality-of-life measures of energy and health change.

In summary, the rationale for studying modafinil as a potential medication to treat methamphetamine dependence is based on several mechanisms. First of all, modafinil may act as a weak substitutive stimulant, providing mild reinforcement and thus decreasing craving and methamphetamine seeking. Modafinil is of particular interest in this regard because it has low abuse potential and does not seem to produce sensitization or tolerance. Secondly, modafinil may be useful for treatment of methamphetamine dependence in an indirect way by improving concentration, daytime alertness and cognitive functions of methamphetamine-dependent subjects and thus allowing them to benefit from CBT and other treatment compliance-enhancing forms of psychosocial therapy. The antidepressant properties of modafinil may contribute to the amelioration of dysphoria that often accompanies early abstinence and thus may promote both sustenance of abstinence and greater engagement in psychosocial therapy. The effects of modafinil are long-lasting and persist for as long as 4 months after treatment and thus contribute to consolidation of abstinence and prevention of relapse to methamphetamine use (Prescribe Int, 1999). Importantly, the results of recently conducted phase 2 clinical trial point to a possible efficacy of modafinil in reducing cocaine use (see section 4.5.2).

4.5 Previous Human Experience with Modafinil

4.5.1 Clinical Trials for the Treatment of Pathological Somnolence

Modafinil was extensively studied for the treatment of pathological somnolence in patients with excessive daytime sleepiness (EDS) associated with narcolepsy. The results of two multicenter, randomized, placebo-controlled trials indicate efficacy of modafinil in the treatment of patients with narcolepsy (Fry, 1998; US Modafinil in Narcolepsy Multicenter Study Group, 1998, 2000). Thus, treatment with modafinil (200 mg and 400 mg daily for 9 weeks) effectively reduced daytime sleepiness in patients with narcolepsy with significant improvement in all subjective and objective measures of sleepiness; more improvement, as recorded on CGI scale, was seen in the modafinil than in the placebo group at all time points ($p<0.001$). Modafinil taken once daily was well-tolerated, with headache being the only AE to occur significantly more often in modafinil treatment group ($p<0.05$).

Modafinil has been shown to be effective and well-tolerated for treating EDS associated with narcolepsy in two open-label extension studies that enrolled patients who had completed one of the two 9-week, double-blind, placebo-controlled, multicenter clinical trials of modafinil (Mitler *et al*., 2000). The results of these 40-week long trials of modafinil (400 mg daily) indicate that the most common treatment-related AEs were headache (13%), nervousness (8%) and nausea (5%), most of which were mild to moderate in nature.

Modafinil seems to have a potential in the treatment of increased daytime sleepiness in patients with Parkinson's disease (Hogl *et al.,* 2002).

4.5.2 Clinical Trials in Cocaine Dependent Populations

In an open-label pilot study, 17 cocaine-dependent subjects were treated with 100 mg modafinil b.i.d. (N=10) or 200 mg modafinil b.i.d. (N=7) in conjunction with twice weekly CBT sessions for 8 weeks (C. Dackis, 2002, Published). The results of this study showed a trend towards

reduction in cocaine use (based on urine toxicology) with average abstinence of 47% and thus suggest a possible efficacy of modafinil in reducing cocaine use. The average treatment retention (measured by attendance of CBT sessions) was 76%. This was followed up by a phase II proof of concept study (n=70) (Dackis *et al* , 2005) which showed significant effect for modafinil vs. placebo in percent clean urine, this effect was observed form week 1 and continued throughout the treatment period of the study.

A phase 1, randomized, double-blind, placebo-controlled, crossover design study to investigate a possible interaction between modafinil and cocaine has been recently conducted at the University of Pennsylvania/Philadelphia VAMC (Dackis *et al.,* 2003). This study evaluated the potential of interaction between the cardiovascular effects of a single dose of cocaine (30 mg) administered by the intravenous route and oral doses of modafinil (200 mg and 400 mg) in 10 adult cocaine experienced volunteers (all male) using several drug-effect questionnaires, performance measures and physiological indices. The results of this study indicate that pretreatment with modafinil did not intensify cocaine euphoria or cocaine-induced craving (assessed by VAS, ARCI and Subjective Symptom Checklist). In fact, cocaine euphoria was significantly blunted in one of the subjective measures (ARCI Amphetamine Scale) ($p=0.02$), and this cocaine-euphoria blunting effect of modafinil may have significant clinical value. Three subjects dropped out of the study; one completed the baseline cocaine infusion and opted out of the study due to anxiety during the infusion, while the other two dropped out because of their reluctance to remain in the hospital for the required number of days.

Another phase 1 study to investigate a possible interaction between modafinil and cocaine has been recently completed at the Medical University of South Carolina (MUSC) Treatment Research Center (R. Malcolm, 2003, Personal communication). This study evaluated the potential of interaction between the two doses of cocaine (20 and 40 mg) administered by the intravenous route and oral doses of modafinil (200 mg and 400 mg) in 12 adult cocaine experienced volunteers (6 males and 6 females) using VAS measures and cardiovascular parameters (SBP, DBP and HR). Evaluation of the mean effects of modafinil (400 and 800 mg daily) interactions with cocaine (20 or 40 mg i.v.) using VAS assessment indicates that modafinil significantly dampened all three VAS measures ("any drug effect", cocaine "high", "worth of cocaine in dollars") as compared to baseline cocaine only condition. For cocaine "high" measure, modafinil reduced VAS by about 45% for the 20 mg cocaine condition and about 35% for the 40 mg cocaine condition, which may have a significant clinical value. Across all VAS measures and both doses of cocaine, the 800 mg dose of modafinil did not add significantly to this blunting effect as compared to the 400 mg dose of modafinil. Thus, the results of this study indicate that pretreatment with modafinil blunts cocaine euphoria and cocaine-induced craving (assessed by VAS). The analysis of safety data indicates that modafinil did not exacerbate the effects of cocaine on blood pressure and heart rate and statistical analysis indicates that an 800 mg daily dose of modafinil may even have some mild protective effect on SBP and HR by attenuating the elevation in these parameters that follows cocaine use.

Behavioral and physiological effects of modafinil have been recently studied in subjects (N=9) with recent histories of cocaine abuse (i.e., positive urine for cocaine or BE during the initial screening) and compared to those of cocaine and placebo (Rush *et al.,* 2002). The effects of single oral doses of modafinil (200, 400 and 600 mg), cocaine (100, 200 and 300 mg) and

placebo were assessed with a battery of self-reported drug-effect questionnaires, performance measures and physiological indices. The results of this study suggest that modafinil has minimal abuse potential because, unlike cocaine, modafinil did not produce stimulant-like self-reported drug effects (e.g., increased ratings of High and Stimulated on Drug-Effect Questionnaire).

A double-blind, placebo-controlled crossover study was conducted in male volunteers with a history of polysubstance abuse that included cocaine to compare the pharmacodynamic profiles and abuse potential of modafinil and methylphenidate (Jasinski, 2000). Each subject (N=24) was given single oral doses of methylphenidate (45 mg or 90 mg), modafinil (200 mg, 400 mg or 800 mg) and placebo. The results of this study indicate that, unlike methylphenidate, modafinil did not induce a significant response on the Amphetamine Scale of Addiction Research Center Inventory and showed greater inhibition of observed and reported sleep, less facilitation of orthostatic tachycardia and less reduction of caloric intake.

4.5.3 Clinical Trials for the Evaluation of Pharmacokinetics, Tolerability and Interactions with Dextroamphetamine and Methylphenidate

The results of a double-blind, placebo-controlled, ascending dose evaluation study of the pharmacokinetics and tolerability of modafinil in healthy human volunteers (N=8; 6 modafinil, 2 placebo) indicate that 200 mg, 400 mg and 600 mg doses of modafinil administered orally once daily for 7 days are well-tolerated while 800 mg dose panel was discontinued after 3 days of treatment due to the clinically significant cardiovascular changes, e.g., sustained increased blood pressure and pulse rate (Wong *et al.,* 1999). The subject's blood pressure and pulse rate returned to normal levels 2 days after discontinuation of modafinil. The safety data from this study suggest that the maximum tolerable single daily oral modafinil dose, without titration, may be 600 mg (Wong *et al.,* 1999).

Studies to examine the potential for modafinil interactions with dextroamphetamine (Hellriegel *et al*., 2002) and methylphenidate (Hellriegel *et al*., 2001) have been conducted and did not reveal substantial or clinically significant interactions. Thus, the potential of drug-drug interaction between modafinil and dextroamphetamine, each at steady state, was investigated in an open-label study in 32 healthy volunteers (Hellriegel *et al*., 2002). All subjects received modafinil orally once daily for 28 days (200 mg on days 1-7, 400 mg on days 8-28); on days 22 to 28, half of the subjects also received dextroamphetamine (20 mg) orally 7 hours after modafinil. The results of this study indicate that administration of low-dose dextroamphetamine in this dosing regimen does not alter the steady-state PK of modafinil and that this drug combination has the same tolerability profile as modafinil alone. Also, AEs in the two groups were similar and mild or moderate in nature.

An analogous study was conducted with methylphenidate. Thus, the potential of drug-drug interaction between modafinil and methylphenidate, each at steady state, was investigated in an open-label study in 32 healthy volunteers (Hellriegel *et al*., 2001). All subjects received modafinil orally once daily for 28 days (200 mg on days 1-7, 400 mg on days 8-28); on days 22 to 28, half of the subjects also received methylphenidate (20 mg) orally 8 hours after their modafinil dose. The results of this study indicate that administration of low-dose

methylphenidate in this dosing regimen does not alter the steady-state PK of modafinil and that this drug combination has the same tolerability profile as modafinil alone. Also, AEs in the two groups were similar and mild or moderate in nature.

Headache and insomnia were the most commonly reported AEs in these two modafinil interactions studies (Hellriegel *et al*., 2001, 2002). Overall, modafinil-emergent AEs were similar in type and severity to those previously reported for patients with narcolepsy in large-scale, placebo-controlled clinical trials (US Modafinil in Narcolepsy Multicenter Study Group, 1998, 2000). All modafinil plus methylphenidate-emergent AEs (Hellriegel *et al*., 2001) and modafinil plus dextroamphetamine-emergent AEs (Hellriegel *et al*., 2002) in patients receiving combination treatment were mild in intensity and all of these AEs were considered unrelated or unlikely to be related to study medication. Modafinil plus methylphenidate and modafinil plus dextroamphetamine were generally well-tolerated (Hellriegel *et al*., 2001, 2002). The incidence of modafinil plus methylphenidate-emergent insomnia appeared to be slightly greater in subjects receiving combination treatment compared with subjects receiving modafinil alone (4 *versus* 1) (Hellriegel *et al*., 2001). The dose of methylphenidate used in this study (20 mg) is below the usual daily doses required for optimal therapeutic response in patients with narcolepsy. This relatively low dose of methylphenidate may be useful, when used in combination with modafinil, for augmenting short-term wakefulness, without the occurrence of problems commonly associated with higher doses of CNS stimulants.

4.5.4 Modafinil/Methamphetamine Phase I Safety and Interaction Study

At NIDA's request, a double-blind, placebo-controlled study of the interaction of modafinil and methamphetamine was recently completed (Jones RT, Mendelson J, personal communication, 2006). Sixteen subjects, ages 18 through 40, were randomized to modafinil or placebo and successfully completed the protocol. Each subject received one dose of modafinil 200 mg/day or matched placebo orally and, if tolerated, advanced to 400 mg/day over the course of seven days. After the 6th dose of modafinil 400 mg, the subjects were admitted to the inpatient study unit for intravenous administration of two 15 mg doses of methamphetamine one hour apart, during which intensive hemodynamic and electrocardiographic monitoring were conducted. In addition to standard measures of vital signs, impedance cardiography was performed to estimate stroke volume. The psychological effects of the combination of methamphetamine with modafinil or placebo were also assessed by VAS scores.

Modafinil was well-tolerated. No subject asked to leave the experiment because of the effects of modafinil.

Modafinil produced a mild statistically significant increase in mean systolic blood pressure compared to the pre-dose condition (130.29 vs 115.43 mmHg, p-value= 0.031). Mean heart rate increased from 61.57 pre-dosing to 70 beats per minute on modafinil (p=0.22). There were no significant changes in diastolic pressure on modafinil compared to baseline (74.43 vs 70.0 mmHg, p=0.44). As assessed by impedance cardiography, stroke volume was unchanged within the group that received modafinil. Mean stroke volume in the group who received placebo was higher in both the pre-dose and post- dose conditions, compared to the mean for the modafinil treatment group.

There was no significant effect of modafinil on the peak cardiovascular changes during the eight hours following intravenous methamphetamine. No clinically abnormal ECGs were recorded in any conditions.

Subject Reported Subjective Drug Effects

VAS scores were reported for Any Drug Effect, Good Drug Effect, Bad Drug Effect, Nervousness, and Tolerable before and after MA infusion for prior to modafinil, and after modafinil or placebo. Compared to the pre-treatment condition, the self-reports indicate virtually no drug effect on VAS scores by modafinil treatment before the MA infusion. Subjective reports of Any Drug Effect and Good Drug Effect occurred following the methamphetamine dose. The drug effect reports from both the modafinil treated and the placebo treated groups are of virtually identical magnitude after methamphetamine, indicating that the seven days exposure to modafinil neither enhanced nor diminished the subjective effects of intravenous MA.

Adverse Events

Two subjects were dropped from participation as a result of cardiovascular changes after the initial methamphetamine infusion, prior to any dosing with modafinil. One subject experienced tachycardia and orthostatic hypotension, and the other experienced transient hypertension after receiving methamphetamine 30 mg. They recovered uneventfully and were discharged. These subjects' data are not included in the results summarized above. One additional subject decided to leave the study after receiving two doses of modafinil. He offered no explanation for withdrawing but denied experiencing adverse events from the two doses of modafinil he had received (Subject 5031). He was replaced and his data was not included in the analysis.

Three subjects experienced adverse events considered to be related to modafinil. These were dizziness, transient nausea, nervousness and mild headache after each modafinil 400 mg dose (Subject 5023); hand tremor, insomnia, mild generalized headache, jitteriness, racing thoughts and tension after starting modafinil 400mg (Subject 5025); and mild generalized headache beginning after modafinil 400 mg daily and continuing intermittently during the dosing period (Subject 6007). All subjects considered these symptoms to be mild, transient, and tolerable.

Two subjects experienced adverse events deemed to be non-study related. These were: tinea capitis (ringworm) treated with application of clotrimazole to the affected areas (Subject 5015); and low-grade fever, and mild frontal headaches which began one week after the last study dose and were reported during the follow-up period (Subject 5031).

Conclusions

Modafinil, given as an oral dose of 200 mg followed by 400 mg daily for 6 days, does not alter the effects of intravenous methamphetamine (30mg) as measured by cardiovascular indices (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, ECG (including QTc interval measures), impedance cardiography indices of stroke volume or subjective reports

of methamphetamine's effects (any drug effect, good drug effect, bad drug effect, nervousness, tolerable).

Slight elevation of preinfusion blood pressure and heart rate in the group of subjects who had received modafinil for seven days is consistent with modafinil's reported cardiovascular effects. However, the magnitude and time course of blood pressure and heart rate increases after intravenous methamphetamine administration were not altered by modafinil. Modafinil also did not significantly alter the subjective effects of methamphetamine.

4.6 Modafinil Pharmacokinetics

Modafinil is a racemic compound. Its chemical name is 2-[(diphenylmethyl)sulfinyl]acetamide, chemical formula is $C_{15}H_{15}NO_2S$ and the molecular weight is 273.36. Modafinil enantiomers have different pharmacokinetics (PK), e.g., the half-life of *l*-isomer is approximately three times that of the *d*-isomer in humans (PDR, 2006; Robertson and Hellriegel, 2003). The enantiomers do not interconvert. At steady state, total exposure to the *l*-isomer is approximately three times that for the *d*-isomer. The trough concentration of circulating modafinil after once daily dosing consists of 90% of the *l*-isomer and 10% of the *d*-isomer. The effective elimination half-life of modafinil after multiple doses is about 15 hours. The enantiomers exhibit linear kinetics upon multiple dosing of 200-600 mg/day once daily in healthy volunteers. Apparent steady states of total modafinil and *l*-(-)-modafinil are reached after 2-4 days of dosing (Wong *et al*., 1999; Robertson and Hellriegel, 2003). Modafinil pharmacokinetics are dose-independent between 200 and 600 mg/day doses (Robertson and Hellriegel, 2003).

Modafinil is rapidly absorbed after oral administration with peak plasma concentrations occurring at 2-4 hours (PDR, 2006). The bioavailability of modafinil tablets is approximately equal to that of an aqueous suspension. The absolute oral bioavailability was not determined because of modafinil's water insolubility (<1 mg/mL), which precludes intravenous administration. Water insolubility of modafinil and its instability at temperatures higher than 180^{o}C reduce the potential for its abuse via intravenous injection and smoking, respectively (Jasinski and Kovacevic-Ristanovic, 2000).

4.7 Modafinil Metabolism

About 90% of modafinil is metabolized by the liver with subsequent renal elimination of the metabolites. Less than 10% of the dose is excreted as unchanged parent compound. Metabolism occurs largely through hydrolytic deamidation with lesser contributions from cytochrome P450 (CYP)-mediated oxidative pathways, CYP3A4 in particular (PDR, 2006; Robertson and Hellriegel, 2003). Due to the involvement of CYP3A4 in metabolism of modafinil, coadministration of potent inducers of CYP3A4 (e.g., carbamazepine, phenobarbital, rifampin) or inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole) could alter the levels of modafinil. The largest fraction of modafinil in urine is modafinil acid, but at least six other metabolites are present in lower concentrations. Only two metabolites reach appreciable concentrations in plasma, i.e., modafinil acid and modafinil sulfone. In preclinical studies, the metabolites were inactive and did not appear to mediate the arousal effects of the parent molecule. In patients who are renally or hepatically compromised, the elimination processes can

be slowed, and in a similar manner (although to a lesser extent), elimination in the elderly may be reduced due to normal effects of aging.

As modafinil may be administered with other medications, the potential for metabolic drug-drug interactions has been examined both *in vitro* and *in vivo* (Robertson *et al.,* 2000; Robertson and Hellriegel, 2003). *In vitro*, modafinil was observed to produce a reversible inhibition of CYP2C19 in human liver microsomes; no irreversible inhibition of any CYP enzyme was observed and there was no evidence of metabolism-dependent inhibition (Robertson *et al.,* 2000). Modafinil itself does not appear to be a substrate for CYP2C19, and there are a relatively small number of marketed pharmaceutical products that are predominantly metabolized by this enzyme. Still, caution should be exercised when initiating therapy with modafinil in patients that receive *S*-mephenytoin, omeprazole, lansoprazole, proguanil, diazepam or propranolol, which serve as substrates for CYP2C19.

Modafinil also caused a small, but concentration-dependent induction of CYP1A2, CYP2B6 and CYP3A4 activities and suppression of CYP2C9 activity in primary cultures of human hepatocytes (Robertson *et al.,* 2000). Of the three CYP450 enzymes inducible by modafinil, only CYP3A4 plays a substantial role in the metabolism of a vast range of pharmaceutical products, including cyclosporine A, triazolam and steroidal contraceptives containing ethinyl estradiol. One case of an interaction between modafinil and cyclosporine A has been reported in a 41-year old woman who had undergone an organ transplant (PDR, 2006). After one month of administration of 200 mg/day of modafinil, her blood levels of cyclosporine A were decreased by 50%. This interaction was postulated to be due to the increased metabolism of cyclosporine A, since no other factor expected to affect the disposition of cyclosporine A has changed. Clinical studies conducted to examine the potential for modafinil interactions with ethinyl estradiol and triazolam indicate that modafinil induces CYP3A4 activity in humans *in vivo* and point to a possibility of metabolic drug-drug interactions between modafinil and substrates of CYP3A4 (Robertson *et al.,* 2002b). The possibility of interaction is higher for triazolam as the modafinil treatment group had a marked decrease in maximum observed plasma concentrations areas under the plasma-concentration-time curve for triazolam relative to placebo, with a much smaller decrease in these parameters for ethinyl estradiol; also, while the half-life of triazolam was decreased, the half-life of ethinyl estradiol did not seem to be affected. These data indicate that induction of CYP3A4 appears to be more gastrointestinal than hepatic in nature and therefore significant metabolic drug-drug interactions are most likely to occur with compounds (such as triazolam) that undergo significant gastrointestinal CYP3A4-mediated first-pass metabolism.

Finally, the apparent suppression of CYP2C9 activity in human hepatocytes by treatment with modafinil (Robertson *et al.,* 2000) is potentially important for only one compound, warfarin (Coumadin), which has a narrow therapeutic index and whose more active enantiomer (*S*-warfarin) is primarily metabolized by CYP2C9. Clinical studies conducted to examine the potential for modafinil interactions with warfarin (Robertson *et al.,* 2002a) indicate that treatment with modafinil does not significantly alter the PK of warfarin compared to placebo; however, limitations arising from this study of single doses of warfarin preclude conclusions about the potential for more subtle interactions after chronic warfarin administration. Thus,

caution should be exercised when initiating therapy with modafinil in patients who are at steady-state warfarin.

4.8 Modafinil Dose Justification

The safety data from a double-blind, placebo-controlled, ascending dose evaluation study of the pharmacokinetics and tolerability of modafinil in healthy human volunteers (200 mg, 400 mg, 600 mg or 800 mg doses administered orally once daily for 7 days) suggest that the maximum tolerable single daily oral modafinil dose, without titration, may be 600 mg (Wong *et al.,* 1999).

The 200 mg and 400 mg daily doses of modafinil to be used in this study are commonly prescribed as a single morning dose in clinical practice for the treatment of narcolepsy-related EDS (PDR, 2006). The effectiveness and tolerability of these doses were previously established in the large-scale, placebo-controlled, double-blind, clinical studies involving patients with narcolepsy (US Modafinil in Narcolepsy Multicenter Study Group, 1998, 2000). These doses of modafinil were shown to be well tolerated, without disturbing nighttime sleep and without evidence of physical dependence. Both doses appear to retain efficacy over long-term treatment, without the development of tolerance (Besset *et al*., 1996; Mitler *et al.,* 2000).

Doses of modafinil proposed in this study (200 mg and 400 mg daily) were used for 8 weeks in an open-label pilot study conducted in cocaine dependent subjects in the outpatient setting at the University of Pennsylvania Treatment Research Center (C. Dackis, 2002, Personal communication).

In the previously cited human laboratory study (R. Malcolm, 2003, Personal communication), modafinil at 400 mg and 800 mg daily did not exacerbate the effects of cocaine on BP and HR.

4.9 Safety of Modafinil

4.9.1 Expected Adverse Events

Modafinil is a wakefulness-promoting agent for oral administration. It has been available in France for the treatment of narcolepsy and idiopathic hypersomnia since 1994 and was approved by FDA for the same indications in 1999. The safety profile of modafinil is well-established. Modafinil has been evaluated for safety in over 2200 subjects; 900 were patients with narcolepsy and the remainder were normal controls. The most commonly reported adverse events (AEs) (>5% of the time) associated with the use of modafinil are mild, usually resolve after a few weeks of treatment and include:

- Headache
- Nervousness
- Nausea
- Anxiety
- Insomnia

In general, modafinil has been used in single or divided doses of 200-400 mg/day. At these doses, modafinil consistently has demonstrated less sympathomimetic side effects, less tolerance,

and less negative effects on nighttime sleep than traditional stimulant medications. Modafinil is well-tolerated, and in many clinical studies, only headache occurs significantly more often in the active treatment group versus placebo.

In a Canadian clinical trial, a 35-year-old, obese narcoleptic male with a prior history of syncopal episodes experienced a 9-second episode of asystole after 27 days of modafinil administration (150 mg twice a day) (PDR, 2006). Three individuals with mitral valve prolapse and/or left ventricular hypertrophy developed chest pain, palpitations, shortness of breath, and transient ischemic T-wave alterations on electrocardiograms. One healthy male volunteer (non-patient) reported sleep deprivation and developed ideas of reference, paranoid delusions, and auditory hallucinations in association with multiple daily 600 mg doses of modafinil; psychosis was completely eliminated 36 hours after modafinil discontinuation. The safety data from a study of modafinil in patients with mild to moderate obstructive sleep apnea syndrome indicate that modafinil did not raise blood pressure or pulse, although most patients were obese with mild hypertension (Heitmann *et al*., 1999). Adverse events were mild with the exception of one case of supraventricular tachycardia, which resolved with medication cessation.

Clinical chemistry, hematology and urinalysis parameters were monitored in US phase 1, 2 and 3 studies of modafinil (PDR, 2006). In these studies, mean plasma levels of gamma-glutamyl transferase (GGT) were found to be higher following administration of modafinil, but not placebo; however, few subjects (1%) had GGT elevations outside of the normal range. Shift to higher but not clinically significantly abnormal GGT values appeared to increase with time in the population treated with modafinil in the 9-week US phase 3 clinical trials. No differences were apparent in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total protein, albumin or bilirubin.

Clinical cases of modafinil overdose have been described with ingested modafinil doses as high as 4.5 gm (PDR, 2006). Doses of 4.0 gm and 4.5 gm were taken intentionally (suicide attempts) by two patients participating in foreign depression studies. In both cases, the AEs observed were limited, expected and not life-threatening, and the patients recovered fully by the next day. The AEs included excitation or agitation, insomnia, and slight or moderate elevations in hemodynamic parameters. In neither of these cases nor in other instances of doses of more than1 gm/day, including experience with up to 21 consecutive days of dosing at 1.2 gm/day, were any unexpected effects or organ toxicities observed. Other observed high dose effects in clinical studies have included anxiety, irritability, aggressiveness, confusion, nervousness, tremor, palpitations, sleep disturbances, nausea, diarrhea and decreased prothrombin time (PDR, 2006). The treatment of overdose is symptomatic as there is no specific antidote and should include cardiovascular monitoring.

4.9.2 Safety of Modafinil for Children with ADHD in Other Dose Strengths

Cephalon, the makers of modafinil, filed an NDA in 2005 for oral modafinil for a new indication of treatment of ADHD in the children ages 6-17, and a revised product formulation (Sparlon oral tablets 85, 170, 255, 340, 425 mg). In three phase 3 trials, in which efficacy for ADHD was demonstrated, there were three subjects who dropped out of the study for the development of severe skin rashes. No subjects on placebo developed skin rashes. A 7 year old receiving 340

mg/day developed a generalized blistering rash which also involved the mucous membranes (Stevens-Johnson syndrome). Another 7 year old receiving 340 mg/day also experience a generalized non-desquamating rash (erythema multiforme) which cleared with antihistamines, steroids and stopping modafinil. The rash reappeared after restarting modafinil. A 9 year old receiving 340 mg/day developed generalized urticaria, facial edema, vomiting and fever, followed by elevation of liver enzymes. In addition there were two subjects in phase 2 trials who received 100 or 200 mg/day who dropped out because of severe rash. An 11 year old developed a generalized morbiliform rash without extension to the mucous membranes (100 mg), and an 8 year old that developed a vesiculobullous rash on the face and lips (200/100 mg). Other subjects experienced rashes which were reportedly less severe. It is possible that the higher incidence of skin rashes in the pediatric population compared to the adult population is due to blood concentrations of the sulfone metabolite of modafinil that are 3 –fold or higher in children..

The FDA issued a non-approvable letter for this NDA in August 2006, and the sponsor has withdrawn the application.

4.9.3 Safety in Pregnant and Lactating Women

Modafinil is assigned pregnancy "Category C" labeling by FDA. Studies in animals have shown that modafinil at a dose of 200 mg/kg/day (10 times higher the maximum recommended daily human dose of 200 mg on a mg/m^2 basis), increases the chance of incomplete or slow development of bones in the fetus with increase in resorption, skeletal variations and hydronephrosis.

The effects of modafinil on labor and delivery in humans have not been systematically investigated. Seven normal births occurred in patients who received modafinil during pregnancy. One patient gave birth 3 weeks earlier than the expected range of delivery dates to a healthy male infant; another woman with a history of spontaneous abortions suffered a spontaneous abortion while being treated with modafinil (PDR, 2006). It is not known whether modafinil or its metabolites are excreted in human milk but caution should be exercised when modafinil is administered to a nursing woman (PDR, 2006).

4.9.4 Safety of Modafinil in Cocaine Using Populations

4.9.4.1 Data from Outpatient Studies

In a recently completed open-label pilot study, 17 cocaine-dependent subjects were treated with 100 mg modafinil b.i.d. (N=10) or 200 mg modafinil b.i.d. (N=7) in conjunction with twice weekly CBT sessions for 8 weeks (C. Dackis, 2002, Personal communication). There were no SAEs or unexpected AEs reported. The most frequent AEs were "difficulty with sleeping" and feelings of "feeling racy" that self resolved in 3-4 days with the exception of two cases when the dosage of modafinil had to be titrated down from 400 mg to 200 mg daily.

4.9.4.2 Data from Inpatient Studies

A phase 1, randomized, double-blind, placebo-controlled, crossover design study to investigate a possible interaction between modafinil and cocaine has been recently conducted at the University

of Pennsylvania/Philadelphia VAMC (Dackis *et al.*, 2003). This study evaluated the potential of interaction between the cardiovascular effects of a single dose of cocaine (30 mg i.v.) and oral modafinil (200 mg and 400 mg) in 10 adult cocaine experienced male volunteers. All subjects received an initial baseline cocaine infusion (30 mg i.v.) followed by 3 cocaine infusion sessions (30 mg i.v. each) performed after 4 days of treatment with low dose of modafinil (200 mg/day), high dose of modafinil (400 mg/day) or placebo. Low dose modafinil always preceded high dose modafinil for safety reasons, and four-day long administration was selected to achieve the steady state of modafinil. Cocaine infusions were performed 3 hours after oral modafinil or placebo administration to assess the interaction at the peak modafinil levels. Vital signs, e.g., systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and ECG were continuously monitored and recorded on the day of each cocaine infusion session. The results of this study indicate that co-administering modafinil and a single dose (30 mg) of cocaine i.v. is not associated with medical risks in terms of blood pressure, pulse, respiratory rate, temperature or ECG measures. Three subjects dropped out of the study; one completed the baseline infusion and opted out of the study due to anxiety during the infusion, while the other two dropped out because of their reluctance to remain in the hospital for the required number of days. Pretreatment with modafinil did not intensify cocaine euphoria or cocaine-induced craving (assessed by VAS, ARCI and Subjective Symptom Checklist). In fact, cocaine euphoria was significantly blunted in one of the subjective measures (ARCI Amphetamine scale) ($p=0.02$), and this cocaine-euphoria blunting effect of modafinil may have significant clinical value.

Another safety study has been recently conducted at the Medical University of South Carolina Treatment Research Center to evaluate the potential for interaction between the cardiovascular effects of cocaine administered by the intravenous route and oral modafinil in 12 adult, cocaine-experienced volunteers (R. Malcolm, 2003, Personal communication). In that study, subjects were treated with 200 mg modafinil b.i.d. for 7 days (days 8-14), then with 400 mg modafinil b.i.d. for another 7 days (days 15-21). A baseline cocaine challenge was done on days 6 and 7, by giving in random order either a saline or cocaine infusion; the 20mg cocaine dose was always given on the first day for safety reasons. After 5 days' administration of 200 mg modafinil b.i.d. (steady-state condition), all subjects were challenged with cocaine (20 or 40 mg i.v.) and placebo (saline) infusions on two consecutive days (days 13 and 14). Again, after 5 days' administration of 400 mg modafinil b.i.d., all subjects were challenged with cocaine (20 or 40 mg i.v.) and placebo on two consecutive days (days 20 and 21). Vital signs, i.e., SBP, DBP, and HR were frequently monitored and recorded during, and for 6 hours after, each infusion session. Table 1a presents the mean and standard deviation of the maximum absolute value of SBP, DBP, and HR reached after each cocaine or placebo infusion (with 0, 400, or 800mg of modafinil). By subtracting that day's shared baseline values of vital signs (not shown), the table also presents the ***maximum increase*** over baseline for each vital sign, after infusions of either cocaine or placebo (saline). Of great interest to us is the cocaine-induced change (elevation) in these hemodynamic measures, expressed by the difference between a vital sign's ***maximum increase*** after cocaine infusion and its ***maximum increase*** after saline. Table 1a shows that this difference must be equivalent to the difference between the maximum absolute value of a vital sign after that day's cocaine infusion and its maximum absolute value after placebo.

Table 1a. Average of 12 Subjects' Vital Sign Values (Mean ± Standard Deviation) for Each Infusion. (R. Malcolm, 2003, Personal Communication)

Study Day	Modafinil Dose	Infusion Dose	Maximum SBP	Maximum SBP Increase*	Maximum DBP	Maximum DBP Increase*	Maximum HR	Maximum HR Increase*
6	0mg	cocaine 20mg	149.92 ± 15.25	25.88 ± 15.96	85.75 ± 8.14	13.07 ± 6.31	97.42 ± 22.59	30.42 ± 17.77
		saline	136.25 ± 7.90	12.22 ± 15.05	81.83 ± 4.90	9.15 ± 11.79	85.58 ± 9.34	18.58 ± 13.93
7	0mg	cocaine 40mg	157.17 ± 18.64	35.39 ± 17.16	94.58 ± 6.16	23.91 ± 7.65	102.42 ± 20.14	35.00 ± 16.21
		saline	138.17 ± 14.29	16.39 ± 18.61	83.00 ± 8.64	12.33 ± 11.83	80.25 ± 9.76	12.83 ± 16.47
13	400mg	cocaine 20mg	144.17 ± 11.91	18.95 ± 8.22	86.58 ± 12.84	11.71 ± 8.25	92.58 ± 13.58	21.13 ± 13.09
		saline	140.50 ± 14.73	15.28 ± 14.84	82.17 ± 10.98	7.30 ± 8.38	85.67 ± 16.05	14.21 ± 21.52
14	400mg	cocaine 40mg	157.67 ± 12.64	34.20 ± 14.28	93.08 ± 12.54	19.00 ± 11.15	107.17 ± 16.17	37.54 ± 16.28
		saline	141.92 ± 8.43	18.45 ± 13.37	82.67 ± 9.36	8.58 ± 8.22	80.67 ± 9.32	11.04 ± 13.12
20	800mg	cocaine 20mg	148.67 ± 15.15	18.56 ± 14.11	87.58 ± 12.10	12.07 ± 10.07	92.25 ± 13.57	18.29 ± 14.72
		saline	143.25 ± 7.52	13.14 ± 14.34	81.92 ± 7.46	6.40 ± 9.84	82.00 ± 9.89	8.04 ± 16.69
21	800mg	cocaine 40mg	149.08 ± 6.83	19.25 ± 10.01	90.25 ± 9.86	12.30 ± 14.30	95.33 ± 13.94	19.50 ± 9.29
		saline	133.00 ± 8.72	3.17 ± 17.36	81.33 ± 11.18	3.38 ± 13.79	86.00 ± 14.30	10.17 ± 20.17

* Increase over baseline pre-infusion values (not shown)

Table 1b shows the calculated mean and standard deviation for each day's difference between the maximum absolute SBP, DBP, and HR after cocaine infusion and the maximum absolute SBP, DBP, and HR after saline infusion, as well as their statistical significance (*p*-values are from R. Malcolm, 2003, Personal communication).

Table 1b. Average of 12 Subjects' Changes in Hemodynamic Variables after Cocaine Infusion, with and without Modafinil. (R. Malcolm, 2003, Personal Communication)

Study Day	Modafinil Dose	Cocaine Dose	Maximum SBP (cocaine) – Maximum SBP (saline)	Maximum DBP (cocaine) – Maximum DBP (saline)	Maximum HR (cocaine) – Maximum HR (saline)
6	0mg	20mg	13.67 ± 16.41*	3.92 ± 9.36	11.83 ± 26.87‡
7	0mg	40mg	19.00 ± 18.08*	11.58 ± 10.97*	22.17 ± 23.87*
13	400mg	20mg	3.67 ± 9.71	4.42 ± 10.49	6.92 ± 17.53
14	400mg	40mg	15.75 ± 12.53*	10.42 ± 15.27*	26.50 ± 17.84*
20	800mg	20mg	5.42 ± 14.80	5.67 ± 10.59†	10.25 ± 16.82†
21	800mg	40mg	16.08 ± 11.52*	8.92 ± 10.88‡	9.33 ± 23.20†

† $p \leq .05$ ‡ $p < .005$ * $p < .0005$

In other words, Table 1b presents the magnitude of blood pressure and heart rate increases after 2 doses of cocaine infusions, with and without modafinil (0, 400 or 800 mg), and whether these increases are statistically significantly different from increases in vital signs after a saline infusion. Data presented indicate that, as expected, there are significant, generally dose-dependent, increases in hemodynamic measures after cocaine 20 mg and 40 mg infusions, both with and without modafinil. One exception was that increases in SBP, DBP and HR during a 20 mg cocaine infusion were not significant when 400 mg of modafinil was in steady state.

To answer whether modafinil caused an interaction, or additive effect with cocaine, Malcolm *et al* computed multiple pair-wise comparisons for various modafinil and cocaine conditions (see Table 2 below). In general, modafinil did not significantly modify the cocaine-induced blood pressure or heart rate increases at either the 400 mg or 800 mg daily dose.

Table 2. Level of Significance of the Difference Between Hemodynamic Variables For Various Modafinil and Cocaine Conditions Based on Pair-wise Comparisons (R. Malcolm, 2003, Personal Communication)

Outcome / Comparisons	Maximum SBP of cocaine infusion – maximum SBP of saline infusion	Maximum DBP of cocaine infusion – maximum DBP of saline infusion	Maximum HR of cocaine infusion – maximum HR of saline infusion
Modafinil 0 mg vs. 400 mg at Cocaine 20 mg	0.02	0.90	0.42
Modafinil 0 mg vs. 800 mg at Cocaine 20 mg	0.06	0.66	0.80
Modafinil 400 mg vs. 800 mg at Cocaine 20 mg	0.69	0.75	0.59
Modafinil 0 mg vs. 400 mg at Cocaine 40 mg	0.46	0.77	0.48
Modafinil 0 mg vs. 800 mg at Cocaine 40 mg	0.50	0.50	0.04
Modafinil 400 mg vs. 800 mg at Cocaine 40 mg	0.94	0.70	0.007
Cocaine 20 mg vs. 40 mg at Modafinil 0 mg	0.22	0.06	0.10
Cocaine 20 mg vs. 40 mg at Modafinil 400 mg	0.007	0.13	0.002
Cocaine 20 mg vs. 40 mg at Modafinil 800 mg	0.02	0.41	0.88

There are several statistically significant exceptions noted in Table 2. One example is the dampening of heart rate increase at cocaine 40 mg when comparing a) modafinil 0 mg vs. 800 mg (p=0.04), and b) modafinil 400 mg vs. 800 mg (p=0.007); it appears that modafinil 800 mg significantly attenuated the expected heart rate increase compared to modafinil 0 or 400 mg. Similarly, the expected increase in systolic blood pressure at cocaine 20 mg, was significantly dampened by modafinil 400 mg compared to modafinil 0 mg (p=0.02). Also, three other statistically significant comparisons show that the increase in SBP and HR at modafinil 400 mg, and in SBP at modafinil 800 mg, was greater for cocaine 40 mg than for cocaine 20 mg. However, this may be an expected dose-dependent response to cocaine, which showed the same tendency but did not reach significance, in the baseline condition of modafinil 0 mg.

In conclusion, the analysis of safety data (Tables 1a,b and Table 2) indicates that modafinil did not exacerbate the effects of cocaine on blood pressure and heart rate in the present sample of subjects with a history of cocaine dependence. Modafinil in steady state (400 and 800 mg daily), added to cocaine (20 or 40 mg i.v.), did not appear to further increase SBP or DBP or HR over the effect of cocaine alone. Rather, the statistical analyses (p-values of pair-wise comparisons presented in Table 2) indicate that at 800 mg daily dose modafinil may even have some mild effect of attenuating the expected increase (protective effect) in SBP and HR in cocaine users.

The four most common AEs for subjects completing this study included headache (ten subjects), insomnia (nine subjects), dyspepsia (four subjects), and nasal congestion (four subjects). Side effects were mild, and either untreated or symptomatically treated, and no subject was terminated from the study due to modafinil side effects.

Evaluation of the mean effects of modafinil (400 and 800 mg daily) interactions with cocaine (20 or 40 mg i.v.) using VAS assessment indicates that modafinil significantly dampened all three VAS measures ("any drug effects", cocaine "high", "worth of cocaine in dollars") as compared to baseline cocaine only condition (R. Malcolm, 2003, Personal communication,). For cocaine "high" measure, modafinil reduced VAS by about 45% for the 20 mg cocaine condition and about 35% for the 40 mg cocaine condition. Across all VAS measures and both doses of cocaine, the 800 mg dose of modafinil did not add significantly to this blunting effect as compared to the 400 mg dose of modafinil.

One study investigated acute behavioral and physiological effects of a single dose of modafinil (200, 400 and 600 mg) and compared it to those of oral cocaine (100, 200 and 300 mg) and placebo in 9 subjects with recent histories of cocaine abuse (i.e., positive urine for cocaine or BE during the initial screening) (Rush *et al.,* 2002). Four (4) subjects completed the modafinil dose-response function and then the cocaine dose-response function while for the other 5 participants this order was reversed; within a drug condition the order of dose administration was quazi-random. Heart rate and blood pressure were recorded for 30 minutes before and at 30-minute intervals after modafinil, cocaine or placebo administration for a total of 5 hours. The effects of cocaine generally were distinguishable from placebo by 0.5-1 hour after oral administration, peaked 1 hour after administration and did not differ from placebo by the end of experimental session. The effects of modafinil were distinguishable from placebo 1 hour after oral administration, peaked 4-5 hours after administration and continued to differ from placebo at the end of experimental session. The results of this study indicate that both cocaine and modafinil dose-dependently increased heart rate and blood pressure but although the highest dose of modafinil (600 mg) increased these measures significantly above the placebo levels it still did not produce clinically significant cardiovascular effects. Thus, significant elevation of heart rate following administration of 600 mg modafinil relative to placebo was largely attributable to a decrease in heart rate across the experimental session following the administration of placebo, and, importantly, the heart rate generally remained below 80 beats per minute following the administration of the highest dose of modafinil. Unlike cocaine, modafinil has a minimal abuse potential and was practically devoid of psychoactive effects across the range of doses tested except for a single instance of 600 mg modafinil-induced increased rating of Any Effect significantly above placebo levels on the Drug-Effect Questionnaire.

A double-blind, placebo-controlled, crossover study was conducted in male volunteers with a history of polysubstance abuse that included cocaine to compare the pharmacodynamic profiles and abuse potential of modafinil and methylphenidate (Jasinski, 2000). Each subject (N=24) was given single oral doses of methylphenidate (45 mg or 90 mg), modafinil (200 mg, 400 mg or 800 mg) and placebo. Both modafinil and methylphenidate produced dose-related increases in 6-hour area-under-the-curve (AUC) scores for supine and standing mean blood pressure and pulse rate. In addition, both agents produced significant orthostatic increases in pulse rate and blood pressure compared to placebo, but the effect of modafinil in enhancing orthostatic tachycardia

was significantly less than that of methylphenidate. The durations of observed and reported sleep following administration of modafinil 200 mg and 400 mg were similar to those observed following methylphenidate 45 mg and 90 mg, while that of modafinil 800 mg was significantly reduced relative to modafinil 200 mg, 400 mg and methylphenidate. When comparing modafinil and methylphenidate, modafinil 200 mg and 400 mg had a significantly lesser effect than methylphenidate on reducing caloric intake, while the effect on caloric intake for modafinil 800 mg was similar to that of methylphenidate 90 mg. The results of this study indicate that at the doses tested, modafinil did not appear to have reinforcing effects and did not induce a significant response on the Amphetamine Scale for Addiction Research.

5 STUDY OBJECTIVES

5.1 Primary Objective

The primary objective of this study is to assess the efficacy of modafinil in increasing the number of methamphetamine non-use weeks in subjects with methamphetamine dependence (DSM-IV criteria).

5.2 Secondary Objectives

Secondary objectives include determining modafinil's:

1. Efficacy in increasing the proportion of subjects who achieve 21 consecutive days of abstinence during the study medication administration phase of the trial.

2. Efficacy in increasing the proportion of subjects who achieve measured reductions in the number of methamphetamine use days (≥25% and ≥50% reductions in the number of use days compared to baseline use).

3. Efficacy in increasing the proportion of subjects who achieve measured reductions in the mean of the $\log_{10}$-transformed quantitative urine methamphetamine levels by ≥25% and by ≥50% compared to mean baseline levels.

4. Efficacy in increasing the maximum number of calendar days of methamphetamine abstinence during the study medication administration period.

5. Efficacy in reducing the proportion of methamphetamine use-days as determined by self-report alone.

6. Efficacy in increasing the overall proportion of [redacted] negative during the study medication administration period.

7. Efficacy in reducing the weekly mean of the $\log_{10}$-transformed quantitative urine methamphetamine levels.

8. Efficacy in the reduction of the severity of methamphetamine dependence (assessed by ASI and ASI-Lite Follow-up, and Self and Observer scored CGI, AISRS, and BIS) and craving (assessed by BSCS).

9. Efficacy in the reduction of cognitive dysfunction (assessed by a battery of eight cognitive tests administered by CANTAB).

10. Efficacy in the reduction of HIV risk taking behaviors (assessed by HRBS).

11. Efficacy in increasing retention during the study medication administration phase.

12. Safety in the study population.

6 STUDY SPONSOR

NIDA is the study sponsor and holds the IND.

7 STUDY SITES

This study will be conducted at up to 8 sites. Each site will enroll 26-40 subjects. All participating institutions will be located within the United States.

8 STUDY DESIGN

This is a double-blind, placebo-controlled, three arm study with a parallel-group design. After a 14 to 21-day screening/baseline period, subjects will be randomly assigned to one of three groups to receive 200 mg modafinil, 400 mg modafinil or matched placebo daily for 12 weeks with a follow-up assessment 4 weeks after completing the study medication administration period or early termination. Randomization to study medication groups will be done by stratifying by clinical site then using an adaptive randomization procedure based on current ADHD, gender, and frequency of methamphetamine use in the 30 days prior to informed consent (≤ 18 *versus* >18). All subjects will receive standardized manual-guided psychosocial therapy, which will consist of manual-guided cognitive behavioral therapy (CBT) three times a week during the 12-week study medication administration period.

9 SUBJECT SELECTION

Two-hundred ten (210) male and female subjects with methamphetamine dependence will be enrolled in the study (70 subjects per arm of the study). Entry into this study is open to both men and women and to all racial and ethnic subgroups. An attempt will be made to randomize at least 30% female subjects. Subjects will be recruited from a variety of sources. The primary source will be subjects seeking treatment for methamphetamine dependence via referrals from local treatment providers, advertising in local media, and word of mouth among subjects themselves. Recruitment advertisements will be approved by NIDA and the site's Institutional Review Board (IRB).

9.1 Inclusion Criteria

Potential subjects must:

1. Be male or female between 18 and 65 years-of-age.

2. Have a DSM-IV diagnosis of methamphetamine dependence as determined by SCID.

3. Be seeking treatment for methamphetamine dependence.

4. Have at least 1 amphetamine or methamphetamine positive urine specimen (> 500 ng/mL) during the 14 to 21-day screening/baseline period prior to the date the subject is eligible to be randomized with a minimum of 4 samples tested (urines should be collected 3 times a week, generally on Monday, Wednesday and Friday).

5. Be able to verbalize understanding of consent form, provide written informed consent, verbalize willingness to complete study procedures, and pass the study consent quiz with 100% accuracy (if necessary quiz may be administered more than one time).

6. If female, should be surgically sterile or 2 years post-menopausal. If of child bearing potential, agree to use one of the following methods of birth control, and to continue to use this method for at least 30 days after the last dose of study drug:

    a. barrier (diaphragm, sponge or condom with spermicide)
    b. intrauterine progesterone or non-hormonal contraceptive system/device (IUD)
    c. complete abstinence from sexual intercourse
    d. oral contraceptives
    e. patch
    f. implant
    g. medroxyprogesterone acetate contraceptive injection
    h. hormonal vaginal contraceptive ring

    Note: Steroidal contraceptives (methods d through h above) must be used in conjunction with a barrier method or IUD. Heterosexual female participants who do not engage in sex must agree to use one of these methods if they decide to have sex during the study and for 30 days after the last dose of study drug.

7. Be willing and able to comply with study procedures.

9.2 Exclusion Criteria

Potential subjects must not:

1. Have current dependence, defined by DSM-IV criteria, on any psychoactive substance (e.g., opioids) other than methamphetamine, nicotine, or marijuana, or have physiological dependence on a sedative-hypnotic (e.g., a benzodiazepine) requiring medical detoxification, or have current or past alcohol dependence.

2. Be mandated by the court to obtain treatment for methamphetamine dependence where such mandate required the results of urine toxicology tests to be reported to the court.

3. Be anyone who in the opinion of the investigator would not be expected to complete the study protocol due to probable incarceration or relocation from the clinic area.

4. Have a psychiatric disorder, such as current major depression, psychosis, bipolar illness, organic brain disorder, or dementia as assessed by SCID interview or ADHD by ACDS assessment, which require ongoing medication treatment or which would make medication compliance difficult. Have had electroconvulsive therapy within the past 90 days before screening, or have a history of Bipolar I Disorder (see Notes).

5. Have current suicidal ideation or plan as assessed by the SCID interview or HAM-D question #3. (Current is identified as within the past 30 days.)

6. Be pregnant or lactating.

7. Have serious medical illnesses including, but not limited to:

   - uncontrolled hypertension or uncontrolled diabetes.
   - history of syncope, presyncope, or chest pain associated with methamphetamine use
   - significant heart disease (including myocardial infarction within one year of enrollment), any clinically significant cardiovascular abnormality (ECG), mitral valve prolapse, or left ventricular hypertrophy
   - hepatic, renal or gastrointestinal disorders that could result in a clinically significant alteration of metabolism or excretion of the study agent,
   - potentially life-threatening or progressive medical illness other than addiction that may compromise subject safety or study conduct.

8. Have clinically significant abnormal laboratory values, in the judgment of the investigator.
   - have liver function tests (LFTs) > 3 times normal.

9. Have AIDS according to the current CDC criteria for AIDS – MMWR 1999; 48 (No. RR-13: 29-31). http://www.cdc.gov/MMWR/preview/MMWRhtml/00018871.htm

10. Have active syphilis that has not been treated or refuse treatment for syphilis (see **Notes**).

11. Have active tuberculosis (positive tuberculin test and confirmatory diagnostic chest x-ray).

12. Be undergoing HIV treatment with antiviral and/or non-antiviral therapy.

13. Have a current or past history of anorexia nervosa or bulimia disorder.

14. Have a diagnosis of adult (i.e., 21 years or older) asthma, or chronic obstructive pulmonary disease (COPD), including those with a history of acute asthma within the past two years, and those with current or recent (past 3 months) treatment with inhaled or oral beta-agonist or steroid therapy (because of potential serious adverse interactions with methamphetamine), or have an FEV_1 <70 %.

15. Be suspect for adult obstructive airways disease, but without formal diagnosis, for example: 1) have a history of wheezing and/or chronic coughing, 2) have a history of adult obstructive airways and/or treatment for this condition more than two years before the current application for the study, 3) have a history of other respiratory illness, e.g., complications of pulmonary disease (exclude if on beta-agonists), 4) use over-the-counter agonist or allergy medication for respiratory problems (e.g., Primatene Mist). If suspect, a detailed history and physical exam should be performed, and possibly pulmonary consult and/or pulmonary function tests, prior to including or excluding from the study.

16. Have received a drug with known potential for toxicity to a major organ system within 30 days prior to screening including, but not limited to, chemotherapeutic agents for neoplastic disease (i.e., methotrexate, vincristine, vinblastine, fluorouracil), agents used for parasitic infections (i.e., isoniazid, chlorambucil, dactinomycin, chloramphenicol), or immunosuppressive and cytotoxic agents (i.e., cyclosporine, tacrolimis, indomethacin, protease inhibitors, amphotericin B, cephalosporins, aminoglycosides, interferon, and sulfonamides).

17. Have received medication that could interact adversely with modafinil, with the time of administration of study agent and other medications based on the longest time interval of A, B, or C, below:

    A) Five half lives of other medication or active metabolite(s), whichever is longer
    B) Two weeks
    C) Interval recommended by other medication's product labeling

    Medications that fall into this category include:
    - Bupropion
    - Antipsychotics
    - Neuroleptics
    - Psychostimulants
    - Tricyclic antidepressants and anxiolytics
    - CNS depressants (tranquilizers, sleeping pills), e.g., secobarbital (Seconal), zolpidem (Ambien), temazepam (Restoril)
    - MAO inhibitors, e.g., phenelzine (Nardil), tranylcypromine (Parnate), selegiline (Eldepryl)
    - Inducers of CYP3A4 (e.g., carbamazepine, phenobarbital, rifampin) or inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole)
    - Substrates of CYP3A4, e.g., cyclosporin A, triazolam and ethinyl estradiol-containing products
    - Substrates of CYP2A9, such as warfarin

- Substrates of CYP2C19, e.g., *S*-mephenytoin, omeprazole, lansoprazole, proguanil, diazepam or propranolol
- Selective serotonin reuptake inhibitors (SSRIs), e.g., citalopram (Celexa, Cipramil, Emocal, Sepram), escitalopram oxalate (Lexapro, Cipralex, Esertia), fluoxetine (Prozac, Fontex, Seromex, Seronil, Sarafem, Fluctin (EUR)), fluvoxamine maleate (Luvox, Faverin), paroxetine (Paxil, Seroxat, Aropax, Deroxat), sertraline (Zoloft, Lustral, Serlain)

18. Have participated in any experimental study within 2 months preceding screening.

19. Have known or suspected hypersensitivity to modafinil.

20. Be taking modafinil for any reason currently or during the past year.

Notes on inclusion/exclusion criterion: All potential subjects will be offered optional HIV testing. This test is offered as a courtesy to the prospective subject along with HIV education. A positive test for HIV is not an exclusion criterion.

Prospective subjects who are positive for syphilis by the RPR test will have a fluorescent treponemal antibody absorbent assay (FTP-abs) or microhemagglutinin assay-Treponema pallidum (MHA-TP) confirmatory test performed. If this test is positive, prospective subjects must be treated for syphilis. If the prospective subject can provide evidence that they have been previously treated for syphilis or undergoes treatment for syphilis, they can be enrolled upon providing proof of successful treatment for syphilis.

The infectious disease panel for hepatitis and tuberculosis is performed as an aid to determine if the prospective subject has active hepatitis or tuberculosis. Either will exclude the prospective subject from participation according to exclusion criterion number 7 (serious medical illnesses) or number 11 (have active tuberculosis). All subjects who test positive for tuberculin PPD will be referred and scheduled to have a chest x-ray. Those that do not actually have tuberculosis will not be excluded from the study. Those that show a positive chest x-ray for tuberculosis will be excluded from the study. Prospective subjects who test positive for hepatitis will be evaluated by the site investigator for eligibility. Those subjects will be excluded if they have acute hepatitis or chronic active hepatitis, based on symptoms serology, and/or abnormal liver functions. Subjects who test positive for hepatitis will be referred for treatment as well as those who show positive chest x-ray for tuberculosis.

If any test results are positive, the subject will be notified of positive and confirmatory test results and will be referred to treatment.

Methamphetamine-induced psychosis does not exclude a candidate from the study, however, the presence of current psychotic symptoms will exclude a candidate from the study until clinically stabilized.

10 INVESTIGATIONAL AGENTS

10.1 Modafinil

Modafinil (Provigil®) is a white to off-white crystalline powder that is practically insoluble in water (<1 mg/mL) and cyclohexane. It is sparingly to slightly soluble in methanol and acetone. Its chemical name is 2-[(diphenylmethyl)sulfinyl]acetamide, the chemical formula is $C_{15}H_{15}NO_2S$ and the molecular weight is 273.36.

Modafinil tablets contain 100 mg of modafinil and the following inactive ingredients: lactose, corn starch, magnesium silicate, crosscarmelose sodium, magnesium stearate, povidone and talc. Modafinil is manufactured by Cephalon, Inc. (West Chester, PA). Modafinil will be supplied for this trial by Cephalon, Inc. and prepared for administration by NIDA's pharmaceutical partner (CSP Pharmacy in Albuquerque) as 100 mg tablets for oral administration.

Modafinil should be stored away from heat, sunlight, and moist areas such as the bathroom where the wetness may cause it to break down.

10.2 Placebo

Placebo will be supplied as an exact match of modafinil by Cephalon, Inc. (West Chester, PA) and prepared for administration by NIDA through the CSP Pharmacy in Albuquerque.

10.3 Dispensing Investigational Agents

Investigational agents for each subject, based on a study medication assignment list provided by CSPCC, Perry Point, will be prepared by the CSP Pharmacy in Albuquerque and distributed to investigators or designated research pharmacists at the clinical sites for distribution to subjects.

A ten-day blinded supply of modafinil and/or matched placebo will be dispensed in blister packs weekly for daily self-administration by subjects. The study medication will be distributed by the research pharmacist directly to the subject or to the investigator or designee for dispensing to the subject. Subjects will be instructed to take the study medication once a day upon awakening (or one dose every 24 hours), by taking one dose (4 tablets) from the study medication blister pack.

Note: Subjects should be instructed to take the missed dose as soon as they remember. However, if it is after 5 PM, they should skip the missed dose and continue their regular dosing schedule. Subjects should not take a double dose to make up for a missed one.

10.4 Randomization Plan

Adaptive random allocation of subjects to study groups will be used to balance groups with respect to screening prognostic variables. The procedure allocates study medication assignment based on the assignments and prognostic variable levels for all previously enrolled subjects. The study medication groups will be balanced within site based on the presence or absence of current ADHD, gender, and frequency of methamphetamine use in the 30 days prior to signing informed consent (≤ 18 *versus* >18). A new subject will be randomized with a "biased coin" procedure,

which uses randomization probabilities, favoring the study medication with the deficit enrollment, to improve the balance on group assignment. Randomized study medication assignment will be performed by the NIDA data management group.

10.5 Blinding Plan

Blinded supplies of modafinil and placebo will be supplied by NIDA through the CSP Pharmacy in Albuquerque and dispensed in blister packs. Four tablets per day will be taken by subjects in all groups (200 mg modafinil, 400 mg modafinil, and placebo).

10.6 Labeling

The investigational agents, modafinil and placebo, will be supplied in blister packs as a 10-day supply. The packages will be labeled by the NIDA pharmaceutical partner with the drug name ("modafinil/placebo"), the study medication kit number, and the following statement - Caution: New Drug - limited by federal law to investigational use. The packages will be distributed to investigational sites. When a subject is randomized, the local site research pharmacist, investigator or designee, will label the appropriate study medication kit based on the study medication kit number assigned to the subject with the following information: subject's study identification number, subject's alpha code, date dispensed, and the number of tablets to take per day. The blister packs will be pre-labeled with study weeks 1-12 within each study medication kit.

10.7 Storage

Investigational agents will be stored at room temperature without exposure to direct sunlight in a DEA-approved secure location in the distributing pharmacy or at each investigator’s facility.

10.8 Record of Administration

Accurate recording of all investigational agent dispensing/administration will be made in the appropriate section of the CRF. On the first clinic visit of each week, subjects will return the used blister packs and all unused investigational agent. Unused study agent will be inventoried for discrepancies. Subjects who have not been taking their tablets regularly will be encouraged to do so in the future. New, unused study agent (a 10-day supply) will then be dispensed to that subject along with a diary card. Subjects will be instructed to use the diary card to record daily study medication use, concomitant medication use, adverse events, and any illicit drug use or alcohol use during the study week. Subjects will be asked to bring their blister pack and diary card to all clinic visits (i.e., 3 times per week) and report medication use since the last clinic visit. Medication use will be recorded on the Weekly Dosing Record.

10.9 Used/Unused Supplies

At the end of the study, all unused investigational agents must be inventoried. If any investigational agent is lost or damaged, its disposition should be documented. Unused investigational agents will be retained at the clinic sites pending instructions for disposition by the Sponsor at the end of the study.

10.10 Safety Considerations

The most commonly reported adverse events (AEs) (>5% of patients) associated with the use of modafinil are mild, usually resolve after a few weeks of treatment and, in order of frequency, include:

- Headache
- Nervousness
- Nausea
- Anxiety
- Insomnia

Rare reports (<1%) of serious skin reactions (including suspected cases of both erythema multiforme and Stevens-Johnson syndrome) have been documented.

In general, modafinil is well-tolerated and in many clinical studies only headache occurs significantly more often in the active medication group *versus* placebo.

To avoid drug-drug interactions, modafinil should not be administered concurrently with:

- Psychostimulants
- Tricyclic antidepressants and anxiolytics
- CNS depressants (tranquilizers, sleeping pills), e.g., secobarbital (Seconal), zolpidem (Ambien), temazepam (Restoril)
- MAO inhibitors, e.g., phenelzine (Nardil), tranylcypromine (Parnate), selegiline (Eldepryl)
- Inducers of CYP3A4 (e.g., carbamazepine, phenobarbital, rifampin) or inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole)
- Substrates of CYP3A4, e.g., cyclosporin A, triazolam and ethinyl estradiol-containing products
- Substrates of CYP2A9, such as warfarin
- Substrates of CYP2C19, e.g., *S*-mephenytoin, omeprazole, lansoprazole, proguanil, diazepam or propranolol
- Selective serotonin reuptake inhibitors (SSRIs), e.g., citalopram (Celexa, Cipramil, Emocal, Sepram), escitalopram oxalate (Lexapro, Cipralex, Esertia), fluoxetine (Prozac, Fontex, Seromex, Seronil, Sarafem, Fluctin (EUR)), fluvoxamine maleate (Luvox, Faverin), paroxetine (Paxil, Seroxat, Aropax, Deroxat), sertraline (Zoloft, Lustral, Serlain)

Subjects will be cautioned not to take concomitant medications, whether prescription, over-the-counter, herbal supplements and health store products, without consulting the study investigator or physician designee.

11 STUDY DRUG ADMINISTRATION PLAN

11.1 Investigational Agents

Depending upon the group assignment, subjects will receive 200 mg modafinil, 400 mg modafinil or matched placebo daily for 12 weeks with a follow-up assessment 4 weeks after study completion.

On the first day of study drug administration, the subject will take the first dose in the clinic and then be sent home with sufficient amount of investigational agent for study week 1, plus enough additional investigational agent for an extra 3 days of dosing. The subjects will be instructed on how to take the investigational agent during the upcoming days (upon awakening or one dose every 24 hours) and asked to bring the blister pack to all clinic visits of study weeks 2 to 12 (i.e., 3 times per week) and report medication use since the last clinic visit.

11.2 Cognitive Behavioral Therapy

The CBT program will consist of three weekly, 90-minute group sessions through the 12-week trial, provided by the Matrix Institute on Addictions. Subjects will maintain thrice weekly attendance to the clinic for study visits. Concepts presented in these sessions include the following: (1) self-monitoring and relapse analysis; (2) identification of "triggers" and cognitive strategies for coping with them; (3) teaching of problem solving skills; (4) education about methamphetamine and methamphetamine dependence; (5) education about HIV and reducing the risk of HIV transmission; and, (6) promotion of pro-social activities.

In order to help potential subjects get ready to stop methamphetamine use, they will be introduced to the counselors during screening and scheduled to attend two 60-minute early recovery skills group sessions each week after signing informed consent up until randomization. Topics covered in these early recovery skills group sessions include: Triggers; Introduction to 12-Step Groups; and Brief Information on HIV (See complete Therapist Manual in the Operations Manual).

The content of the group topics is prearranged and sequenced using a manual format. This is a feasible treatment that is known to be well-accepted by subjects and it represents an appropriate, ethically defensible standard treatment condition to serve as the "platform" for the medication trial. Staff members who provide CBT counseling will have attended training in the use of these materials. The CBT specialist will have a minimum of a master's degree (or equivalent) or a bachelor's degree plus counseling experience with substance users. To ensure that the integrity of these sessions is maintained, all sessions are audiotaped and a random selection of tapes is reviewed centrally by the CBT trainers. Our experience is that these sessions are valued by subjects and attendance is excellent. Thus, psychosocial involvement is seen as a standard or platform for the proposed pharmacotherapy evaluation.

12 STUDY PROCEDURES

12.1 Subject Recruitment

Interested candidates who are seeking treatment and are available to come to the clinic for 18 to 20 weeks will meet with the investigator or designated investigational staff and receive an explanation of the study purpose and requirements. If still interested after receiving an explanation of the study, the candidate will be given an opportunity to review, inquire about, and sign the informed consent form. All potential subjects will meet with the site investigator or study physician prior to undergoing any medical procedures. Subjects are given a copy of the signed informed consent. Any subject who has difficulty understanding the information contained in the consent will be rescheduled and the consent process will be repeated. Research staff will work closely with the participant in an effort to help them understand the requirements of their participation. Persons with literacy problems will be assisted to the extent possible. Any subject who is unable to demonstrate understanding of the information contained in the informed consent will be excluded from study participation and assisted in finding other sources of treatment. Persons who are excluded, or who decline participation, will be given referrals to other resources in the area.

12.2 Screening and Baseline Assessments

Screening and baseline assessments will be conducted as shown in Table 3. These assessments may be conducted concurrently; therefore, this period could be as short as 14 days or as long as 21 days (assessments are described in section 13). Subjects must provide at least 4 urine specimens in the 14-21 day screening/baseline period, at least one of which must be positive for urine amphetamine or methamphetamine (> 500 ng/mL). Screening assessments are considered valid if the subject is randomized within 25 days after consent is signed.

12.3 Subject Randomization

If the prospective subject meets all of the study inclusion criteria, does not meet the exclusion criteria (a checklist will be provided in the CRFs), and has signed the informed consent form, then the subject can be randomized into the study. If any subject does not actually receive any investigational agent after they have been randomized, the subject will still be included in the intent-to-treat population.

The VA Cooperative Studies Program Coordinating Center (CSPCC) in Perry Point, MD will act as the Data Management Center for this trial. Information pertinent to the randomization variables for study medication assignment will be obtained from site personnel through the CSPCC's Interactive Touch Tone Randomization System (ITTRS). The ITTRS is an automated phone system which is able to provide random study medication assignments 24 hours/day, 7 days/week.

12.4 Study Medication Administration Phase

Subjects will be scheduled for assessments three times per week, usually on a Monday, Wednesday, and Friday for the duration of the study medication administration period (12 weeks). Study medication may start any day of the week. Study visits on two consecutive days may be scheduled around holidays or other scheduling conflicts. All subjects will be offered an opportunity for HIV testing and HIV/AIDS education (**Appendix I**). All subjects will be provided with standardized manual-guided CBT three times a week during the 12-week study administration period. Clinical evaluations are described in detail in section 13.

At the end of week 12 or immediately upon the time of study termination, subjects will be asked to have a brief physical exam, ECG, and a final blood draw. Subjects will also be asked to complete a full set of questionnaires and interviews that are very similar to what were asked at study admission. Regardless of whether all 12 weeks of the study are completed, subjects will be contacted and asked to complete the follow-up interview.

12.5 Follow-Up

Four weeks after study completion/termination, subjects will be asked to come to the clinic for a follow-up visit. The subject will be asked to provide a urine specimen for methamphetamine/creatinine and urine toxicology screening, urine pregnancy test, if female, provide a self-report of substance use, and to report any AEs or SAEs. The subject will be asked to report any current treatments for drug or alcohol abuse and to give an overall impression of the study agent. If it is not possible to arrange for the subject to return to the clinic, the subject will be telephoned and asked about any current methamphetamine use and other drug use, any current treatment for drug or alcohol abuse, AEs/SAEs, and an impression of the study agent.

12.6 Maintaining and Breaking the Study Blind

The decision to break the study blind for an individual subject should be made by the site principal investigator (PI) and/or with the NIDA medical monitor, but should be resorted to only in cases of a life-threatening emergency when knowledge of the assigned group investigational agent will influence clinical management.

12.7 Subject Compensation

Subjects will be compensated for travel expenses, for providing data, and for time contributed to this research study. Subjects will receive $10 in retail scrip or vouchers or other acceptable form of compensation for each clinic visit in which a urine specimen is provided during screening/baseline and the 12 weeks of study medication administration as compensation for their time and travel expenses. Travel expenses (bus and cab fares) may be paid with an acceptable form of compensation. Subjects will be paid $25 in retail scrip or vouchers or other acceptable form of compensation for the study termination interview and the follow-up assessment (only if done in person and not over the phone). Payment will be made upon completion of the specified requisite assessments for a maximum payment of $490 in retail scrip or vouchers. If a subject is withdrawn from study medication for any reason and continues to

participate in the study (providing data and urine samples, and attending CBT sessions), he/she will continue to receive $10 for each clinic visit attended. This compensation is for time and expenses incurred (e.g., gasoline, public transportation), not for compliance to the protocol.

12.8 Study Termination

12.8.1 Subject Termination

An investigator or sponsor may terminate a subject if s/he deems it clinically appropriate or for any of the following reasons:

1) significant side effects from the investigational agents
2) serious or unexpected AEs which would make further study participation not in the subject's best interest
3) inability to comply with the study protocol
4) serious or chronic protocol violations
5) 7 consecutive missed visits
6) serious intercurrent illness
7) pregnancy
8) administrative reasons such as presenting a danger to staff and other participants.

No study procedures will be performed on, nor assessments obtained from, any individual during the time he or she may be considered a prisoner through the course of the trial. A prisoner is defined as any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing (45CFR46.303, October 1, 2004).

A subject may withdraw from the study anytime s/he wishes. A subject may miss six consecutive visits and still continue to receive study agent. If seven consecutive visits are missed, the subject may not continue to receive study medications.

A subject may be administratively terminated for non-compliance if they fail to return two blister packs during the study medication administration period.

A subject who is discontinued from receiving the investigational agent for any reason will be allowed to continue psychosocial therapy per the approval of the investigator.

Any subject who discontinues prematurely, regardless of the reason, will be requested to return for a final visit to perform the necessary end of study/early termination procedures listed in Table 3. Whenever a study subject stops coming to the clinic without notification, staff will make a concerted effort to contact the subject (or the designated contact person if subject cannot be contacted) to assure that they have had no untoward effects from study participation.

Study subjects withdrawn from the protocol secondary to a medical or psychiatric concern will be referred for appropriate treatment. Subjects will be asked to sign a general consent for the release of information to the referred health care. Study staff may request transportation for emergency treatment of a subject if medically appropriate (e.g., for acutely psychotic or suicidal subjects).

Every study subject will be encouraged to carry a wallet card that identifies him or her as a subject in a clinical research study. The card will provide the name and phone number of the investigator (physician) at the site who can be contacted in the event of an emergency. The card may also instruct the non-study physician rendering emergency care to provide information to the study physician regarding that care.

12.8.2 Trial Discontinuation

The study sponsor, NIDA, has the right to discontinue the investigation at any time.

12.9 Concomitant Medications

Any medications (including prescription, over-the-counter, herbal supplements and health store products) to be taken during the study must be approved by the investigator. Modafinil should not be administered concurrently with:

- Neuroleptics
- Antipsychotics
- Psychostimulants
- Tricyclic antidepressants and anxiolytics
- CNS depressants (tranquilizers, sleeping pills), e.g., secobarbital (Seconal), zolpidem (Ambien), temazepam (Restoril)
- MAO inhibitors, e.g., phenelzine (Nardil), tranylcypromine (Parnate), selegiline (Eldepryl)
- Inducers of CYP3A4 (e.g., carbamazepine, phenobarbital, rifampin) or inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole)
- Substrates of CYP3A4, e.g., cyclosporin A, triazolam and ethinyl estradiol-containing products
- Substrates of CYP2A9, such as warfarin
- Substrates of CYP2C19, e.g., *S*-mephenytoin, omeprazole, lansoprazole, proguanil, diazepam or propranolol
- Selective serotonin reuptake inhibitors (SSRIs), e.g., citalopram (Celexa, Cipramil, Emocal, Sepram), escitalopram oxalate (Lexapro, Cipralex, Esertia), fluoxetine (Prozac, Fontex, Seromex, Seronil, Sarafem, Fluctin (EUR)), fluvoxamine maleate (Luvox, Faverin), paroxetine (Paxil, Seroxat, Aropax, Deroxat), sertraline (Zoloft, Lustral, Serlain)

13 CLINICAL EVALUATIONS

Study assessments should be completed according to the schedule provided in Table 3.

Table 3. Overview of Study Assessments

Assessment	Screening/Baseline		Study Medication Administration						Follow-up
Study Week	14-21 days prior to randomization		1-3	4	5-7	8	9 -11	12/ Term	16
Screening									
Informed consent	X								
SCID/Psychiatric evaluation	X								
Medical history	X								
ACDS assessment (ADHD diagnosis)	X								
Meth Timeline Followback	X								
Prior medications	3X/week								
Infectious disease panel/syphilis test/PPD	X								
HIV test (optional)	X								
Alcohol breathalyzer[f]	3X/week		X[a]	X[b]	X[b]	X[b]	X[b]	X[c]	
Safety									
Physical exam	X							X[c]	
Vital signs**	3X/week		X[a]	X[b]	X[b]	X[b]	X[b]	X[c]	
Hematology	X							X[c]	
Blood chemistries	X							X[c]	
HAM-D	X			X[b]		X[b]		X[c]	
Medical urinalysis	X							X[c]	
Pregnancy test	X		X[g]	X[b]		X[b]		X[c]	X
ECG	X							X[c]	
Adverse events[d]	3X/week[d]		3X[d]	3X[d]	3X[d]	3X[d]	3X[d]	3X[d]	X
Concomitant medications			3X	3X	3X	3X	3X	3X	X
Efficacy									
ASI***	X								
ASI-Lite Follow-up					X[b] wk 6			X[c] X[e]	
HRBS***	X							X[c]	
BSCS	Weekly[i]		X[b]	X[b]	X[b]	X[b]	X[b]	X[c]	
CGI-S	Weekly[i]		X[b]	X[b]	X[b]	X[b]	X[b]	X[c]	
CGI-O	Weekly[i]		X[b]	X[b]	X[b]	X[b]	X[b]	X[c]	
CANTABelect[J]	Twice				X wk 6			X	
Barratt Impulsiveness Scale	X				X wk 6			X	
ACDS	X								
AISRS assessment	X			X		X		X	
SUR	3X/week		3X	3X	3X	3X	3X	3X	X
Urine for meth/tox screen/creatinine	3X/week		3X	3X	3X	3X	3X	3X	X
Urine tox screen on site test device**	3X/week								
Medication Administration			X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	
Modafinil compliance			3X	3X	3X	3X	3X	3X	
CBT compliance ****[h]	2X/week[h]		3X	3X	3X	3X	3X	3X	
End of trial form								X[c]	
Follow-up interview									X

RANDOMIZATION

Notes on the Schedule of Assessments

* Screening and baseline assessments may be conducted concurrently, and both must be completed within 21-days prior to randomization.

** Vital Signs and On-site Urine Toxicology Screen are both screening and baseline measures, and will serve as a possible basis for exclusion from study.

*** ASI and HRBS also serve as both screening and baseline measures, but will not be used as a basis for exclusion from study.

****CBT to be conducted three times a week during 12-week study medication administration period.

X[a] - Vital signs are taken at each visit for the first three study weeks, then weekly thereafter, preferably at the first visit of the week.

X[b] - Once per week preferably at the first visit of the week. If the study physician has medical concerns, blood may be drawn again to assess blood chemistry (for example, liver enzymes). In addition, at weeks 4 and 8, if female, a urine pregnancy test will be performed.

X[c] - **At the final scheduled study visit (preferably last visit of week 12) or if the subject discontinues prematurely.** If the study physician has medical concerns, additional ECGs may be performed.

X[d] - AEs will be assessed and recorded by investigative staff nurse or physician or PIs designee at every visit. A study physician will meet with the subject once a week to review the AEs and to assess for any additional AEs.

X[e] -If there is a clear indication that a participant will terminate early and not return for the termination interview, the ASI-Lite Follow-up interview should be conducted as soon as possible during any scheduled or unscheduled visit.

X[f] - The alcohol breathalyzer test will only be performed if the subject is suspected to be intoxicated at clinic visits in accordance with institutional and state regulations.

X[g] - On study day 1, prior to randomization.

X[h] - During screening/baseline, subjects will attend 2 60-minute early recovery skills sessions each week.

X[i] - Obtained weekly during screening/baseline.

X[J] – CANTABelect tests should be completed twice during the screening/baseline period. The IED test (Intra-Extra Dimensional Set Shifting) will only be done at week 12 or the termination visit, whichever comes first.

Screening/Baseline Assessments. Prior to randomization, subjects will be screened to determine if they meet eligibility requirements. In addition, certain screening/baseline assessments that are part of determining eligibility will also provide physiological, psychological, and disease status information prior to randomization. Because the screening/baseline period can occur simultaneously, screening/baseline can be as short as 14 days or as long as 21 days. After completing the screening/baseline period and meeting all eligibility criteria, subjects can be randomized on Day 15 to Day 25 after informed consent. Subjects cannot be randomized on or before Day 14 and cannot be randomized after Day 25 (Table 3).

Screening/baseline assessments to occur over a 14 to 21-day period will include the following:

1. Urine toxicology screen using an on-site testing device. Subjects must provide at least 4 urine specimens in the 14 to 21-day period, at least one of which must be positive for urine amphetamine or methamphetamine (> 500 ng/mL). Ideally, 3 of the specimens will be obtained in one week and 3 in the next week. No more than 4 of the specimens may be obtained in one week of the screening/baseline period and no more than two specimens can be collected on consecutive days.

2. Urine methamphetamine plus creatinine measurements at a central laboratory. Note: These assays will be performed at a central laboratory only on the urine samples collected for the subjects who are randomized in the study.

3. The following must be obtained weekly for at least two weeks during the screening/baseline period:
   a. BSCS
   b. CGI-S
   c. CGI-O
   d. Urine toxicology screening at a central laboratory. Note: This assay will be performed at a central laboratory only on the urine samples collected for the subjects who are randomized in the study.

4. Daily report of methamphetamine, marijuana, nicotine, alcohol, opiates, and cocaine use will be recorded at each visit on a SUR CRF.

5. HAM-D, ASI, ACDS, AISRS, Barratt Impulsiveness Scale and HRBS assessments must be obtained once. The CANTABelect assessments must be obtained twice.

6. AEs will be assessed and recorded at each screening/baseline visit and reviewed by site investigator or study physician weekly.

Assessments During Study Medication Administration. Throughout the study medication administration period, subjects will be scheduled to return to the clinic three times per week for assessments. Some assessments will be collected three times per week (typically on a Monday, Wednesday, and Friday) and some will be collected once per week per the schedule in Table 3. Except for week 12, those assessments occurring once per week should be performed at the first clinic visit of the week whenever possible.

Assessments at End of Study (Week 12) or Early Termination. Urine methamphetamine and creatinine, SUR, concomitant medications and medication compliance are to be assessed three times during the last week of the study medication administration period. All other assessments scheduled for study week 12 (Table 3) should be completed, ideally at the final scheduled study visit. When a subject discontinues prematurely, regardless of the reason, all Table 3 week 12 assessments are to be completed. This may require requesting the subject to return specifically for final assessments.

Assessments at Follow-up (Week 16). The follow-up visit should be scheduled to occur approximately 4 weeks after the final in-clinic examination during the study medication administration period as per Table 3. Overview of Study Assessments. At the follow-up visit, record only those AEs which are serious and clinically significant; these must then be followed to resolution.

13.1 Assessment Methods

13.1.1 Structured Clinical Interview (SCID)

A SCID (Spitzer *et al.,* 1995) will be conducted during screening to assess the subject's methamphetamine dependence and any other drug dependence, severity of depression, and other Axis-I disorders, according to DSM-IV criteria

.13.1.2 Medical History

To monitor the health of all study subjects, health profiles will be collected prior to participation in the study. A review of systems will be conducted by the site principal investigator/study physician to assure medical fitness.

13.1.3 Prior Medications

All medications (includes prescribed, over-the-counter, and herbal preparations) taken by the subject for the 60 days prior to informed consent will be documented on a Prior Medication CRF. The reported medications will be reviewed and approved by the site principal investigator/study physician.

13.1.4 Vital Signs

Vital signs to be assessed include oral temperature, sitting blood pressure, heart rate, and respiratory rate.

13.1.5 Physical Exam

A physical exam of the oral cavity, head, eyes, ears, nose and throat, cardiovascular system, lungs, abdomen (liver/spleen), extremities, skin, neuropsychiatric mental status and sensory/motor status, musculoskeletal system and general appearance should be performed. Height and weight should be recorded.

13.1.6 Hematology

Blood will be collected in anticoagulant containing vacutainer tubes for hematologic assessments. Complete blood counts (CBC) with differentials and platelet count will be performed. Laboratories performing these assessments should be either directly regulated by the College of Pathologists (CAP) or the Clinical Laboratory Improvement Act of 1988 (CLIA) or indirectly according to CLIA guidelines. The laboratory will need to provide a copy of current certification, and each laboratory should provide the Laboratory Normals for their laboratory values to determine the upper limit of normal (ULN).

13.1.7 Blood Chemistries

Blood will be collected in serum separation vacutainer tubes and serum separated according to standard procedures. Blood chemistries (LFTs = albumin, total Bilirubin, direct Bilirubin,

alkaline Phosphatase, GGT SGPT, SGOT and Chem 7 = BUN, creatinine, sodium, potassium, chloride, bicarbonate, glucose) will be performed at a clinical laboratory. Laboratories performing these assessments should be either directly regulated by CAP or CLIA or indirectly according to CLIA guidelines. The laboratory will need to provide a copy of current certification.

13.1.8 Infectious Disease Panel and Syphilis Tests

Blood will be collected in serum separation vacutainer tubes and serum separated according to standard procedures. Qualitative analysis reporting positive/negative results will be performed for the following analytes: Hepatitis B surface antigen, Hepatitis B surface antibody, Hepatitis B core antibody, and Hepatitis C virus antibody. A purified protein derivative (PPD) skin test for tuberculosis will be performed on all subjects and, if positive, a chest x-ray is required to assess active tuberculosis. If the subject reports that they have been previously positive for the PPD test, the PPD test will not be performed and a chest x-ray will be required. A rapid plasma reagin test (RPR) for syphilis will be performed. If positive, a fluorescent treponemal antibody absorption (FTA-abs), a microhemagglutination for *Treponema pallidum* (MHA-TP) or a *Treponema pallidum* particle agglutination (TPPA) confirmatory test will be performed. If any tests are positive, the subject will be notified of the test results and referred to treatment.

13.1.9 HIV Test

All subjects will be offered the opportunity to have an HIV test performed. This test is not requisite for study participation. Subjects will be referred to a clinic for HIV testing. The clinic will use its own HIV test consent form. An HIV antibody test will be performed on a serum sample collected from the subject after the HIV test consent form is signed. The results of HIV test will not be reported.

13.1.10 Pregnancy Test

An FDA-approved rapid-result urine pregnancy test will be used (i.e., dipstick test). All female subjects will be tested regardless of their child-bearing capacity.

13.1.11 Urine Collection and Analyses

Urine will be collected for four types of analyses as follows:

1) Methamphetamine/amphetamine, creatinine, tetrahydrocannabinol, cocaine, opiates, and benzodiazepines analyses performed at a central laboratory.
2) Urine Toxicology Screen performed with a qualitative onsite test device for methamphetamine, cocaine, tetrahydrocannabinol, amphetamines, barbiturates, opiates and benzodiazepines.
3) Medical urinalysis performed at a local laboratory.
4) Pregnancy test.

Depending upon the assessment schedule, urine samples will be collected and aliquoted into the appropriate number of specimens. One specimen will be held frozen at the clinical site as a back-

up. The others will be tested immediately or will be frozen as appropriate. Specimens will be collected and tested as follows:

Methamphetamine, Creatinine, Tetrahydrocannabinol, Cocaine, Amphetamines, Opiates, and Benzodiazepines Analysis.

During the screening/baseline period of the study, urine will be collected 3 times per week (generally Monday, Wednesday, and Friday, barring holidays and schedule conflicts). Urine samples will be tested using the onsite testing device. Subjects qualifying for entry into the study will be randomized. Upon randomization, the urine samples collected from subjects and stored during the screening/baseline period will then be sent to a central laboratory. The central laboratory will a) perform qualitative analysis for the 1st sample of the week for cocaine, tetrahydrocannabinol, methamphetamine/amphetamines, opiates, benzodiazepines and creatinine, b) perform qualitative analysis the 2nd and 3rd samples of the week for amphetamines/methamphetamine, creatinine , and c) perform quantitative analysis for methamphetamine and amphetamines for all the samples qualitatively screened positive for methamphetamine/amphetamines.

Note: The sites will store samples from screening/baseline until the subject is randomized, and once randomized then samples can be sent to the central laboratory for analysis.

Following randomization, during the medication administration phase of the study and at the follow-up visit, urine will be collected 3 times per week (generally Monday, Wednesday, and Friday, barring holidays and schedule conflicts) and sent to a central laboratory. The central laboratory will a) perform qualitative analysis for the 1st sample collected each week for cocaine, methamphetamine/amphetamines, tetrahydrocannabinol, opiates, and benzodiazepines, b) screen all samples for amphetamines/methamphetamine, creatinine, and c) will quantitate amphetamines and methamphetamine for all samples, qualitatively screened positive for methamphetamine/amphetamines.

All specimens collected and screened positive by the central laboratory for methamphetamine/amphetamines will be subjected to methamphetamine quantitative analysis performed at central laboratory. The back-up sample retained at the site will be stored frozen until the NIDA data coordinating center has notified the site that it can be disposed.

Urine Toxicology Screen Using an Onsite Testing Device. During the screening/baseline period, urine will be collected 3 times per week (generally Monday, Wednesday, and Friday, barring holidays and schedule conflicts). After the backup aliquot and the central laboratory testing aliquot have been obtained, the sample will be analyzed using an on-site testing device (tetrahydrocannabinol, methamphetamine, cocaine, amphetamines, barbiturates, opiates and benzodiazepines). Samples positive for amphetamine/methamphetamine (the on-site testing device has a cutoff of greater than or equal to 500 ng/mL) will be considered as positive for methamphetamine for inclusion criteria purposes.

Medical Urinalysis. Urine will be collected and analyzed for color, appearance, specific gravity, pH, blood, protein, glucose, ketones, leukocytes, bilirubin and nitrites. Analysis will be conducted at a local laboratory.

Urine Pregnancy Test. An on-site qualitative urine pregnancy test that evaluates human β-chorionic gonodotropin will be used. This test will be provided to sites by the CSP Pharmacy.

13.1.12 Breathalyzer Test

The breathalyzer or breath alcohol test will be administered to assess recent alcohol use and will only be performed if the subject is suspected to be intoxicated at clinic visits in accordance with institutional and state regulations.

13.1.13 ECG

Twelve-lead electrocardiograms will be performed according to standard procedures. The results will be reviewed by a board-certified cardiologist for interpretation.

13.1.14 Adverse Events (AEs)

AEs will be assessed and recorded at each visit by an investigative staff nurse or physician or PIs designee who is medically trained. If an AE that requires medical attention is reported to a nurse or medically trained designee, it will be reported to a study physician immediately. A study physician will meet with the subject once a week to review the AEs recorded by the nurse or medically trained designee and to assess for any additional AEs. The investigator or study physician will assess subjects for any medical or psychiatric side effects. Both the staff nurse, medically trained designee or the physician will assess AEs by asking the participant, "How have you been feeling since I saw you last." The type of AE, severity of the AE, and the relationship to the study treatments will be recorded on an AE CRF according to the procedures described in section 14.8.

13.1.15 Concomitant Medications

All medications taken by the subject after consent (during screening/baseline, during the study medication administration phase, and at the final follow-up assessment) will be recorded on a Concomitant Medications form. The reported medications will be reviewed by the site investigator/study physician for possible drug interactions.

13.1.16 Hamilton Depression Rating Scale (HAM-D)

The HAM-D is an interviewer-administered assessment of the subject's level of depression (Williams, 1988). The HAM-D for this study includes three additional questions all associated with methamphetamine dependence (22. Helplessness, 23. Hopelessness, and 24. Worthlessness). The HAM-D will be administered by study research staff (i.e., study coordinator, research assistant).

13.1.17 Addiction Severity Index (ASI) CF Version and ASI-Lite Follow-up

The ASI and ASI-Lite, (McLellan *et al.,* 1992), will be administered by a research staff member having at least a bachelor's degree in the social sciences or equivalent training and experience as determined by the site's investigator. Composite scores will be calculated, according to the procedures described by McGahan *et al*. (1982) and Carroll *et al*. (1994), which indicate the severity of the subject's status in seven areas (medical, employment, drug use, alcohol use, legal, family/social, and psychological).. The Lite version is a shorter version of the ASI that still retains all questions used to calculate the ASI composite scores. ASI-Lite Follow-up will be administered at weeks 6 and 12; it eliminates demographic and other questions that do not change over time.

13.1.18 Barratt Impulsiveness Scale

The revised Barratt Impulsiveness Scale (BIS-11) is a 30-item self-administered assessment that has shown internal consistency in a group of substance abuse patients (Patton *et al*., 1995). The items are all scored on a 4-point scale (never/rarely, occasionally, often, almost always/always), with 1 indicating the least and 4 the most impulsive response. Item analysis identified three second-order factors: Attentional, Motor, and Nonplanning Impulsiveness.

13.1.19 Cambridge Neuropsychological Test Automated Battery (CANTABelect)

The CANTABelect is an automated series of cognitive tests that uses a touch screen tablet PC to administer the test battery. This test battery was developed by Cambridge Cognition Limited and has established sensitivity to a large number of drugs and disorders and is likely to predict clinical outcomes such as long-term abstinence. The test battery includes eight tests – Motor Screening (MOT), Rapid Visual Information Processing (RVP), Pattern Recognition Memory (PRM – immediate and delayed), Spatial Working Memory (SWM), One-Touch Stockings of Cambridge (OTS), Intra-Extra Dimensional Set Shifting (IED – will be assessed only during week 12 or termination), Stop Signal Task (SST), and Cambridge Gamble Task (CGT). A full description of each test and the outcome measure for each test can be found in Appendix IV. This test battery will be assessed at screening, baseline, week 6, and week 12.

13.1.20 Adult ADHD Clinical Diagnostic Scale (ACDS) V 1.2

The Adult ADHD Clinical Diagnostic Scale is a semi-structured interview, which documents current symptoms that contribute to the diagnosis of ADHD in an adult. It has 18 items that match the 18 symptom domains of ADHD noted in DSM-IV. There are suggested probes to establish the presence and extent of ADHD symptoms, as well as their severity and impact on patient functioning. The childhood component of the ACDS is an adaptation of the ADHD module of the Schedule for Affective Disorders and Schizophrenia for School Aged Children (K-SADS-PL; Kaufman J *et al*., 1997). Scoring is on a 4-point Likert scale: None, Mild, Moderate or Severe. This assessment will be done once, during screening.

13.1.21 Adult ADHD Investigator Symptom Rating Scale (AISRS)

The Adult ADHD Investigator Symptom Rating Scale consists of the 18 items and their probes from the ACDS, albeit, in a different order. It is used to take repeated measures of ADHD symptoms, in order to observe changes over time. A version of this instrument was used to test the reliability of ratings obtained from different, trained raters (Adler LA *et al.*, 2005). This assessment will be done four times, at baseline and Weeks 4, 8, and 12.

13.1.22 Substance Use Report (SUR)

The SUR includes the subject's report of use of methamphetamine, marijuana, nicotine, alcohol, opiates, and cocaine use for each day of the week. The subject is asked to report any use during days since the last clinic visit. The day that the subject is reporting use is not scored until the subsequent visit as use may occur later in the day. The exception to this is if the subject reports any use for the day of the clinic visit (prior to coming in), this should be noted on the form so it is not forgotten at a subsequent visit.

13.1.23 Brief Substance Craving Scale (BSCS)

The BSCS is a self-administered assessment that asks the subject to rate his or her craving for methamphetamine. The tool also asks the subject to assess the craving for a second and third craved substance, if any. The BSCS used for this study is a modification of the State of Feelings and Cravings Questionnaire (Mezinskis *et al*., 1998).

13.1.24 Clinical Global Impression-Observer (CGI-O)

The CGI-O requires the observer to rate the global severity of the subject's methamphetamine dependence symptoms and to rate the improvement of the subject's methamphetamine dependence symptoms since the beginning of the study. The severity of the subject's methamphetamine dependence is rated according to eight specific problem areas often associated with methamphetamine dependence.

13.1.25 Clinical Global Impression-Self (CGI-S)

The CGI-Self is a self-administered assessment that asks the subject to rate the global severity of his or her methamphetamine dependence symptoms and to rate the improvement of his or her methamphetamine dependence symptoms since the beginning of the study.

13.1.26 HIV Risk-Taking Behavior Scale (HRBS)

The HRBS is a brief 11-item interviewer-administered scale (Darke *et al.,* 1991), to which a 12th item ("Have you had an HIV test come back positive?") was added by NIDA. It measures two distinct HIV risk factors in the behavior of intravenous drug users: one related to injecting behaviors and the other to sexual behaviors. Study personnel are not to offer interpretations of the questions.

13.1.27 End of Study Form

During the termination visit, reason for termination and the date of the final on-study clinic visit will be collected.

13.1.28 Study Medication Compliance

Study medication compliance will be monitored by recording the amount of investigational agents taken by each subject on a weekly dosing form. The timeline follow-back method will be used to assist the subject in reporting of the amount of tablets taken between clinic visits. The timeline follow-back will be administered by the research staff three times a week and reviewed weekly by a physician. Subjects will be asked to bring their blister pack to all clinic visits (i.e., 3 times per week). Self-report of medication use since the last clinic visit will be recorded on the Weekly Dosing Record. Subjects will be provided with a weekly diary card to record daily study medication use, as well as concomitant medication use, adverse events, and any illicit drug use or alcohol use during the study week.

13.1.29 Cognitive Behavioral Therapy (CBT) Compliance

Compliance with CBT will be monitored by recording the length of time the subject spent in attendance at each therapy session and recorded on a form for each visit.

13.1.30 Follow-up Questionnaire

The Follow-up Questionnaire will document the information collected at the 30-day follow-up interview including if contact was made with the subject or documenting the subject's death. In addition, the form asks questions regarding the subject's drug use, and current treatment for drug and alcohol abuse.

13.1.31 Timeline Follow-Back

Detailed histories of methamphetamine use over the 30 days prior to informed consent will be obtained using the timeline follow-back method. The timeline follow-back method was described and validated by Sobell *et al.* (1986) for reporting alcohol use. It has also been found to be a reliable method for assessing the history of psychoactive substance use in drug-abusing populations (Fals-Stewart *et al.,* 2000).

If the subject is unable to self-administer any assessment (e.g., physical handicap, poor reading skills) study personnel can assist by reading the questions out loud to the subject and/or marking the subject's response on the CRF. However, study personnel are not to offer interpretations of the questions.

14 REGULATORY AND REPORTING REQUIREMENTS

14.1 Good Clinical Practices

This study will be conducted in accordance with the most current version of the International Conference on Harmonization Guide for Good Clinical Practices (GCP). An Operations Manual will be provided to all investigational sites as a study quality assurance tool.

14.2 FDA Form 1572

The investigator at each study site will sign a Statement of Investigator (FDA Form 1572) prior to initiating this study.

14.3 IRB Approval

Prior to initiating the study, each site investigator will obtain written IRB approval to conduct the study. Should changes to the study protocol become necessary, protocol amendments will be submitted in writing to the IRB by the investigator for IRB approval prior to implementation. In addition, IRBs will approve all advertising materials used for subject recruitment and any educational materials (e.g., HIV/AIDS Education, **Appendix I**) given to the subject once NIDA has approved them. Annual reports and progress reports will be submitted to the IRB annually or at a frequency requested by the IRB.

14.4 Informed Consent

All potential candidates for the study will be given a current copy of the Informed Consent Form to read. The investigator, sub-investigators, study physician or designated staff at each site will explain all aspects of the study in lay language and answer all of the candidate's questions regarding the study. If the candidate desires to participate in the study, s/he will be asked to sign the Informed Consent. No study procedure will be performed prior to signing Informed Consent. No medical procedures will be performed until each subject meets with the study physician or qualified staff member. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

14.5 Disclosure of Protected Health Information

At the time of informed consent, all potential candidates will be asked to sign a waiver authorizing the release and use of protected health information in this study. Clinical sites will employ a Protected Health Information Disclosure that details the health information that will be collected as part of this research and the agencies that may access that information during the study and after the study has been completed.

Health information gathered during this research study may be reviewed by representatives of NIDA and/or the Food and Drug Administration (FDA) for monitoring purposes. All data collected on CRFs for this study will be sent to the VA CSPCC in Perry Point, MD for processing and analyses. This data will be transmitted to the VA CSPCC electronically via a secured fax. From this data, a limited database will be constructed and maintained according to the HIPAA Privacy Rule. Access to the database will be limited to data management personnel

only. All informed consent documents that arrive at the VA CSPCC will be maintained by administrative personnel and will be housed separately from study data in locked cabinets within restricted areas.

Data from the cognitive test battery will be transmitted to Cambridge Cognition Limited via encrypted memory stick. A limited database will be constructed, maintained according to ICH guidelines, FDA recommendations and NIDA's data standards requirements, and analyzed by Cambridge Cognition Limited at the end of the trial.

At the conclusion of the study, the VA CSPCC and Cambridge Cognition Limited will provide final limited datasets to Information Management Consultants (IMC), a data management firm that is contracted by NIDA to store and retrieve study data. Data transfer between the VA CSPCC and IMC will take place electronically through secure internet connections. The VA CSPCC has entered into a Data Use Agreement with NIDA and IMC that mandates their compliance with all aspects of the HIPAA Privacy Rule and their employment of all necessary precautions to prevent unauthorized use of, or access to the data. In accordance with this agreement, IMC may not release data to any agency other than the FDA without the express written approval of NIDA and the Director, VA CSPCC. IMC will store the data indefinitely until instructed, in writing, by NIDA to destroy the data.

14.6 Drug Accountability

Upon receipt, the investigator/pharmacist is responsible for taking inventory of the investigational agents. A record of this inventory must be kept and usage must be documented. Any unused or expired investigational agent shall be returned to the sponsor or sponsor designee unless otherwise instructed.

14.7 Outside Monitoring

Data and Safety Monitoring Board: Safety data will be reviewed by a Data and Safety Monitoring Board (DSMB) according to their Standard Operating Procedures. The DSMB may meet earlier if deemed necessary. Additional meetings after that will be held on an *ad hoc* basis. The board will be blinded to subjects' actual study assignments, but may break the blind if safety concerns arise from the blinded data.

Medical Monitor: The NIDA medical monitor will be available for making recommendations to the investigator on the severity of any SAEs, the relatedness to the study medication, and for determining if an SAE should be reported to the FDA in a 7- or 15-day expedited report or an annual report (**Appendix II**). The NIDA medical monitor will also be responsible for tracking and assessing trends in the SAEs reported.

Clinical Monitors: All investigators will allow NIDA or their representatives to periodically audit, at mutually convenient times during and after the study, all CRFs and corresponding source documents for each subject. These monitoring visits will provide NIDA or their representative with the opportunity to evaluate the progress of the study and to inform NIDA of potential problems. The monitors will assure that submitted data are accurate and in agreement with source documentation; verify that investigational agents are properly stored and accounted

for, verify that subjects' consent for study participation has been properly obtained and documented, confirm that research subjects entered into the study meet inclusion and exclusion criteria, and assure that all essential documentation required by good clinical practices guidelines are appropriately filed.

Monitors will conduct a site initiation visit prior to the start of the study. At this visit, they will assure that proper study-related documentation exists, assist in training investigators and other site personnel in study procedures and good clinical practice's guidelines, confirm receipt of study supplies, and assure that acceptable facilities are available to conduct the study.

Routine monitoring visits by NIDA through the Albuquerque monitoring staff will be scheduled at appropriate intervals but more frequently at the beginning of the study. A monitoring visit soon after the first one or two subjects have been randomized is recommended. At these visits, the monitors will verify that study procedures are being conducted according to the protocol guidelines and review AEs and SAEs. At the end of the study, they will advise on storage of study records and return of unused study agents. All sites should anticipate visits by NIDA, their representatives, and the FDA.

14.8 Adverse Events Reporting

In accordance with FDA reporting requirements, all AEs occurring during the course of the clinical trial will be collected, documented, and reported by the investigator or sub-investigators according to the specific instructions detailed in this section of the protocol and **Appendix II**. The occurrence of AEs will be assessed starting at the completion of the informed consent process and at each study visit and an AE CRF completed weekly.

An AE is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered related to the investigational agent or clinically significant. For this study, AEs will include events reported by the subject, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant clinical laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs. All AEs must be recorded on the AE CRF. The AE CRF is also used to record follow-up information for unresolved events reported on previous visits.

14.9 Serious Adverse Events

Each adverse event or reaction will be classified by a study physician as being serious or non-serious. Based on the seriousness of the adverse event or reaction, appropriate reporting procedures will be followed. The Code of Federal Regulations Title 21 part 312.32 and International Conference on Harmonization (ICH) Guideline for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH-E2A March 1995, as implemented by the U.S. Food and Drug Administration, defines a serious adverse event (SAE) or serious adverse drug experience as any untoward medical occurrence at any dose that:

- results in death;
- is life-threatening; *(NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)*
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect.

In addition, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug reaction, when based on appropriate medical judgment, that may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Subjects that become pregnant during study participation will be taken off study drug. However, subjects may continue to receive counseling for substance abuse or be referred for appropriate treatment. Subjects will be asked to sign a release of information form for study personnel to access medical records to obtain information regarding the outcome of the pregnancy.

An unexpected adverse event is one that is not described with respect to nature, severity, or frequency in the current Investigator's Brochure or product package insert.

Reporting of AEs and SAEs is described in **Appendix II.** There can be serious consequences including ultimately, criminal and/or civil penalties for sponsors who fail to comply with FDA regulations governing the reporting of SAEs to FDA. The investigators in this study have the responsibility of promptly reporting all SAEs to NIDA and the Investigator-Sponsor in order that the Investigator-Sponsor can comply with these regulations.

If a study subject withdraws from the study or if an investigator decides to discontinue the subject from the study because of an SAE, the subject must have appropriate follow-up medical monitoring including, if necessary, hospitalization. Monitoring will continue until the problem prompting hospitalization has resolved or stabilized with no further change expected or is discovered to be clearly unrelated to study medication or progresses to death.

15 ANALYTICAL PLAN

15.1 Statistical Hypotheses

Primary Outcome: It is hypothesized that modafinil, as compared to placebo, will increase the number of methamphetamine non-use weeks over time as measured by [redacted] for methamphetamine.

Secondary Outcomes: It is hypothesized that modafinil, as compared to placebo, will increase the proportion of subjects with 21 consecutive days of abstinence during which time all [redacted] urine drug screens must be methamphetamine-negative (both with and without self report), increase the proportion of subjects who reduce their methamphetamine use as compared to baseline use, the weekly mean proportion of methamphetamine non-use days according to self-report alone, the proportion of methamphetamine negative urine samples, and treatment retention. It is further hypothesized that modafinil will reduce the severity of methamphetamine

dependence, craving, and comorbidity as assessed by the ASI-Lite, the BSCS, the CGI-S, the CGI-O, the Adult ADHD Investigator Symptom Rating Scale (AISRS), and the Barratt Impulsiveness Scale. The effects of modafinil on specific domains of cognitive functioning will be tested using the CANTABelect test scores. It is anticipated that modafinil will improve impulsivity, decision making, risk-taking preferences, executive function, working memory, and planning.

15.2 Outcome Measures

There is no generally accepted definition of clinically significant improvement in the treatment of methamphetamine dependence. The primary and secondary outcome variables are intended to explore various aspects of the response to modafinil and to help define a clinically meaningful response. The primary outcome has been chosen because it is an objective measure of stopping methamphetamine use and it measures reduction in methamphetamine use over the treatment period. Some of the secondary outcome variables add a measure of clinical relevance to the reduction of use by requiring either sustained abstinence (21 Days) or a predetermined, substantial overall reduction in use days (25% and by 50% of their baseline use).

15.2.1 Primary Efficacy Outcome Measure

The primary efficacy outcome measure is methamphetamine use or non-use weeks during the study medication administration period. Use weeks are defined as each 7-day period starting with the first day of investigational product administration. A use week is any week in which at least one of the [redacted] urine drug screens for methamphetamine was positive. A non-use week is any week in which all of the [redacted] urine drug screens for methamphetamine were negative. If no drug screening results are available, the data for that week is considered as missing.

15.2.2 Secondary Outcome Measures

Effect on methamphetamine use

A. The score of the study week's urine samples for methamphetamine during the study medication administration period. Three urine collection days are scheduled per week. Weekly methamphetamine use is scored as "0" if all [redacted] in the week were negative. Even if only one sample is collected and is negative for methamphetamine, the weekly methamphetamine use will be scored as "0." Weekly methamphetamine use is scored as "1" if at least one [redacted] is negative and at least one sample is positive for methamphetamine during the week. Weekly methamphetamine use is scored as "2" if all [redacted] collected during the week are positive. If no samples are tested during a week, the score is considered to be missing.

B. The proportion of subjects with 21 consecutive days of abstinence during the study medication administration period, during which time all [redacted] urine drug screens must be methamphetamine-negative. Study days between urine specimens are considered to be methamphetamine-negative days. If more than three calendar days of

qualitative urine drug screens are missing, then this period is not considered to be abstinent.

C. The proportion of subjects with 21 consecutive days of abstinence during the study medication administration period, during which time all urine drug screens must be methamphetamine-negative and there is no self-report of methamphetamine use. If one to seven calendar days of are missing, self-reported methamphetamine use will be used for evaluation. If no use is reported and there are no missing self-reports during this time, this period will be considered abstinent. If more than seven calendar days of are missing or if any self-report is missing, then this period is not considered to be abstinent.

D. The proportion of subjects who decrease the overall proportion of negative methamphetamine use days by SUR during the study medication administration period by 25% or more of their self-reported use in the baseline period.

E. The proportion of subjects who decrease the overall proportion of negative methamphetamine use days by SUR during the study medication administration period by 50% or more of their self-reported use in the baseline period.

F. The proportion of subjects who decrease the mean of the $\log_{10}$-transformed methamphetamine quantitative urine concentration during the study medication administration period by 25% or more of their mean of methamphetamine quantitative urine concentration in the baseline period.

G. The proportion of subjects who decrease the mean of the $\log_{10}$-transformed methamphetamine quantitative urine concentration during the study medication administration period to 50% or less of their mean of methamphetamine quantitative urine concentration in the baseline period.

H. Maximum number of calendar days of abstinence during the study medication administration period, during which time all urine drug screens must be methamphetamine-negative. Study days between are considered to be methamphetamine-negative days. If more than three calendar days of are missing, then this period is not considered to be abstinent.

I. Maximum number of calendar days of abstinence during the study medication administration period, during which time all urine drug screens must be methamphetamine-negative and there is no self-report of methamphetamine use. If one to seven consecutive days of are missing, evaluate self-reported methamphetamine use. If no use is reported and there are no missing self-reports during this time, this period will be considered abstinent. If more than seven calendar days of are missing or if any self-report is missing, then this period is not considered to be abstinent.

J. Weekly mean proportion of methamphetamine non-use days based on subject's self report of use (SUR) during the study medication administration period.

K. The overall proportion of negative [redacted] during the study medication administration period.

L. Weekly mean of the log_{10}-transformed quantitative urine methamphetamine levels during the study medication administration period.

M. Weekly mean proportion of non-use days of other drug use by self report only.

N. Weekly mean proportion of negative [redacted] for other drug use.

Reduction in the severity of methamphetamine dependence and craving and comorbidity

O. CGI-O scores (dependence).

P. CGI-S scores (dependence).

Q. Change in ASI composite scores from baseline to weeks 6 and 12 and the last available ASI.

R. BSCS scores (craving).

S. Change in adult ADHD scores based on the AISRS from baseline to week 4, 8, 12 and the last available AISRS score.

T. The overall proportion of subjects who show a 30% improvement in the AISRS score from baseline to week 4, 8, 12 and the last available AISRS.

U. Change in the subset of adult ADHD scores-hyperactive/impulsive score (based on the even numbers of AISRS) from baseline to week 4, 8, 12 and the last available AISRS.

V. Change in the subset of adult ADHD scores-inattentive score (based on the odd numbers of AISRS) from baseline to week 4, 8, 12 and the last available score.

W. Change in impulsivity scores on the Barratt Impulsiveness Scale from baseline to the last available score.

X. Change in attention (i.e., greater target sensitivity and reduced latency) as assessed by RVP test scores (outcome measures: A prime, total hits and mean latency, respectively) from baseline to week 6, 12 and the last available score.

Y. Change in visual memory and pattern recognition capabilities, (i.e., improved accuracy and reduced latency) based on PRM (immediate and delayed) test scores from baseline

(outcome measures: percent correct and mean correct latency), week 6, week 12 and the last available score.

Z. Change in executive function, spatial working memory and planning, (i.e., reduced errors and improved strategy) as assessed by SWM test scores (outcome measures: between search errors, strategy), and increased number of problems solved on first attempt and reduced latency as assessed by OTS test scores (outcome measures: problems solved on first choice, mean choices to correct, mean latency to first choice) from baseline, week 6, week 12 and the last available score.

AA. Change in impulsivity, decision making and risk-taking preferences (i.e., improved quality of decision making, reduced deliberation time, proportion of points gambled in overall proportion bet) as assessed by CGT test scores (outcome measures: quality of decision making, deliberation time, overall proportion bet) and increased ability to withhold a prepotent motor response as assessed by SST test scores (outcome measures: stop signal reaction time and median correct RT on Go trials) from baseline, week 6, week 12 and the last available score.

BB. Change in cognitive flexibility and attentional switching (i.e., reduced number of times the subject fails to select the stimulus compatible with the current rule on the stage where the dimension shift occurs and increased number of problems that the subject successfully completed) as assessed by IED test scores (outcome measures: IED EDS number of errors and stages completed) assessed at termination.

HIV Risk-taking Behaviors

CC. Change in HRBS scores from baseline to week 12 and to the last available score.

Treatment Retention

DD. Time from randomization to last study visit during the study medication administration phase.

Safety of Modafinil

EE. AEs, laboratory data, ECG, physical exams, vital signs, and HAM-D.

15.3 Subject Populations

The intent-to-treat (ITT) population is defined as the subjects who are randomized to treatment, and who receive the first dose of investigational product. The evaluable population is defined as the ITT subjects who contribute at least six (6) usable on-study urine samples and 21 days of self report. Treatment completers are the ITT population who take at least one dose of study medication in week 12, provide at least one urine sample in week 12, and provide self reports of substance use through the last day of week 11.

15.4 Analysis Plan

15.4.1 Efficacy Assessments

Each primary and secondary efficacy outcome measure will be analyzed for the ITT, the evaluable, and the treatment completer populations. Major differences in the results, if any, will be further explored.

All statistical tests will be two-sided at a 5% Type I error rate. Confidence intervals will be two-sided with a 95% confidence coefficient.

Primary Efficacy Outcome

The primary outcome measure for each subject is methamphetamine use or non-use weeks during the study medication administration period. This will be compared between treatment groups using Generalized Estimating Equations (GEE). GEE provides a model-based regression methodology applicable for the analysis of the correlated data that will result from this repeated measures longitudinal study. The GEE procedure proposed by Liang and Zeger (1986) and Zeger and Liang (1986) models the population average and has several useful features:

1. It can be used to analyze different types of outcomes such as continuous, binary, or count.
2. It can be used to analyze an unbalanced design caused by either differing numbers of observations per person or by observations taken at different times.
3. The parameter estimates are consistent even if assumptions about the variance structure are not completely accurate.

As a secondary analysis, the individual effects, if any, of age, race, gender, site, usual route of methamphetamine use (oral/nasal inhalation versus intravenous/smoked), historical self-report of methamphetamine use in the 30 days prior to informed consent (≤ 18 days *versus* > 18 days), impulsivity and the presence or absence of current ADHD on the primary treatment effects will be determined. The first order interactions of treatment with gender, historical self-report of methamphetamine use (use in the 30 days prior to informed consent [≤ 18 days *versus* > 18 days]), presence/absence of current ADHD, and impulsivity will also be included in the model.

Secondary Efficacy Outcomes

Unless the primary outcome analysis implies the need for a more elaborate model, between-group comparisons of the secondary outcomes will be performed as follows:

Outcome Measure	Test
B, C, D, E, F, G, K, T	Chi-squared test or Fisher's Exact Test
H, I, Q*, W, X*, Y*, Z*, AA*, BB*, CC	One-way ANOVA (with Dunnett's multiple comparison test) or Kruskal-Wallis
A, J, L, M, N, O, P, R, S*, U*, V*	GEE
DD	Kaplan-Meier Curves with log-rank test statistic

* In the case of insufficient data points, ANOVA with Dunnett's multiple comparison test will be performed.

GEE for ordinal categorical responses (outcome measure A) will be performed according to Lipsitz *et al*.(1994), if the proportional odds assumption satisfied.

15.4.2 Safety Outcomes

The severity and frequency of adverse events, laboratory data, ECG, physical exams, and vital signs, will be reported in tabular format. Adverse events will be coded using Medical Dictionary of Regulatory Affairs (MedDRA) preferred terms and grouped by body system. The frequencies of adverse events by type will be compared between study arms using Chi-square analyses; however, this analysis will be considered exploratory.

15.4.3 Descriptive Statistics

Summaries of the characteristics of the subject population in all three treatment arms at baseline will be prepared for the ITT, the evaluable, and the study completer subjects. A summary will be prepared to show dropouts/retention over time in each treatment arm and for a priori-defined subgroups (methamphetamine use in the last 30 days prior to informed consent (≤18 vs >18), gender, ADHD (yes/no) and site), along with the reason for early termination. The number of missing observations will be compared between treatment arms. Weekly treatment compliance of each treatment arm will be summarized. The types and frequency of other drugs used by self-report of use and by positive [redacted] urine drug screen will also be reported for each treatment arm. The proportion of subjects in each treatment arm that are abstinent at Week 16 will be summarized (abstinent is defined as no self-reported use since Week 12 and the Week 16 [redacted] urine drug screen is negative [redacted]).

15.5 Randomization Plan/Control of Bias

Adaptive randomization will be used to balance treatment arms within site with respect to the presence or absence of current ADHD, gender, and frequency of historical self report of methamphetamine use in the 30 days prior to informed consent (≤ 18 *versus* >18).

15.6 Sample Size Calculation

No formal power analysis can be performed for this study's outcomes because there is no available information to determine the effect of modafinil on the study population. The study sample size is 70 subjects in each treatment arm and will detect a moderate effect size (~ 0.48) at a type-I error rate of 5% and a power of 80%. The number of 70 in each arm was selected based on other NIDA studies of substance abuse as a number that is sufficient to provide an estimate of treatment effect, which can then be used in planning a future, pivotal trial, should it be warranted.

15.7 Exploratory Analyses

Additional *exploratory* analyses may be performed to evaluate other confounding factors on outcomes such as depression or routes of methamphetamine use at baseline and after treatment.

The following lists some of the exploratory analyses that may be performed:

1. Determine if the effects of modafinil, as compared to placebo, differ in the subjects with ≤18 days of methamphetamine use in the last 30 days prior to informed consent compared to subjects with >18 days of methamphetamine use in the last 30 days prior to informed consent.
2. Determine if modafinil, as compared to placebo, is more effective in the subgroup of subjects that demonstrated higher methamphetamine craving.
3. Determine if modafinil, as compared to placebo, is more effective in the subgroup of subjects that demonstrated greater compliance with CBT.
4. Determine if modafinil, as compared to placebo, is more effective in the subgroup of subjects that demonstrated greater study medication compliance.
5. Determine if modafinil, as compared to placebo, is more effective at increasing the proportion of subjects that are abstinent at Week 16 separately by self-report and by urine drug screen (abstinent is defined as no self-reported use since Week 12 or the Week 16 urine drug screen is negative).
6. Determine if modafinil, as compared to placebo, results in better retention in the study and less methamphetamine use as a result of improvement in cognitive functioning as assessed by CANTABelect cognitive test battery.
7. Determine if Modafinil, as compared to placebo, improves cognition in general which is expected to correlate with better retention in the study and less methamphetamine use.

16 DATA MANAGEMENT AND CASE REPORT FORMS (CRF)

Data management activities and statistical analytical support will be coordinated through the Data Management Center. An operations manual will be prepared for this study that incorporates procedures from this protocol with those procedures necessary for the day-to-day conduct of the trial. The operations manual will be used to train study staff, to provide reference for study procedures, and to guide quality assurance activities.

16.1 Data Collection

Data will be collected at the study sites onto paper CRFs. CRFs should be completed according to the instructions in the study operations manual. The site principal investigator is responsible for maintaining accurate, complete and up-to-date records for each subject. The site principal investigator is also responsible for maintaining any source documentation related to the study, including any films, tracings, computer discs or tapes.

16.2 Data Editing and Control

CRFs received at the Data Management Center will be reviewed. If incomplete or inaccurate data are found, a data clarification request will be forwarded to the clinical site for a response. The site will resolve data inconsistencies and errors prior to returning CRFs to the data-coordinating center.

Study monitors will routinely visit the study sites to assure that data submitted on the appropriate forms are in agreement with source documents. They will also verify that the investigational products have been properly stored and accounted for, subject informed consent for study participation has been obtained and documented, all essential documents required by Good Clinical Practice regulations are on file, and sites are conducting the study according to the research protocol. Any inconsistencies will be resolved, and any changes to the data forms will be made using the Data Management Center procedures.

16.3 Data Processing and Analyses

At study completion, when all data have been entered into the clinical database and the database has been checked for quality assurance and is locked, statistical analysis of the data will be performed by the Data Management Center statisticians in accordance with the analytical plan section of this protocol. Periodically, during the investigation, data sets will be submitted to the NIDA DPMC central data repository according to procedures specified in the study Operations Manual.

16.4 Study Documentation and Records Retention

Study documentation includes all CRFs (electronic and paper), data correction forms, workbooks, source documents, monitoring logs and appointment schedules, Investigator-Sponsor correspondence and regulatory documents (e.g., signed protocol and amendments, IRB correspondence and approved consent form and signed informed consent forms, Statement of Investigator form, and clinical supplies receipt and distribution records).

Source documents include all original recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Accordingly, source documents include, but are not limited to, laboratory reports, ECG tracings, X-rays, radiologist reports, subject diaries, biopsy reports, ultrasound photographs, subject progress notes, hospital charts or pharmacy records and any other similar reports or records of any procedure performed in accordance with the protocol.

Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

Government agency regulations and directives require that the investigator must retain all study documentation pertaining to the conduct of a clinical trial. These documents must be kept for a minimum of two years after discontinuation of the IND or 2 years after the approval of an NDA.

16.5 Confidentiality

16.5.1 Confidentiality of Data

Particular attention is drawn to the regulations promulgated by the Food and Drug Administration under the Freedom of Information Act providing, in part, that proprietary information furnished to clinical investigators and Institutional Review Boards will be kept confidential by the Food and Drug Administration only if maintained in confidence by the clinical investigator and Institutional Review Board.

By signing this protocol the investigator affirms to NIDA that information furnished to the investigator by NIDA will be maintained in confidence and such information will be divulged to the Institutional Review Board, Ethical Review Committee, or similar or expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

16.5.2 Confidentiality of Subject Records

To maintain subject confidentiality, all laboratory specimens, CRFs, reports and other records will be identified by a random alpha code and subject number only. Research and clinical records will be stored in a locked cabinet. Only research staff and NIDA program officials or their designee will have access to the records. Subject information will not be released without written permission, except as necessary for monitoring by the FDA, the NIDA data management and monitoring contractors, or NIDA. NIDA will file for a certificate of confidentiality that will cover all sites participating in the study.

By signing the protocol the investigator agrees that within local regulatory restrictions and ethical considerations, NIDA or any regulatory agency may consult and/or copy study documents in order to verify CRF data.

The procedure for applying for a certificate of confidentiality is provided in **Appendix III**.

17 PUBLICATIONS OF THE STUDY RESULTS

NIDA and the investigative group agree that data will be made available to individual investigators to encourage other publications, either by a group or by an individual investigator provided that: manuscripts based on the use of modafinil for the treatment of methamphetamine dependence may not be submitted for publication until the main findings of the study have been published or in press and this study has been accepted by the FDA for filing to the IND or NDA.

Review of manuscripts resulting from this study or from data generated during this study must occur according to the NIDA DPMC Publications Policy prior to submission for publication. Authorship shall be consistent with NIDA and DPMC policies.

18 SIGNATURES

NIDA REPRESENTATIVES

Typed Name	Signature	Date
Ahmed Elkashef, M.D. NIDA Co-Chairperson	_____	_____
Elmer Yu, M.D. VA Co-Chairperson	_____	_____
Ann Anderson, M.D. NIDA Investigator	_____	_____
Roberta Kahn, M.D. NIDA Medical Monitor	_____	_____
Liza Gorgon, M.S. NIDA Project Officer	_____	_____
Erin Iturriaga, R.N., CCRC NIDA Project Director	_____	_____

INVESTIGATOR (S)

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment with the IRB approval. I also agree to report all information or data in accordance with the protocol, and in particular I agree to report any serious adverse experiences as defined in section 14.7 of this protocol.

Typed Name	Signature	Date
Richard Rawson, Ph.D. Site Principal Investigator	_____	_____
Mark Hrymoc, M.D. Site Sub-Investigator	_____	_____
Donnie Watson, Ph.D. Site Sub-Investigator	_____	_____
Jan Campbell, M.D. Site Principal Investigator	_____	_____

Charles Gorodetzky, M.D., Ph.D. _____ _____
Site Sub-Investigator

William Haning, M.D. _____ _____
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Barry Carlton, M.D. _____ _____
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Deborah Goebert, Dr., PH., M.S. _____ _____
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R. Bradley Sanders, D.O. _____ _____
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Thomas P. Beresford, M.D. _____ _____
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Christopher J. Stock, Pharm. D. _____ _____
Site Principal Investigator

Ruth Dickinson, M.D. _____ _____
Site Sub-Investigator

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APPENDIX I: HIV/AIDS Education

Discuss with the Subject:

- Modes of transmission
- High risk behaviors
- Prevention behaviors
  - stop drug use
  - don't share needles
  - clean "works" before using
  - use of condoms

HIV Testing
- What test is for
- Confidential vs anonymous
- Optional
- What +/- test results mean
- Anxiety related to waiting for results

Demonstration of:
- Use of alcohol swipes
- Use of bleach kits

Subject wishes to be tested?
- If yes, talk through the consent
- Obtain signature

Offer outside referrals

APPENDIX II: Instructions For Evaluating and Reporting Adverse Events and Serious Adverse Events

A. GENERAL INSTRUCTIONS

1. The Adverse Event (AE) must be assessed at each visit, recorded on AE CRF and reviewed weekly by a study physician.

2. Record AEs as soon as the informed consent process is completed.

3. Report the severity of the event following the guidance in section B below.

4. Report the relatedness of the event to the study agent administration according to the guidance in section C.

B. DEFINITIONS – SEVERITY OF EVENTS

Mild: Awareness of symptom, but easily tolerated.

Moderate: Discomfort enough to cause interference with usual activity.

Severe: Incapacitating with inability to work or do usual activity.

C. DEFINITIONS – RELATEDNESS OF EVENTS

The investigator and/or study physician is responsible for defining, in his/her best judgment, the relationship of the AE/SAE to the study drug/placebo. The degree of certainty for which the AE/SAE is attributed to the study drug or alternative causes (e.g. natural history of the underlying disease, concomitant therapies, etc.) should be determined by how well the experience can be understood in terms of one or more of the following:

- ***Exposure:*** Is there evidence that the subject was actually exposed to the drug/placebo?

- ***Timing of the study drug/placebo:*** Did the AE/SAE follow in a reasonable temporal sequence from administration of the drug test?

- ***Consistency with study drug profile:*** Known pharmacology and toxicology of the study drug in animals and man; reaction of similar nature having been previously described with the study drug.

- ***Alternative explanations*** for the adverse event such as concomitant medications, concurrent illness, non-medicinal therapies, diagnostic tests, procedures or other confounding findings.

- ***Response to discontinuation*** of the study drug/placebo.

Terms and definitions to be used in assessing the study agent relationship to the AE/SAE are:

- ***Unknown:***
  Use this category only if the cause of the AE/SAE is not possible to determine

- ***Definitely Not Related:***
  The subject did not receive the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is not reasonable, or there is another obvious cause of the AE/SAE.

- ***Remotely Related:***
  There is evidence of exposure to the test drug or there is another more likely cause of the AE/SAE.

- ***Possibly Related:***
  There is evidence of exposure to the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is reasonable, but the AE/SAE could have been due to another equally likely cause.

- ***Probably Related:***
  There is evidence of exposure to the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is reasonable, and the AE/SAE is more likely explained by the test drug than by any other cause.

- ***Definitely Related:***
  There is evidence of exposure to the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is reasonable, the AE/SAE is more likely explained by the test drug than by any other cause, and the AE/SAE shows a pattern consistent with previous knowledge of the test drug or test drug class.

D. SPECIFIC INSTRUCTIONS – LABORATORY/ECG ADVERSE EVENT

A laboratory or ECG AE is any clinically significant worsening in a test variable that occurs during the course of the study, whether or not considered to be study agent related. For each such change, provide the information requested on date of test, severity, likelihood of a relationship to investigational agent, change in investigational agent dosage due to the AE, and treatment required.

All laboratory AEs should be specified as an increased or decreased test result (e.g., "increased glucose," "decreased potassium") or as a term that implies an abnormality (e.g., hypercalcemia, azotemia, hypokalemia, or bradycardia). Any abnormal laboratory value that is considered not clinically significant will be recorded as such on the clinical laboratory report CRF along with a comment providing justification for that determination.

E. SERIOUS ADVERSE EVENT AND UNEXPECTED ADVERSE EVENT REPORTING

24 hour Reporting Requirements

Any SAEs due to any cause, that occur during the course of this investigation, whether or not related to the investigational agent, must be reported within 24-hours by telephone or entered into the Serious Adverse Event Tracking and Reporting System (SAETRS) to: the Study Medical Monitor and the NIDA Project Director as follows:

NIDA Medical Monitor: Roberta Kahn, M.D. 301/443-2281

NIDA Project Director: Erin Iturriaga, R.N., CCRC 301/443-9807

The following information must be provided with the initial report of an SAE or unexpected AE:

- Name of person reporting the SAE/unexpected AE
- Subject's I.D. number
- Name of the principal investigator and institution
- Date the subject signed informed consent
- Date of first dose of study medication
- Description of the SAE/unexpected AE
- Date and time of Onset
- Date/time of administration of last dose of study agent/placebo prior to the SAE/unexpected AE
- Severity of the SAE/unexpected AE
- Investigator's assessment of the relationship of the SAE/unexpected AE to study drug (related, possibly related, probably related, unlikely related, not related)
- Any action taken with the study drug, alteration to protocol defined schedule, diagnostics, and treatments secondary to the SAE/unexpected AE.

3-day Supporting Documentation Requirements

SAETRS will be used for recording all SAEs in this trial. Documentation for all SAEs/unexpected AEs must be received by the NIDA Medical Monitor and the NIDA Study Director within 3 days of reporting the event. Required documents that must be submitted include the following:

- SAE entry in SAETRS

Additional documentation may include:

- Adverse Events CRF pages
- Copies of source documents pertinent to the event (lab reports, ECG tracings, medical chart notes, etc.)

- Any other relevant information necessary to facilitate the investigator's judgment regarding the SAE's relatedness to the severity OR by request of the Medical Monitor/Alternate

These documents may be submitted by facsimilie, as email attachments, or via overnight courier.

Follow-Up of All Adverse Events/Serious Adverse Events

All adverse medical events must be followed until they are resolved, or until all attempts to determine the resolution of the AE/SAE are exhausted. This may require an extended hospitalization period or a change in status from outpatient to inpatient. All treatments, outcomes and information regarding whether or not the subject was referred to their Primary Care Provider for additional follow-up must be recorded in the source document. All serious and unexpected adverse events occurring 30 days after administration of the last dose of study drug/placebo must be reported. All follow-up week 16 AEs will be recorded and followed to resolution only if they are serious, or if the study physician assesses them to be clinically significant.

The site investigator is required to provide the Medical Monitor and the NIDA Study Director with all relevant follow-up information necessary to facilitate a thorough understanding of the event and judgment regarding the relationship to the study drug/placebo.

Reporting to the FDA

The IND sponsor is required to report SAEs to the FDA:

- in 7 days if the SAE is unexpected (or, if expected, unusually serious or rarely seen), life-threatening or lethal, and at least possibly related to the investigational product, with a follow-up written report in 8 days;

- in 15 days if the SAE is unexpected (or, if expected, unusually serious or rarely seen), but not immediately life-threatening; and

- in an annual report in all other cases.

APPENDIX III: Procedure for Applying for a Certificate of Confidentiality

The only people who will know the identity of the subjects are members of the research team and, if appropriate the physicians and nurses. No information about the subjects, or provided by the subjects during the research, will be disclosed to others without the subjects' written permission, except:

- if necessary to protect subjects' rights or welfare, or
- if required by law.

When the results of the research are published or discussed in conferences, no information will be included that would reveal subjects' identity. Authorized representatives of the FDA and NIDA study monitors may need to review records of individual subjects. As a result, they may know subjects' names, but they are bound by rules of confidentiality not to reveal their identity to others. The results of this study including laboratory results and clinical information collected during this study will be submitted to the FDA and may be used for research purposes. The results of this study may be published but will not personally identify any subjects. All records will be kept in locked storage locations that will be accessible only to authorized study personnel.

Applying for a Certificate of Confidentiality

A Certificate of Confidentiality helps researchers protect the privacy of subjects in health research projects against compulsory legal demands (e.g., court orders and subpoenas) that seek the names or other identifying characteristics of research subjects. The certificate was developed to protect against the involuntary release of personally identified research information of a sensitive nature sought through any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. This authority was granted under the Comprehensive Drug Abuse Prevention and Control Act of 1970, Public Law No. 91-513, Section 3(a).

Investigators will obtain a certificate to avoid being required to involuntarily disclose personally identifiable research information about individual study subjects. Under this statute:

"The Secretary [of the Department of Health and Human Services] may authorize persons engaged in biomedical, behavioral, clinical, or other research (including research on mental health, and on the use and effect of alcohol and other psychoactive drugs) to protect the privacy of individuals who are the subject of such research by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals" (Public Health Service Act 301 (d), 42 U. S. C. 241 (d), as amended by Public Law No. 100-607, Section 163 (November 4, 1988)).”

Accordingly, this special privacy protection can be granted only to research (i.e., a systematic investigation, designed to develop or contribute to generalizable knowledge). It is granted only when the research is of a sensitive nature where the protection is judged necessary to achieve the research objectives.

The Investigator will submit the application, as outlined in the Confidentiality Certificate Application Instructions (http://www.nida.nih.gov/Funding/ConfidentialityInstruct.html), along with IRB review documentation and a copy of the informed consent/assent forms to be used in the study. The Principal Investigator must sign the application and submit everything to:

Ms. Anne Jarrett
NIDA Certificate of Confidentiality Coordinator
Office of Extramural Affairs
6101 Executive Boulevard, Room 200
Bethesda, Maryland 20852-8401
Rockville, MD 20852 (courier or express mail)
TEL: 301-402-6020

Since a certificate is generally issued to a sponsoring research institution, the application and its assurances, must be signed by a faculty member or a senior official. The principal investigator, or their staff, will not represent the issuance of a Certificate to potential participants as an endorsement of the research project by DHHS or use it in a coercive manner for recruitment of subjects. The investigator must use the authority of the Certificate to resist compulsory disclosure of individually identifiable research data.

The study subjects should be informed that a Certificate is in effect, and be given a fair and clear explanation of the protection it affords, including the limitations and exceptions. This information will be included in the informed consent. Please see below some suggested wording:

"We have received a Certificate of Confidentiality from the National Institute on Drug Abuse, which will help us protect your privacy. The Certificate protects against the involuntary release of information about your participation in this study. The researchers involved in this project cannot be forced to disclose your identity or your participation in this study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, you or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if you or your guardian requests disclosure of your participation, the researchers will provide research data. The Certificate does not protect against that voluntary disclosure.

Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or a Food and Drug Administration request under the Food, Drug and Cosmetics Act."

or

"A Certificate of Confidentiality has been obtained from the Federal Government for this study to help insure your privacy. This Certificate means that the researchers cannot be forced to tell people who are not connected with the study, including courts, about your participation, without your written consent. If we see [learn] something that would immediately endanger you, your child, or others, we may discuss it with you, if possible, or seek help."

Study subjects will be notified that a Certificate has expired if they are recruited to the study after the expiration date of the Certificate and an extension of the Certificate's coverage has not been granted.

If the research scope of a project covered by a Certificate should change substantially, the PI will request an amendment to the Certificate; however, the NIDA Certificate Coordinator may require a new Certificate depending on the extent of the change in scope. An extension of coverage must be requested if the research extends beyond the expiration date of the original Certificate, as research information collected after the expiration of a Certificate is not protected from compelled release.

A Certificate of Confidentiality is a legal defense against a subpoena or court order, and is to be used by the researcher to resist disclosure. The researcher should seek legal counsel from his or her institution if legal action is brought to release personally identifying information protected by a certificate. The Office of General Counsel for DHHS is willing to discuss the regulations with the researcher's attorney.

APPENDIX IV: CANTABelect Test Descriptions and Outcome Measures

Motor Screening (MOT)

This test is given at the beginning of each visit to familiarize subjects with the touchscreen concept and apparatus. The subjects are required to touch a series of flashing crosses displayed sequentially at different locations on the screen.

The outcome measure analyzed for this test will be Mean Latency from the display of a cross to a sufficiently accurate response from the subject.

Rapid Visual Information Processing (RVP)

RVP is a test of continuous performance and visual sustained attention. A white box appears in the centre of the screen, inside which digits from 2 to 9 appear, one at a time, in a pseudo-random order. Subjects are required to detect a series of target sequences of digits (2,4,6; 3,5,7; and 4,6,8) registering their responses using the press pad.

The outcome measures to be analyzed for this test will be RVP A' (A prime). This is the signal detection measure of sensitivity to the target, regardless of response tendency (range 0.00 to 1.00; bad to good). In essence, this measure is a measure of how good the subject is at detecting target sequences; Total Hits, the total number of target sequences correctly responded to in the allowed time; and Mean Latency, the mean time taken to respond to the target sequences.

Pattern Recognition Memory (PRM)

PRM measures the ability to encode and subsequently recognize visual information. In the presentation phase patterns appear sequentially on the screen, one at a time, and subjects are instructed to try to remember them. Immediately following the encoding phase, subjects carry out a recognition test, in which each pattern from the encoding phase is presented with another pattern of similar form and color, and participants must choose, by touching it, the pattern that they think occurred in the presentation phase. Half of the patterns are tested immediately and half after an interval of twenty minutes.

The outcome measures to be analyzed for this test will be Percent Correct and Mean Correct Latency from the display of the stimulus to the subject's response.

Spatial Working Memory (SWM)

SWM is a task of executive function, requiring strategy, implementation and the manipulation of information in short-term memory. This self-ordered search task measures the ability to retain spatial information and to manipulate remembered items in working memory. For each problem, a number of colored boxes are shown on the screen By touching the boxes and using a process of elimination, the participant must find one blue 'token' in each box and use them to fill up an empty column on the right hand side of the screen. The number of boxes is increased, until it is necessary to search a total of eight boxes. The critical instruction is that the subject must try to avoid returning to a box where a token has previously been found.

The outcome measures analyzed for this test will be Between Errors, the number of times a subject returns to a box in which a token has previously been found and Strategy, the total number of differently located boxes used by the subject to begin a new search for a token within the same problem. Using the same boxes to start a search on successive trials, providing a token was not in that box on the previous trial, is indicative of the use of a strategy.

One Touch Stockings of Cambridge (OTS)

This is a test of executive function, spatial planning and working memory based upon the 'Tower of Hanoi' test.. The screen is divided into an upper and lower display each with three colored balls. At the bottom of the screen is a row of 'boxes' containing the numbers 1 to 6 that will be used in the 'One Touch' assessed phase. The subject task is to calculate the number of moves required to move the balls in the lower arrangement to match the upper arrangement. This concept is explained in a practice phase where the subject actually moves the balls using the touchscreen control. The One-Touch test phase increases the demand to plan the sequence of moves in advance ('in their mind's eye'), to calculate the minimal number of moves to solve the problem. The subject responds by touching one of the numbered boxes, for example number two if he/she thinks two moves are required. The number of correct responses given at the first attempt, and the time taken to solve the problems constitute the main outcome measures.

The outcome measures analyzed for this test will be Problems Solved on First Choice, the number of assessed problems on which the first choice made was correct; Mean Choices to Correct, the mean number of attempts (unique box choices) that the subject required on each problem to make the correct choice (including the correct choice); and Mean Latency to First Choice.

Cambridge Gambling Task (CGT)

CGT is an established test of decision-making and risk-taking preferences. In this task subjects are presented with an array of 10 boxes, consisting of a varying number of red and blue boxes (e.g. 6 red, 4 blue). Subjects are instructed that a token is hidden under one box, and they must guess whether the token is under a red box or a blue box. After this probability judgment, subjects must place a bet on their decision. Bets are offered to the subject in an ascending or descending sequence (over two conditions of the test), to separate genuine risk preference from delay aversion or motor impulsivity. The CGT uses an independent-trials structure to minimise the demands for learning, working memory, and reversal learning that complicate the interpretation of other gambling tasks such as the Iowa Gambling task.

The outcome measures analyzed for this test will be Quality of Decision Making, the proportion of occasions, during the initial phases of each trial, on which the subject chose the majority box color calculated over all assessment trials on which the number of boxes in each color differed; Deliberation Time, the mean latency from presentation of the boxes to the subject screen-touch to select the color on which to gamble (this is calculated over all assessment trials); and Overall proportion bet, the mean proportion of current points gambled by the subject on all assessment gamble trials.

Stop Signal Task (SST)

SST is a more sensitive adaptation of the classic Go-No Go paradigm that has been widely used in translational research. The subject must suppress an automatic motor response that has already been initiated, when they detect an auditory stop signal. The subject makes rapid two-choice button presses on a keypad, to left or right facing arrows appearing on the screen (i.e. left arrow, left button). These Go trials constitute 75% of all trials, and so they become rapid and automatic ('prepotent'). On the other 25% of trials, the Go arrow is followed after a short delay by an auditory BEEP. On hearing the beep, subjects must try to override their motor response. By varying the delay between the Go arrow and the Stop Signal, the difficulty of stopping can be manipulated. The use of a tracking algorithm allows the task difficulty to be titrated to the individual subject, in order to assess their Stop Signal Reaction Time (SSRT); the key measure of inhibitory control.

The outcome measures to be analyzed for this task are RT on GO Trials, the median latency from the time of stimulus presentation to the time of button press; and Stop Signal Reaction Time, calculated by taking the subject's (SSD*) from their RT on GO Trials.

*SSD (Stop Signal Delay) is the time between the presentation of the stimulus and the time of the stop signal on trials where the subject correctly inhibited their response.

Intra- Extra Dimensional Set Shifting (IED)

IED is a test of rule acquisition, reversal learning and attentional set shifting derived from the Wisconsin Card Sorting Test (WCST). Relative to the WCST, the IED enjoys much simplified task administration and can be used in translational research (mouse, rat, monkey, man). Task performance requires: visual discrimination learning, attentional set formation, and maintenance, shifting and flexibility of attention. Two artificial dimensions are used in this test; color-filled shapes and white lines. Simple stimuli are made up of just one of these dimensions, whereas compound stimuli are made up of both, namely white lines overlying color-filled shapes. The subject starts by seeing two simple color-filled shapes, and must learn which one is a correct example of the current rule by touching it. Feedback teaches the subject which stimulus is correct, and after six correct responses, the stimuli and/or rules are changed. These shifts are initially intra-dimensional (e.g. color-filled shapes remain the only relevant dimension), then later extra-dimensional (white lines become the only relevant dimension).

The outcome measures to be analyzed for this task are EDS Errors, the number of times the subject failed to select the stimulus compatible with the current rule on the stage where the dimension shift occurs; and Stages Completed, The number of problems that the subject successfully completed.