

PHASE I CLINICAL STUDY PROTOCOL

SAFETY EVALUATION OF COCAINE TREATMENT MEDICATION, MODAFINIL: INTERACTIONS WITH INTRAVENOUS COCAINE

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1. INTRODUCTION

- Epidemiology and Magnitude of the Problem

Cocaine abuse and dependence remains a major cause of morbidity and mortality in the United States today. Although total use has declined in the decade from 1985 until 1995, regular weekly users have remained constant at one-half to three-quarter of a million individuals and crack cocaine use has tripled during this decade (Gfroer & Brodsky, 1993). From 1992 until 1995, cocaine abuse has steadily increased among the young (National Household Survey on Drug Abuse, 1996). Monthly cocaine use among individuals under the age of twenty has risen 166% from 1994 to 1995. Cocaine-related emergency room admissions were up 19% during this same interval (DAWN Report, 1996). The total number of cocaine-related ER visits has increased annually since 1985, and more users are less educated and under employed (Johanson & Schuster, 1995). Sociological evidence from the popular culture indicates that cocaine abuse as well as other forms of substance abuse, are becoming more widely accepted among youth again.

In the United States, psychosocial treatments remain the most commonly used modalities of treatment. Estimates of the success of treatments vary widely depending on patient population and treatment modality. Among disadvantaged groups of cocaine dependent patients receiving low intensity outpatient treatment, abstinence rates were 19% at a six- to twelve-month follow-up (Kang et al., 1991). Among cocaine dependent patients who had the advantage of private insurance, initial inpatient treatment, and outpatient aftercare treatment lasting several months, there was still only a 50% abstinence rate at one-year follow-up (Strickler et al., 1987). In either case, there is clearly room for improvement in treatment outcomes. It has been estimated that only 20% of those needing treatment for cocaine dependence receive treatment. Thus, while the magnitude of cocaine dependence and abuse remains problematic for our nation, treatment remains inadequate and unavailable to many who need it.

- Traditional Pharmacological Trials for Treatment of Cocaine Dependence

The less than optimal outcome with standard psychosocial treatments has led clinicians to try an array of pharmacologic agents for the treatment of cocaine dependence. Most of the early trials involved traditional psychopharmacologic agents, and were primarily short-term open-label exploratory studies. The earliest pharmacologic trials in cocaine dependence involved tricyclic antidepressants (Gawin, 1986; Giannini et al., 1986). In one study, desipramine-treated subjects were shown to have higher rates of short-term abstinence than placebo-treated subjects (Gawin et al., 1989a). In preliminary, open-label studies, Halikas and colleagues found that carbamazepine increased abstinence rates among cocaine dependent

patients (Halikas et al., 1989; 1991; 1992). Other agents that have been briefly studied include mazindol (Berger et al., 1989), L-dopa (Rosen et al., 1986), buprenorphine (Mello et al., 1989), flupenthixol (Gawin et al., 1989b), fluoxetine (Pollack & Rosenbaum, 1991), bupropion (Margolin et al., 1991), ondansetron (Jansowski et al., 1991), and haloperidol (Hall et al., 1993). Results of those studies were inconclusive. Replications of these findings in well-controlled, double-blind studies with appropriate outcome measures have been lacking (Weddington, 1990). More recently, trials of some of the above agents that have been more rigorously controlled with longer term follow-up have also been disappointing. Studies with fluoxetine (Grabowski et al., 1995), carbamazepine (Montoya, 1994), and desipramine (Arndt et al., 1992; Carroll et al., 1994a) have all failed to find a significant benefit of drug over placebo in evaluating relapse to cocaine use. While early reports of dopamine agonists reducing cocaine craving in cocaine-dependent subjects appeared promising (Tennant & Sagherian, 1987; Giannini et al., 1987), the results of double-blind, placebo-controlled trials with amantadine (Handelsman et al., 1995), bromocriptine (Eliler et al., 1995; Handelsman, 1997), and bupropion (Margolin et al., 1997) yielded no difference between placebo and dopamine agonists in reducing cocaine use as measured by urine drug screen results. In a more recent controlled trial with amantadine, this agent showed modestly favorable outcomes when compared to placebo (Shoptaw et al., 1998). Very preliminary work with disulfiram in cocaine dependence is also encouraging (Carroll, et al., 1998). An early trial with selegiline also shows promise and will lead to a phase III multicenter trial (personal communication, NIDA staff, April 1999).

- Conclusions on Pharmacologic Trials for Cocaine Dependence:

The observation that early trials appear to show encouraging results for treatment and later more rigorously controlled trials have failed to show any benefit on relapse prevention is undoubtedly due to a number of reasons. Placebo effects were likely to occur during the first 2-4 weeks; "sicker" subjects dropping out of the trial early would enrich the sample with more highly motivated subjects who were likely to have better treatment outcomes. Trials were too brief, and there was failure to standardize "dosing" of psychosocial treatments which led to a high degree of treatment outcome variability. The use of vaguely defined nonobjective outcome treatment criteria clouded data interpretation. In some substance abuse populations, measures of craving were not well-correlated with cocaine use behaviors as measured by urine drug screens (UDS) (Miller & Gold, 1994). Another problem with outcome in early trials was the use of a single weekly qualitative (negative or positive) urine drug screen to assess outcome. Subtle increases or decreases in cocaine use were missed with this approach; individuals also had a "window of opportunity" to use cocaine without being detected for the first few days immediately after the previous urine drug screen. More frequent urine drug screens (twice-weekly) and alterations in quantitative urine benzococaine levels are likely to be a more meaningful measure of cocaine use (Batki et al.,

1993). Statistical methods which failed to use either analysis of rigorous outcome measures such as UDS, or subject retention in treatment as measured by survival analysis, also presented problems for study interpretation.

In summary, pharmacological treatments for cocaine dependence are presently inadequate. Preclinical studies on the reinforcing aspects of cocaine have led to much useful knowledge about fundamental neuroscience principles of cocaine use, but thus far have not led to an effective treatment in humans. Human clinical trials with medications originally derived from psychiatric and neurologic yielded initial promising results in cocaine dependence, but in larger, more rigorous studies have demonstrated disappointing results.

- Pharmacologic, Behavioral, and Clinical Properties of Modafinil

Modafinil (Provigil®) has recently been approved by the FDA and is now marketed for the treatment of narcolepsy and idiopathic CNS hypersomnia. Recent reviews (Roth & Roehrs, 1996; Fry, 1998; Green & Stillman, 1998) have concluded that modafinil is at least as effective as traditional dopamine-acting stimulants for narcolepsy.

Modafinil, (di-phenyl-methyl)-sulfinyl-2-acetamide, is a novel stimulant which increases vigilance and wakefulness in mammals including humans but has less propensity for central and peripheral side effects associated with conventional psychostimulants (Bastuji & Jouvet, 1988). In contrast to amphetamine and other stimulants, modafinil increases motor activity in mice, rats, and cats, but does not induce stereotypies. This may suggest that the behavioral activation induced by modafinil does not involve direct effects on dopaminergic pathways (Rambert et al., 1990). Modafinil decreases GABA release in the median preoptic area and in the posterior hypothalamus in rats (Ferraro et al., 1996). It decreases GABA release in the nucleus accumbens but has minimal direct effects on dopamine release in the accumbens in rats (Ferraro et al., 1997). A recent study has indicated that micro-infusion of NMDA into the nucleus accumbens induces reinstatement of cocaine-seeking behavior in rats (Vorel et al., 1999). Since modafinil appears to promote glutamate release and stimulation of NMDA receptors, it too may have an indirect effect in the nucleus accumbens. Modafinil appears to increase glutamate release in ventral medial thalamus, ventral lateral thalamus, and hippocampus of the rat (Ferraro et al., 1997). Despite promoting glutamate release, other investigators have demonstrated that modafinil reduces the neurotoxic effects of excessive glutamate stimulation in cultured cortical neurons (Antonelli et al., 1998). Using 2-deoxy-glucose on a radiography in the rat brain, Engber and colleagues (1998) compared regional brain metabolic activity between amphetamine and modafinil. Both modafinil and amphetamine increase glucose utilization in all subregions of the hippocampus and in the central lateral 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. Using c-fos immunocytochemistry techniques in the cat, similar differences in metabolic activity among amphetamine, methylphenidate, and modafinil were found (Lin, Hou & Jouvet, 1996) as in the Engber study. 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 enhance glutamate and inhibit GABAergic functions.

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 & 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. Gold and Balster (1996) evaluated the discriminative stimulus and reinforcing effects of modafinil in comparison to amphetamine and ephedrine. Modafinil was reinforcing in rhesus monkeys. In the rat drug discrimination studies, modafinil produced dose-dependent responses in cocaine lever selection. Amphetamine showed greater selectivity than modafinil or ephedrine in producing cocaine-like discriminative stimulus effects. Both ephedrine and modafinil were weaker than amphetamine in both the stimulus discriminate model and reinforcing effects in rhesus monkeys maintained on intravenous cocaine self-administration. However, these studies indicate that modafinil, like other stimulants, can serve as a reinforcer similar to amphetamine and cocaine.

In summary, modafinil is a unique stimulant with little effect on dopaminergic systems but major effects on glutamate and GABA. Modafinil is reinforcing, and in some, but not all, operant tasks, it is similar to amphetamine. In humans it improves daytime alertness and concentration. It appears to have little propensity to increase blood pressure, pulse, or anxiety and few adverse effects on sleep. This agent produces minimal tolerance or dependence, and appears to have a low potential for interactions with other drugs. Headache is the only common side effect.

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 series, only headache occurs significantly more often in the active treatment group vs placebo. In general modafinil has been used in divided doses of 200-400 mg/day. Heitmann and colleagues (1999) studied modafinil in patients with mild to moderately obstructive sleep apnea syndrome. Most patients were obese with mild hypertension. Modafinil did not raise blood pressure or pulse. Adverse events were mild

with the exception of one case of supraventricular tachycardia, which resolved with medication cessation. Modafinil did not demonstrate any significant effects on REM sleep, non-REM sleep, or total sleep time. Modafinil is well-absorbed after oral administration, has a terminal elimination half-life of 10-15 hours.

Potential Pharmacokinetic Interactions Between Modafinil and Cocaine

To predict the potential pharmacokinetic interactions and subsequent pharmacodynamic consequences of combining cocaine and modafinil, the basic pharmacokinetics, metabolism and plasma protein binding of the two drugs is first summarized below.

Pharmacokinetics and Metabolism of Modafinil

Absorption of modafinil from tablets is rapid, with peak plasma concentrations occurring at 2-4 hours. The absolute oral bioavailability has not been determined due to the aqueous insolubility (<1 mg/mL) of modafinil, which preclude intravenous administration. Food has no effect on overall modafinil bioavailability; however, its absorption (t_{max}) may be delayed by approximately one hour if taken with food. Modafinil is well distributed in body tissue with an apparent volume of distribution (~0.9 L/kg) larger than the volume of total body water (0.6 L/kg). The major route of elimination (~90%) of modafinil is metabolism, with subsequent renal elimination of the metabolites. Metabolism occurs through hydrolytic deamidation, S-oxidation, aromatic ring hydroxylation, and glucuronide conjugation. Only modafinil acid and modafinil sulfone reach appreciable concentrations in plasma. The formation of the major metabolite, modafinil acid, is believed to be unrelated to cytochrome P450 (CYP) and is formed via the hydrolytic cleavage of the amide. Formation of modafinil acid was dose-dependent; this metabolic pathway was considered to be saturable for modafinil within the dose range of 200 to 400 mg (Moachon et al, 1996). It is thought that the sulfone is a product of modafinil acid metabolism, which is perhaps mediated by CYP3A4. Less than 10% of an administered dose is excreted in the urine as the parent compound. The largest fraction of the drug in urine was modafinil acid, but at least six other metabolites have been formed in lower concentrations. In non-human species, these modafinil metabolites did not appear to mediate the arousal effects of modafinil.

Modafinil is a chiral drug with a single stereogenic sulfur atom, resulting in two enantiomers when it is synthetically prepared (Prod Info Provigil®, 1998). The clinically administered formulation is a 50:50 mixture of the two enantiomers, *l*-(-)- and *d*-(+)- modafinil (a racemic mixture). Both enantiomers are thought to contribute to its therapeutic activity. The enantiomers appear to be metabolized at different rates by humans, leading to marked enantioselective disposition following an oral dose. The *d*- enantiomer has an apparent steady-state oral clearance approximately three-fold larger than that of its antipode (Wong et

al. 1999a, 1999b). The trough concentration ($C_{\text{min,ss}}$) of circulating modafinil after once daily dosing consists of 90% of the *l*-isomer and 10% of the *d*-isomer (Wong et al. 1999b). The effective elimination half-life of modafinil after multiple doses is about 15 hours. The enantiomers of modafinil exhibit linear kinetics upon multiple dosing of 200-600 mg/day once daily in healthy volunteers. Apparent steady-state of total modafinil and *l*-(-)-modafinil is reached after 2-4 days of dosing. The clinical consequences of this enantioselective disposition are unclear, however, pharmacokinetic studies should employ chiral assay methodologies to resolve what is effectively two different active compounds in plasma.

The pharmacokinetics of modafinil do not appear to be affected by gender or renal impairment, however, dosage adjustment may be necessary in the elderly or patients with significant hepatic impairment (Prod Info Provigil®, 1998; Wong et al 1998a, 1998b, 1999a, 1999b).

In a study in patients with narcolepsy, chronic dosing of modafinil at 400 mg once daily resulted in a ~20% mean decrease in modafinil plasma trough concentrations by week 9, relative to those at week 3, suggesting that chronic administration of modafinil might have caused induction of its own metabolism (Prod Info Provigil®, 1998). In *in vitro* studies using primary human hepatocyte cultures, modafinil was shown to slightly induce CYP1A2, CYP2B6 and CYP3A4 in a concentration-dependent manner (Prod Info Provigil®, 1998). A modest induction of CYP3A4 by modafinil has been indicated by other results, including a case report which has described an organ transplant recipient who experienced a 50% reduction in her cyclosporine (a CYP3A4 substrate) plasma concentration following one month of therapy with modafinil 200 mg daily (Le Cacheux et al 1997). It was postulated that modafinil induced the metabolism of cyclosporine, possibly *via* CYP3A.

Pharmacokinetics and Metabolism of Intravenously-Administered Cocaine

The average elimination half-life of cocaine following intravenous injection was 1.07 hours (Perez-Reyes et al. 1994). Approximately 85% to 90% of a dose of an intravenous dose of cocaine is recovered in the urine, with 1 to 5% being the unchanged parent compound (Jatlow, 1988). Two major metabolites, benzoylecgonine and ecgonine methyl ester, account for 29 to 45 and 32 to 49 percent of the dose found in urine, respectively, both of which probably have clinically insignificant psychoactive properties. Benzoylecgonine is measurable in urine within 1 to 4 hours and persists for up to 144 hours (Hamilton et al, 1977). N-demethylation products (ecgonine, norbenzoylecgonine and norecgonine) account for 1 to 3 percent of urinary metabolites (Stewart et al, 1979). Serum and liver pseudocholinesterases are responsible for cocaine hydrolysis to benzoylecgonine, and N-demethylation takes place in the liver (Stewart et al, 1979). Benzoylecgonine, a major metabolite of cocaine formed by hydrolysis, was not produced enzymatically in either serum

or liver; the rate of spontaneous formation at physiological pH suggests that this metabolite may arise nonenzymatically (Stewart et al 1979).

N-demethylation of cocaine to norcocaine has been shown in rodents and *in vitro* human cell systems to be mediated by CYP3A (Roberts et al. 1991; Pasanen et al. 1995; Pellinen et al., 1996). It has been demonstrated in mice that repeated administration of cocaine induces CYP3A activity at high doses (60 mg/kg) which enhances clearance of cocaine via this metabolic pathway (Pellinen et al., 1996).

Potential for Metabolic Interactions between Modafinil and Cocaine

Previous Drug Interaction Studies

Pharmacokinetic drug interactions studies for modafinil have been performed separately with methylphenidate (40 mg), dextroamphetamine (10 mg) and clomipramine (50 mg) which primarily undergo deesterification, deamination and demethylation, respectively (Prod Info Provigil®, 1998; Wong et al, 1998a, 1998b). These studies did not find any significant alterations in the pharmacokinetics or pharmacodynamic parameters measured of any of the agents studied.

CYP3A4 Induction by Modafinil and Cocaine

The apparent potential of modafinil and cocaine to induce CYP3A is unlikely to affect the overall disposition and pharmacodynamics of cocaine. This is because the formation of norcocaine by this isoform is a relatively minor route of elimination, accounting for only 1-3 % of an administered intravenous dose and even a doubling of activity would not be expected to have a major impact on cocaine pharmacokinetics.

While administration of modafinil may be associated with induction of CYP3A, the reported effect of this induction on modafinil clearance is questionable. Firstly, it is unlikely that an increase in the rate of formation of a secondary metabolite would have a major effect on the clearance of the parent drug to its primary metabolite. In addition, formation of modafinil acid from modafinil is considered to be saturable within the dose range of 200 to 400 mg (Moachon et al, 1996) and thus is the rate-limiting step in this enzymatic cascade at therapeutically used doses. Therefore, any effect on CYP3A would be limited to a relatively increased formation of the therapeutically inactive sulfone from the therapeutically inactive acid. Regardless, the purported effect on its own metabolism is small (~20 % increase in clearance) and these observations probably result from the wide interindividual and intraindividual (with respect to time) alterations in CYP3A activity and is unlikely to be of clinical significance. For the same reasons, a concomitant increase in CYP3A activity

associated with the repeated administration of cocaine is unlikely to have a clinically significant influence on modafinil clearance.

Plasma Protein Binding Interactions

In vitro studies in human plasma found modafinil is moderately bound to plasma proteins (~60%), with 90 % of this amount being bound to human serum albumin. It is not known whether this binding is enantioselective. At serum concentrations obtained at steady-state after doses of 200 mg/day, modafinil exhibits no displacement of protein binding of warfarin, diazepam, or propranolol. Even at much larger concentrations (1000 μ M; >25 times the C_{max} of 40 μ M at steady state at 400 mg/day), modafinil had no significant effect on warfarin binding. Modafinil acid at concentrations >500 μ M decreases the extent of warfarin binding, but these concentrations are >35 times those achieved therapeutically. *In vitro* evidence suggests cocaine binds to a high affinity site on α_1 -acid glycoprotein and a low-affinity binding site on human serum albumin (Bailey, 1995). Given the moderate binding of modafinil and the multiple binding sites for cocaine, it appears unlikely that a significant plasma protein binding site displacement interaction between modafinil and cocaine will occur when they are co-administered. If such an interaction were to occur, its effects would probably be transient with unbound (but not total) concentrations returning to concentrations observed prior to administration of cocaine due to more unbound drug being available for hepatic clearance and renal excretion (Wilkinson and Shand, 1975).

Given our current state of knowledge regarding the pharmacokinetics and metabolism of modafinil and cocaine, a pharmacokinetic drug interaction between these two agents appears unlikely. Nevertheless, since the enzyme responsible for the formation of the major metabolite of modafinil, modafinil acid, is unknown, a metabolic interaction between these two agents cannot be discounted at this point. However, since cocaine is mainly metabolized by pseudocholinesterase, and no reports of cholinesterase deamidation have been located, an interaction with this enzyme also appears unlikely.

The proposed study will allow a rigorous assessment of any pharmacokinetic interaction between modafinil and cocaine.

- Potential Pharmacodynamic Interactions between Modafinil and Cocaine

Modafinil

The precise mechanism(s) through which modafinil acts as a central nervous system stimulant is unknown (Prod Info Provigil®, 1998). Modafinil has wake-promoting actions like sympathomimetic agents including amphetamine and methylphenidate, although the

pharmacologic profile is not identical to that of sympathomimetic amines. At pharmacologically relevant concentrations, modafinil does not bind to most potentially relevant receptors for sleep/wake regulation, including those for norepinephrine, serotonin, dopamine, GABA, adenosine, histamine-3, melatonin, or benzodiazepines. Modafinil also does not inhibit the activities of MAO-B or phosphodiesterases II-V. As stated above (see Pharmacologic, Behavioral, and Clinical Properties of Modafinil) modafinil appears to primarily enhance glutamate and inhibit GABAergic functions.

Modafinil is not a direct- or indirect-acting dopamine receptor agonist and is inactive in several animal models capable of detecting enhanced dopaminergic activity (Prod Info Provigil®, 1998). In vitro, modafinil binds to the dopamine reuptake site and causes an increase in extracellular dopamine, but no increase in dopamine release.

Cocaine

Cocaine stimulates the sympathetic nervous system by blocking reuptake of catecholamines at the presynaptic clefts of adrenergic nerve endings, leading to an excess of neurotransmitters at the postsynaptic receptor sites, thus potentiating both inhibitory and excitatory responses of sympathetically innervated structures to endogenous and exogenous serotonin, dopamine, norepinephrine, and epinephrine (Coleman et al, 1982; Blum, 1976). Cocaine may also release norepinephrine stored in sympathetic nerve terminals and may stimulate the release of catecholamines from the adrenal glands (Chiueh & Kopin, 1978; Starke & Montel, 1973).

Cocaine has a central effect on the heat regulating center in the diencephalon and along with vasoconstriction, increased muscle activity and reduced heat radiation may lead to dangerous elevations in body temperatures. The vasomotor and vomiting centers may also be affected. Cocaine has direct cardiotoxicity and sensitizes the myocardium to arrhythmias (Gay et al, 1973).

Given the lack of data concerning the receptor pharmacology of modafinil, it is difficult to predict pharmacodynamic consequences of co-administration of modafinil and cocaine. It appears that modafinil is neither directly complimentary or a direct antagonist of cocaine and does not act through the adrenergic, serotonergic or dopaminergic systems. This study proposes to rigorously assess additive, synergistic or antagonistic pharmacodynamic effects of co-administration of modafinil and cocaine by way of cardiovascular monitoring (heart rate, ECG, blood pressure), vital signs, spontaneous adverse events reporting and the Visual Analogue Scale (Modified VAS-9906).

- Rationale for Modafinil Treatment of Cocaine Dependence

In treatment-seeking cocaine-dependent individuals, modafinil may have at least two mechanisms by which it may improve treatment outcome. First modafinil may act as a weak substitutive stimulant, providing reinforcement, decreasing craving and cocaine-seeking. Modafinil is of particular interest in this regard because it has less abuse potential and less tolerance when compared to traditional stimulants. Secondly, it may act indirectly on cocaine dependence by improving concentration and daytime alertness, allowing patients to profit from CBT and other forms of psychosocial treatments.

2. STUDY OBJECTIVES

The primary objectives of this study are to determine:

1. The safety/tolerability of modafinil as a cocaine treatment medication in cocaine dependent subjects.
2. If administration of intravenous cocaine to subjects (who have demonstrated ability to tolerate the intravenous (i.v.) cocaine administration) maintained on modafinil results in any adverse effects.
3. To determine if there is a pharmacokinetic interaction between cocaine and modafinil.

The secondary objective is to determine:

The ability of modafinil to modify the cocaine-related “high” as well as dysphoric reactions to cocaine withdrawal.

3. STUDY DESIGN

The general study design is described below.

This will be an inpatient placebo-controlled escalating dose drug interaction study. A total of 12 cocaine users will be enrolled in the study at a single study site. All subjects will be admitted to the research unit approximately 48 hours prior to the first dosing. The first dose will not be given until the urine toxicology screen shows negative for benzoylecgonine. The subjects will stay at the research unit throughout the entire study treatment. There will be a total of four infusion sessions: 1) screening/habituation, 2) baseline, 3) after 400 mg/day steady-state modafinil and 4) after 800 mg/day steady-state modafinil. Each group of infusion sessions will be two days in duration. The infusion sessions are:

- Day 1, a placebo saline infusion and cocaine 20 mg at least one hour apart, in random order
- Day 2, a placebo saline infusion and 40 mg cocaine, again at least one hour apart, in random order

The only single blind is that the 20 mg of cocaine will always occur on the first day, whereas the order of cocaine and placebo will be double blinded. There will be frequent monitoring of the blood pressure, ECG and oxygen saturation during infusion and for the following one hour. The study physician will remain in the room during the infusion and for one hour or more after each infusion and a cardiology fellow will be on call on the same floor of the hospital during and for at least one hour following the infusion.

The screening/habituation infusion will be used to determine the subject's ability to tolerate the two doses of cocaine and to determine whether they can discriminate between placebo-saline in each of the two doses of cocaine. Data from the screening/habituation infusions will be discarded. Subjects with adverse events during the screening/habituation infusions or subjects who are unable to make discriminations among saline and doses of cocaine will be dropped from the study and will be replaced.

There will be approximately 36 hour period between the two days of screening/habituation infusion and the baseline/control infusion. Baseline/control infusion will be identical in procedure to the screening/habituation infusions and blood will be drawn for cocaine analysis. After completion of the baseline/control procedures, subjects will begin receiving oral modafinil. On the afternoon of the completion of the baseline/control infusions, subjects will receive their first dose of 200 mg of oral modafinil. For the following five days, subjects will receive 200 mg of modafinil twice daily (400 mg/day).

After steady-state modafinil (200 mg twice daily) has been achieved (5½ days), subjects will receive another round of infusions of placebo-saline and cocaine, either 20 mg or 40 mg over two days with identical monitoring as with the previous infusions and blood drawing for cocaine and modafinil analysis. The 20 mg of cocaine will occur first as in the baseline/control infusions. On the afternoon of the completion of the second round of infusions, subjects will receive their first dose of 400 mg of oral modafinil. For the following five days, subjects will receive 400 mg of modafinil twice daily (800 mg/day).

After steady-state modafinil (400 mg twice daily) has been achieved (5½ days), subjects will receive another round of infusions of placebo-saline and cocaine, either 20 mg or 40 mg over two days with identical monitoring as with the previous infusions and blood drawing for cocaine and modafinil analysis. The 20mg of cocaine will occur first as in the previous

infusions. Subjects will be discharged the next morning. A follow up visit will be scheduled 7 days after discharge to discuss potential treatment options.

Prior to enrollment, eligible subjects will undergo a baseline screening exam for entry criteria and give written informed consent. For safety concern, subjects will be enrolled sequentially, i.e., not all at one time. Subjects will be asked not to use any psychoactive drugs or other drugs (except acetaminophen, aspirin, nicotine or caffeine) for at least 24 hours prior to each dosing and during the entire study period. Subjects will not be allowed to have coffee on the morning of any of the four infusions, nor will they be able to smoke or have access to a nicotine replacement patch the A.M. prior to infusions. Subjects will be monitored closely for heart rate, blood pressure and ECG immediately prior to and for 4 hours after each cocaine/placebo injection. Visual analogue scale (Modified VAS-9906) which assess response to cocaine administration will be obtained at various time points up to 6 hours after each cocaine/placebo injection. Blood samples will be collected at various times up to 12 hours after each cocaine administration for determination of plasma concentrations of cocaine and benzoylecgonine. Steady-state levels of the modafinil will also be determined during the modafinil phase. After physical assessments and blood samplings for the modafinil phase have been completed, subjects will be receive a modified SCID prior to being discharged as one of the discharge assessments. If the subject's vital signs and mental status have returned to baseline, the subject will be discharged from the research unit. **After subject 4, 8, & 12 have been completed, the data will be reviewed by NIDA's Data & Safety Monitoring Board (DMSB).**

4. STUDY SUBJECTS AND ENTRY CRITERIA

Volunteers will be recruited from the local community via referral or advertisement. Prospective subjects will receive a screening examination for entry criteria within 2 weeks of the first dosing of study medication. A sufficient number of current cocaine users by either intravenous route or by smoked route of administration not seeking treatment will be screened to identify a total of 12 eligible subjects. The eligibility of the volunteers will be evaluated based on the following criteria.

Inclusion Criteria

Potential subjects must:

1. Be volunteers who are dependent on cocaine and are non-treatment seeking at the time of study.

2. be male or female of any race, between 18 and 45 years of age.
3. meet DSM-IV criteria for cocaine abuse or dependence
4. currently use cocaine by smoked or intravenous route of administration and confirmed by positive urine screen for benzoylecgonine within 2 weeks prior to study entry. The subjects currently use cocaine by smoked route must have a history of intravenous exposure to drugs of abuse.
5. be in stable physical and mental health as judged by interview and physical examinations.
6. for female subjects, test non-pregnant and use adequate birth control. All female subjects will have a urine pregnancy test performed prior to the first dose of study medication. All females will have a second urine pregnancy test the morning of the day of discharge from the hospital.
7. be capable of providing written informed consent to participate in this study.
8. be able to comply with protocol requirements and be likely to complete all study treatments.

Exclusion Criteria

Potential subjects must not:

1. have current dependence, defined by DSM IV criteria, on any psychoactive substance other than cocaine, alcohol, nicotine, or marijuana or physiological dependence on alcohol requiring medical detoxification
2. have a history of significant hepatic, renal, endocrine, cardiac (i.e., arrhythmia requiring medication, angina pectoris, myocardial infarction, left ventricular hypertrophy as determined by electrocardiogram or clinical data), stroke, seizure, neurological, non-drug-related psychiatric, gastrointestinal, pulmonary, hematologic or metabolic disorders.
3. have a history of adverse reaction to cocaine including loss of consciousness, chest pain, psychosis, or seizure.
4. have a history of adverse reaction/hypersensitivity to modafinil or drugs of the same class.

5. test positive upon urine toxicology screen for opiates, benzodiazepines, barbiturates or related CNS depressants, amphetamines or related stimulants.
6. have clinically significant abnormal laboratory measurements in liver function tests (AST and ALT levels greater than 3 times of the upper limit of normal), hematology (CBC, differential, platelet count), serum chemistries (SMA-24) and EKG.
7. have any significant active medical, or psychiatric illness which might inhibit their ability to complete the study or might be complicated by administration of modafinil.
8. have active hypertension as defined by American Heart Association criteria.
9. currently receive any medications for the treatment of any medical conditions, specifically, subjects with an FEV₁ of less than 75 % of predicted values, any history of current or past asthma and/or the use of albuterol or other beta-agonist inhalers will be excluded.
10. be suffering from or have any history of migraine headaches.
11. have any medical history or condition considered by the investigator(s) to place the subjects at increased risk.
12. do not actively meet the inclusion criteria at the time of screening.

Institutional Review and Subject Informed Consent

The investigator should ensure that a duly constituted institutional review board (IRB) at the study site that complies with the FDA regulations (21 CFR part 56) will review the protocol and the volunteer informed consent form. The investigator will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others and will not make any changes in the protocol without IRB approval, except where necessary to eliminate immediate hazards to human subjects.

The investigator will explain the purpose and nature of the study, including the risks to the prospective volunteers before his/her participation in the study. The investigator will inform the volunteer that he is free to withdraw from the study at any time after enrollment. The volunteer must sign, in the presence of a witness, the informed consent form supplied by the investigator in accordance with the FDA regulations (21 CFR Part 50) and approved by the

institutional review board. A copy of the signed informed consent form will be provided to the volunteer.

5. STUDY MEDICATIONS AND ADMINISTRATION

Study Medications

Cocaine will be provided by NIDA and the sterile cocaine injection formulation will be prepared by the NIDA Pharmacy and stored appropriately at the MUSC IOP under the supervision of Dr DeVane. Modafinil 200 mg tablets will be purchased from Cephalon and supplied by Cephalon and will be stored and dispensed by the MUSC IOP Pharmacy. Certificates of analyses of cocaine injection and modafinil will be provided in the study report.

Study Drug Administration

Cocaine will be administered intravenously by constant infusion over 1 minute using a calibrated Harvard infusion pump, with an infusion rate of 20 mg/min for the 20 mg dose and 40 mg/min for the 40 mg dose. Cocaine/placebo infusion during the modafinil phases of the study will be administered at approximately the time when the average peak effect of modafinil occurs (2-4 hours). Commercially available modafinil tablets will be administered orally under supervision at 7 a.m. and 7 p.m. as dictated in this protocol.

Dietary Restriction

Subjects will be in fasted state each morning for modafinil administration. **Subjects will be allowed to eat 1.5 hours after modafinil administration.** Subjects will also not have access to food 1.5 hours before or after evening administration of modafinil. On the days of cocaine administration, subjects will not have breakfast, but will be given **lunch** approximately 3 hours after the first cocaine infusion. Subjects will not be allowed to smoke or have caffeine-containing beverages for 4 hours before or after cocaine administration. **Meals** will be provided to study subjects during their entire stay at the research facility.

6. MEASUREMENT AND SAMPLING PROCEDURES

Screening Examination

A sufficient number of prospective volunteers will be identified and screened for their eligibility for participation in this study. The screening examinations include a comprehensive interview, review of medical and drug abuse histories, physical and psychiatric examinations (eg. *ASI-lite*, *SCID*), fasting clinical laboratory tests (CBC, differential, platelet count, urinalysis) and a urine drug screen for amphetamines, barbituates, benzodiazepines, cocaine metabolites and opiates. Quantitative analysis will be performed for the following analytes: glucose, urea nitrogen, albumin, alkaline phosphatase (ALP), total bilirubin, direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LD), cholesterol, gamma glutamyl transferase (GGT), total protein, triglyceride and thyroid stimulating hormone (TSH). A urine pregnancy test will be given to all female volunteers.

Subjects will also be screened for HIV, 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 and if positive a chest x-ray 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 only a chest x-ray will be required. Volunteers will give written informed consent prior to screening examinations. The laboratory 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.

Pre-Infusion Period

Subjects meeting entry criteria will be admitted to the research facility approximately 48 hours before the first injection of cocaine/placebo and remain at the research unit until 24 hours following administration of the last dose of cocaine in the modafinil phase. The first dose of cocaine/placebo shall not be administered until the urine tested negative for benzoylecgonine. For safety concerns, subjects will be enrolled sequentially, i.e., not all at one time. They will be asked not to use any psychoactive drugs or other drugs (except acetaminophen, aspirin, nicotine or caffeine) for at least 48 hours prior to the first dose of cocaine/placebo and during the entire study period. Subjects will also be instructed not to smoke cigarettes before and four hours after each infusion. The infusion periods will consist of four two-day phases. These include screening/habituation infusion, baseline/control

infusion, and post-steady-state modafinil infusions at two doses of modafinil. The treatment period will consist of a control phase followed by a modafinil (test-drug) phase.

Control/Habituation Phase

After determining that subjects are medically and psychiatrically stable and have negative urines for benzylecognine according to NIDA guidelines (Preston *et al.*, 1997), they will proceed, accompanied by staff, to the GCRC for their screening/habituation infusion. As with all infusions, subjects will be randomized on a 1:1 basis to receive placebo (normal saline) and 20 mg (all doses are calculated as free base) of cocaine intravenously on the first day of infusion. Infusion of cocaine and placebo-saline (or vice versa) will be separated by a one hour interval. Infusions will take place over 1 minute. Should an adverse event occur as defined in the Stopping Criteria paragraph of the “Volunteer Discontinuation and Replacement” section below (page 21), subjects will be terminated from the study and not allowed to proceed with the remaining phases. Subjects will not be terminated from the study for adverse events unless considered clinically necessary by the Principal Investigators. Data from this session will be discarded.

Baseline/Control Phase

This will occur approximately 36 hours after screening/habituation infusions. On day 1 (study day 6) of the baseline, subjects will be randomly assigned (1:1 ratio) to receive a single dose of placebo and 20 mg cocaine. Infusion of cocaine and placebo-saline (or vice versa) will be separated by a one hour interval. All doses will be infused over 1 minute delivered via a calibrated Harvard pump in a double-blind fashion. On study Day 2, subjects will be randomly assigned in a 1:1 ratio to receive a single dose of placebo and 40 mg of cocaine infused in a 1 minute period with infusions separated by one hour. Blood samples will be collected for cocaine analysis (see below). Subjects who successfully complete this phase will proceed to the modafinil phase.

Modafinil Phase

The modafinil phase will be run in a single blind manner with escalating doses of modafinil (400 mg/day followed by 800 mg/day). On the evening of the second day of the 40 mg cocaine infusion, subjects will receive a single dose of 200 mg of modafinil orally. The subjects will have nursing supervision with visual observations of subjects during the four hours immediately after modafinil ingestion. **Temperature, pulse, and blood pressures**

will be taken at two and four hours after the dose. A physician will be immediately available for evaluation of the patient during and for four hours after this first oral modafinil ingestion. Subjects will continue to take 200 mg modafinil twice daily for the next 5 days with blood sampling prior to dosing after day 3 to ensure steady-state has been reached. If steady-state is confirmed prior to the end of day 5 (consecutive trough blood samples within 15 %), the investigators may choose to advance the subject to the next phase at this time.

Subjects will return to the GCRC and undergo two rounds of cocaine/placebo infusions identical to those received in the baseline/control phase. Blood samples will be withdrawn frequently for modafinil and cocaine analysis (see below). **During this time the subjects continue to take 200 mg modafinil twice daily.**

On the evening of the second day of cocaine/placebo infusions while taking modafinil 200 mg twice daily, subjects will receive a single dose of 400 mg of modafinil orally and monitored as for the first 200 mg modafinil dose. Subjects will continue to take 400 mg modafinil twice daily for the next 5 days with blood sampling prior to dosing after day 4 to ensure steady-state has been reached. If steady-state is confirmed prior to the end of day 5 (consecutive trough blood samples within 15 %), the investigators may choose to advance the subject to the next phase at this time.

Subjects will return to the GCRC and undergo two rounds of cocaine/placebo infusions, identical to those received in the baseline/control phase. **During this time the subjects continue to take 400 mg modafinil twice daily.** Blood samples will be withdrawn frequently for modafinil and cocaine analysis (see below).

A follow up visit will be scheduled 7 days after discharge to discuss potential treatment options.

Blood Sampling

Blood samples (4-5 mL for each sampling time) will be obtained using a syringe through an intravenous catheter in the forearm of the non-dominant arm. For each cocaine/placebo injection, samples for evaluating pharmacokinetics of cocaine and benzoylecgonine will be obtained immediately before dosing and at 0, 3, 10, 20, 30, 45, 60, 63, 70, 80, 90, 105 minutes and at 2, 3, 4, 6, 8 and 12 hours after the first infusion.

Each blood sampling tube will be labeled with protocol number, volunteer number, date, and time of collection. The actual sampling time for each sample will be recorded. Upon collection, 3.5mls of blood will be put into a vacutainer tube containing sodium fluoride and

potassium oxalate for cocaine analysis, the remaining 1.5ml will be put in a separate tube for modafinil analysis (**modafinil phase only**). These tubes will be placed on wet ice or in a refrigerator and plasma/serum will be separated by centrifugation within 30 minutes of blood collection. Plasma and serum samples will be stored in properly labeled tubes and kept frozen at -70 EC until assayed.

Day 3 and Day 4 – Cocaine/Placebo infusions – Screening Phase

No blood sampling

Day 6 and Day 7 – Cocaine/Placebo infusions – Cocaine alone

4 ml blood samples into heparinized vacutainers: immediately pre-dose, 0, 3, 10, 20, 30, 45, 60, 63, 70, 80, 90, 105 minutes and at 2, 3, 4, 6, 8 and 12 hours after the first infusion. **Upon collection, blood will be put into a vacutainer tube containing sodium fluoride and potassium oxalate for cocaine analysis.** Centrifuge blood and aspirate plasma into plastic tubes appropriately labeled for cocaine analysis, freeze immediately at –20 or –70°C.

Days 10, 11 and 12 – Steady-State Confirmation for 200 mg bid Modafinil p.o.

Single 2 ml blood samples into a syringe immediately prior to evening dose of modafinil tablet. Centrifuge blood and aspirate serum into plastic tubes appropriately labeled for modafinil analysis, freeze immediately at –20 or –70°C. These samples will be used for verification of modafinil steady-state conditions.

Days 13 and 14 - Cocaine/Placebo infusions with 200 mg bid Modafinil p.o.

5 ml blood samples into heparinized vacutainers: immediately pre-dose, 0, 3, 10, 20, 30, 45, 60, 63, 70, 80, 90, 105 minutes and at 2, 3, 4, 6, 8 and 12 hours after the first infusion. Upon collection, 3.5mls of blood will be put into a vacutainer tube containing sodium fluoride and potassium oxalate for cocaine analysis, the remaining 1.5ml will be put in a separate tube for modafinil analysis. Centrifuge blood and aspirate plasma/serum into plastic tubes appropriately labeled for cocaine analysis. Freeze tubes immediately at –20 or –70°C.

Days 17, 18, and 19 – Steady-State Confirmation for 400 mg bid Modafinil p.o.

Single 2 ml blood samples into a syringe immediately prior to evening dose of modafinil tablet. Centrifuge blood and aspirate serum into plastic tubes appropriately labeled for modafinil analysis, freeze immediately at –20 or –80°C. These samples will be used for verification of modafinil steady-state conditions.

Day 20 - Cocaine/Placebo infusions with 400 mg bid Modafinil p.o.

5 ml blood samples into syringes: immediately pre-dose, 0, 3, 10, 20, 30, 45, 60, 63, 70, 80, 90, 105 minutes and at 2, 3, 4, 6, 8, 12, 24 hours after the first infusion. Upon collection, 3.5mls of blood will be put into a vacutainer tube containing sodium fluoride and potassium oxalate for cocaine analysis, the remaining 1.5ml will be put in a separate tube for modafinil analysis. Centrifuge blood and aspirate plasma/serum into plastic tubes appropriately labeled for cocaine analysis. Freeze both tubes immediately at -20 or -80°C .

Days 20 and 21- Cocaine/Placebo infusions with 400 mg bid Modafinil p.o.

5 ml blood samples into heparinized vacutainers: immediately pre-dose, 0, 3, 10, 20, 30, 45, 60, 63, 70, 80, 90, 105 minutes and at 2, 3, 4, 6, 8, 12, and 24 hours after the first infusion. Upon collection, 3.5mls of blood will be put into a vacutainer tube containing sodium fluoride and potassium oxalate for cocaine analysis, the remaining 1.5ml will be put in a separate tube for modafinil analysis. Centrifuge blood and aspirate plasma/serum into plastic tubes appropriately labeled for cocaine analysis. Freeze both tubes immediately at -20 or -70°C . The extra sample at the end of this phase will be used to characterize the elimination phase of cocaine metabolites and modafinil.

Once the subject has completed the study, cocaine plasma samples will be shipped on dry ice via overnight courier to Dr. David Moody at the University of Utah (David E. Moody, PhD, University of Utah, Centre for Human Toxicology, 20 S 2030 E, Salt Lake City, UT 84112-9457, (801) 581-5117). The details of the shipping process are outlined in the operating procedures manual supplied by the sponsor and modafinil samples will be hand-delivered on ice to Dr DeVane, Laboratory of Drug Disposition and Pharmacogenetics, Room 254 North, Institute of Psychiatry, MUSC, 67 President St, Charleston, SC 29407 Ph: (843) 792 5448) and will be stored there at -70°C in a freezer fitted with a low temperature alarm until analysis.

Measurements of Cocaine/Benzoylecgonine and Modafinil in Plasma/Serum

Plasma concentrations of cocaine, benzoylecgonine, and modafinil enantiomers will be determined using sensitive and specific assay methods. The assay methods will be validated with regard to specificity, precision, accuracy and limit of quantitation. Plasma profiles of cocaine/benzoylecgonine and modafinil enantiomers obtained during the control phase will be compared to those obtained during the modafinil phase. Modafinil will be assayed at Dr. DeVane's laboratory at MUSC according to FDA guidelines on assay validation.

Primary Outcome Measures

For safety assessment, primary outcome measures are heart rate, blood pressure, oxygen saturation, oral temperature and ECG measures. Primary outcome measures are to determine clinical safety and pharmacokinetic interactions when cocaine and modafinil are co-administered, by comparing the hemodynamic response to cocaine before and after modafinil administration and determining plasma or serum concentrations of both drugs following cocaine administration, respectively. Heart rate, oxygen saturation, oral temperature and a 3-lead EKG will be monitored 30 and 15 minutes prior to each cocaine/placebo injection to the first hour after dosing and recorded every 15 minutes after dosing begins and through the 1 hour of the second dosing. ECGs will then be recorded every 30 minutes for the remaining 3 hours in the GCRC. This will be provided by telemetry services located in the GCRC. Any tachycardia or brady cardia arrhythmia will be recorded and printed for the records. The last ECG for the day of infusions will be a 12 lead ECG taken at the IOP approximately 12 hours after the first infusion. Blood pressure shall be monitored every 3 minutes from 15 minutes prior to cocaine/placebo dosing, and then every 3 minutes for 21 minutes immediately following the first infusion of cocaine/placebo, then at 25, 30, 40, 50, 55 and 59 minutes. Similarly, blood pressure shall then be monitored every 3 minutes for 21 minutes after the second cocaine/placebo infusion then at 25, 30, 40, 50, 55 and 59 minutes after the second cocaine/placebo infusion. Blood pressure shall be then be monitored at 2.5, 3.0, 3.5, 4, 4.5 and 5 hours after the starting of the first infusion. Monitoring of other primary outcome measures will be performed as the clinical situation dictates.

Secondary Outcome Measures

Secondary outcome measures are to determine the effects of modafinil on cocaine related “high” as well as dysphoric reactions to cocaine withdrawal. The visual analogue scale (Modified VAS-9906) which assess the responses to cocaine will be administered before and at 3, 10, 20, 45, and 60 minutes and hourly from 2 to 6 hours after each cocaine/placebo injection during the control and modafinil phases.

7. STUDY MANAGEMENT AND ADMINISTRATIVE ISSUES

Concomitant Medications

Study participants will be asked not to use any psychoactive drugs or other drugs (except acetaminophen, aspirin, nicotine or caffeine) for at least 24 hours prior to the first dose of cocaine/placebo and during the entire study period. If they require medications for their illnesses, an accurate record of all concomitant medications used (including names, dosage regimens, duration and purposes) must be documented.

Risks and Discomforts

Risks of Modafinil: Modafinil has been evaluated for safety in over 2200 subjects, 900 in patients with narcolepsy and the remainder were normal controls. The most commonly occurring adverse events (>5% of the time) associated with the use of modafinil for several days occurring more frequently than with placebo patients include headache, nausea, nervousness, anxiety, and insomnia. In a Canadian clinical trial, a 35 year old, obese narcoleptic male with a prior history of syncopal episodes experienced a nine second episode of asystole after 27 days of modafinil administration (150 mg twice a day). 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 (nonpatient) developed ideas of reference, paranoid delusions, and auditory hallucinations in association with multiple daily 600 mg doses of Provigil® and sleep deprivation. Psychosis was completely eliminated 36 hours after drug discontinuation.

Risks/Discomforts of IV Cocaine Administration: The risks of cocaine use include cardiac arrhythmia, coronary ischemia and infarction, hypertension, hypotension tachycardia, seizure, psychosis, panic states, and death. Deaths attributable to the cocaine administration in experimental setting have not been reported. Risk to subjects will be minimized by a slow infusion over 1 minute. The quantity of cocaine used in this study (maximal 40 mg for a day) is in general less than or comparable to the amount that a cocaine abuser might have consumed. In the event of effects intense enough to present a health risk, adequate medical support and resource will be immediately available.

Risks of Modafinil with Cocaine: The likelihood of potential risks are unknown. The potential risks include increasing the probability of cardiac arrhythmia, coronary ischemia, possible myocardial infarction, hypertension, seizure, psychoses, panic states, and death. Deaths attributable to the cocaine administration in experimental settings have not been reported. Risk to subjects will be minimized by a slow infusion over 1 minute. The quantity

of cocaine used in this study (maximal 40 mg for a day) is in general less than or comparable to the amount that a cocaine abuser might have consumed. In the event of effects intense enough to present a health risk, adequate medical support and resource will be immediately available.

Reporting Adverse Experiences

Volunteers will be monitored for adverse experiences throughout the entire study period under direct, close supervision by the investigator or designated staff. The investigator or designated staff will evaluate the intensity, seriousness, and causal relationship to the study medication(s) of all serious or unexpected adverse experiences. Adverse events are defined in Appendix 1. If an adverse event occurs the principal investigators will follow the protocol in Appendix 1. Physicians designated to be available for evaluation of the patient during and for four hours after this first oral modafinil ingestion include Robert Malcolm, M.D., Ziad Nahas, M.D., Robert Malanuk, M.D., and Thomas Cawthon, M.D. Any alteration in physicians will be submitted in writing to NIDA staff.

Volunteer Discontinuation and Replacement

Stopping Criteria: A volunteer may drop out of the study at any time if he/she so chooses or if the investigator feels it is clinically appropriate. A volunteer will be discontinued from the study due to a serious or unexpected adverse experience or a serious concurrent illness which warrants withdrawal of the subject from the study as determined by the principal investigators.

In addition, cocaine intravenous administration will be discontinued if any of the following events occurs:

- Systolic blood pressure > 165 mm-Hg.
- Diastolic blood pressure > 100 mm-Hg.
- Heart rate > 130 bpm.
- Behavioral manifestation of cocaine toxicity, e.g., agitation, psychosis, inability to cooperate with study procedures.

Further participation will be terminated upon a second occurrence of vital sign abnormality, behavioral manifestation of cocaine toxicity or if any of the following occur:

1. Discontinuation criteria do not return to acceptable limits within appropriate time frames (e.g. 30 minutes).
2. Discontinuation criteria are met for a second time within the protocol.
3. Systolic blood pressure > 180mmHg sustained for 5 minutes or more.
4. Diastolic blood pressure > 120mmHg sustained for 5 minutes or more.
5. Heart rate > 170 bpm or $[(220 - \text{age}) \times 0.85]$ bpm for 5 minutes or more.

Patients who experience significant adverse effects from modafinil will not participate in cocaine challenges. Medical follow-up will be provided as necessary when subjects are discontinued and the occurrence of discontinuation criteria must be reported to the subject.

If a volunteer is discontinued prematurely due to adverse events, this subject will not be replaced. If a volunteer is discontinued prematurely due to administrative reasons, a substitute volunteer may be enrolled. The substitute volunteer will be assigned a new subject number and receive study treatments in the same order as the discontinued subject. The aim of this study is to have approximately 12 subjects completing the study as planned.

Study Termination and Review Criteria

The study may be discontinued or terminated at any time if, in the opinion of the investigator, continuation of the study would present a serious medical risk to the subjects. After completion of the first subject, the study results (safety measures) will be reviewed by the principal investigators prior to continuation of subject enrollment. After completion of every 4 subjects, the results will be reviewed by NIDA's Data and Safety Monitoring Board. If the rate of subject discontinuation due to adverse events is $\geq 50\%$ among the first 4 subjects enrolled, then subject enrollment will be discontinued and a safety review be conducted to determine whether the study should be terminated. These criteria will apply to subsequent review of data after completion of every four subjects enrolled in the study.

8. DATA ANALYSIS

Pharmacokinetic Analysis of Plasma Data of Cocaine and Modafinil

Plasma concentration-time profiles of cocaine and benzoylecgonine after each cocaine injection will be analyzed using noncompartmental and compartmental methods to obtain pharmacokinetic parameter estimates using the P-Pharm pharmacokinetic modeling program.

Comparisons of pharmacokinetic parameter estimates of cocaine and benzoylecgonine between the control and modafinil phases will be performed for each dose level using analysis of variance (ANOVA). Confidence intervals (90%) for each parameter will be determined. Plasma profiles of cocaine and benzoylecgonine will also be compared between the two dose levels (20 mg vs. 40 mg) to further aid data interpretation.

Trough levels of modafinil (at least 3 measurements) will be analyzed using an appropriate statistical method to determine whether a steady state has been achieved. Plasma concentration-time profiles of modafinil and its metabolites after placebo and each cocaine injection will be analyzed using noncompartmental and compartmental methods to obtain pharmacokinetic parameter estimates using the P-Pharm® pharmacokinetic modeling program to estimate their pharmacokinetic parameters at steady state (C_{min} , C_{max} , T_{max} , AUC, apparent $t_{1/2}$, CL/F). Comparisons of pharmacokinetic parameter estimates of modafinil and its metabolites between the control and cocaine administration will be performed for each dose level using analysis of variance (ANOVA).

Analysis of Primary and Secondary Outcome Measures

Baseline (pre-cocaine) resting heart rate and blood pressure, averaged over 1 minute, will be compared to heart rate and blood pressure after each cocaine injection (placebo, 20 mg and 40 mg doses). Changes (from baseline) in heart rate and blood pressure induced by cocaine injection along with modafinil will be compared to those without modafinil, by cocaine dose level (placebo, 20 and 40mg doses), using repeated measures ANOVA. Changes (from baseline) in heart rate and blood pressure induced by cocaine doses of 0 (placebo), 20 and 40mg will be compared with each other for the control phase as well as for the modafinil phase using repeated measure ANOVA. Secondary outcome measures obtained in the control phase will be compared, by cocaine dose level, to those in the modafinil phase to determine the extent to which these measures are modified by the administration of modafinil using repeated measures ANOVA.

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APPENDIX 1. DOCUMENTATION OF ADVERSE EVENTS

In accordance with FDA reporting requirements, all AEs occurring during the course of the clinical trial will be collected, documented, and reported by the study investigators or study physicians according to the specific instructions detailed in this section of the protocol and Appendix IV. The occurrence of AEs will be assessed starting as soon as the informed consent process is completed and at each study visit by reviewing the subject's diary and asking about the subject's health status. An AE CRF will be 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.

Each week, a study investigator must review the AE CRF completed for the previous week for any events that were reported as continuing. All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed by study investigators until satisfactory resolution. AEs must be reported up to 4 weeks following completion of, or termination from treatment.

Serious Adverse Events

Each adverse event or reaction will be classified by the study investigator as serious or non-serious. Based on the seriousness of the adverse event or reaction appropriate reporting procedures will be followed. The 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 serious adverse event (SAE) or reaction as any untoward medical occurrence that at any dose:

results in death;

is life-threatening; (*NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient 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.

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

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 to: the Study Medical Monitor, the NIDA Project Officer, and the sponsor-investigator. The telephone report is to be followed within 3-days by submission of a completed SAE Form with demographic information and a narrative explanation of the event. Attached to the SAE Form should be photocopies of the AE Form, the Concomitant Medication Form, and the Medical History Form from the subject's CRFs. All serious medical events are also to be reported to the responsible institutional review board according to local regulatory requirements. All participating investigators will be notified of any serious and unexpected AE requiring submission to the FDA in an IND safety report from the sponsor-investigator.

Any fatal or life-threatening SAE that is investigational agent related and unexpected must be reported by the sponsor-investigator initially to the FDA within 7 calendar days via telephone, facsimile or e-mail. A followup written report must be submitted in 8 days to the FDA. All AEs that are both serious and unexpected but not life-threatening or lethal must be reported to the FDA, in writing, within 15 calendar days of notification of the sponsor-investigator of the SAE. All other SAEs will be reported in an annual report or more frequently as necessary. Any additional clinical information that is obtained must be reported to the FDA, as it becomes available, in the form of an information amendment. The sponsor-investigator will inform NIDA of all SAEs that occur during the study.

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 study investigators in this study have the responsibility of promptly reporting all SAEs to NIDA and the sponsor-investigator in order that the sponsor-investigator 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 a SAE, the subject must have appropriate follow-up medical monitoring. If the subject is hospitalized, medical monitoring will consist of not less than daily evaluation by physical examination, vital signs, laboratory evaluations, and if applicable, ECG

monitoring for significant treatment-emergent abnormalities. 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.

A. GENERAL INSTRUCTIONS

The Adverse Event (AE) CRF must be completed for each visit 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 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).

E. SERIOUS ADVERSE EVENT AND UNEXPECTED ADVERSE EVENT REPORTING

24 hour Reporting Requirements

Any serious adverse event, including death due to any cause, which occurs to any subject from the time of admission through discharge whether or not related to the study drug/placebo, must be reported ***within 24 hours*** to the NIDA Medical Monitor, the NIDA Project Officer, and the principal investigator (IND sponsor).

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
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

Written documentation for all SAEs/unexpected AEs must be received by the NIDA Medical Monitor/Alternate and the IND sponsor **within 3 days of reporting the event**. Required documents that must be submitted include the following:

SAE Form

Concomitant Medication CRF pages

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

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 inpatient 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.

The investigator is required to provide the Medical Monitor/Alternate and the IND sponsor 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 principal investigator, who is 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 study agent, with a followup 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.