NIDA-MDS-Disulfiram-0001

PHASE I, DOUBLE-BLIND, PLACEBO-CONTROLLED ASSESSMENT OF POTENTIAL INTERACTIONS BETWEEN INTRAVENOUS COCAINE AND ETHANOL AND ORAL DISULFIRAM

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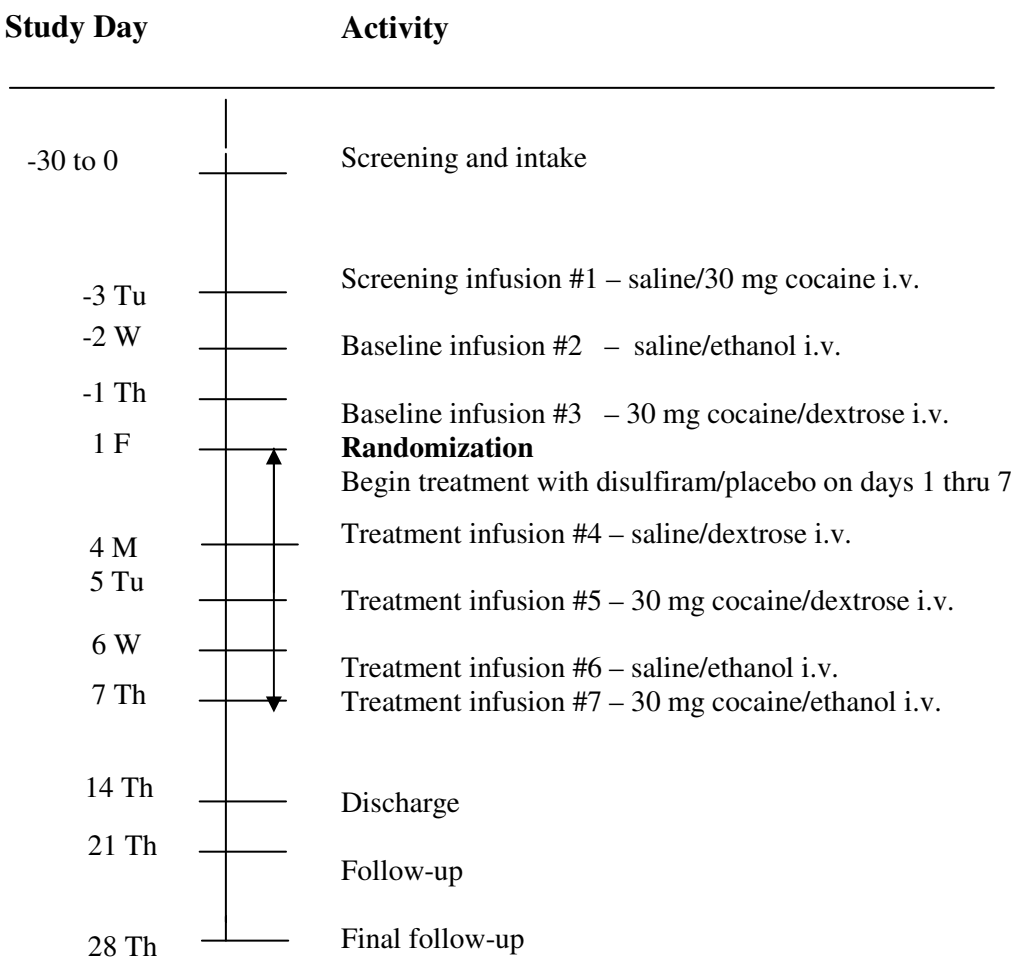
1 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvic transaminase
ANOVA	analysis of variance
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminse
AUC	area under the plasma concentration time curve
BAL	breath alcohol level
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CAP	College of American Pathologists
CLIA	Clinical Laboratory Improvement Amendment of 1988
CRF	Case Report Form
CPK	creatinine phosphokinase
CYP2D6	cytochrome P450 2D6 isoform
CYP3A4	cytochrome P450 3A4 isoform
DBH	dopamine beta hydroxylase
DER	disulfiram-ethanol reaction
DSMB	Data and Safety Monitoring Board
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
DTR&D	Division of Treatment Research and Development
ECG	electrocardiogram
FDA	Food and Drug Administration
GCRC	General Clinical Research Center
GGT	gamma glutamyltranspeptidase
HIV	human immunodeficiency virus
HPA	hypothalamic-pituitary-adrenal
HR	heart rate
IL-6r	interleukin-6 receptor
IRB	Institutional Review Board
i.v.	intravenous(ly)
LDH	lactate dehydrogenase
mg	milligrams
mL	milliliter
mPSRS	modified Positive Syndrome Rating Scale
MAO	monoamine oxidase
NIDA	National Institute on Drug Abuse
PK	pharmacokinetic
POMS	Profile of Moods State
SAE	serious adverse event
SAMHSA	Substance Abuse and Mental Health Services Administration
SCID	structured clinical interview for DSM-IV

Abbreviation	Definition
TNFr	tumor necrosis factor receptor
UCLA	University of California at Los Angeles
VAS	visual analog scale

2 STUDY SCHEMA



3 ABSTRACT

STUDY OBJECTIVES: This is a human laboratory clinical pharmacology study to assess potential interactions between intravenous cocaine and intravenous ethanol administration in cocaine-dependent subjects treated with oral disulfiram.

Primary: The primary objective of this study is to determine safety of alcohol use in cocaine-dependent subjects that used cocaine after treatment with disulfiram. This will be achieved by measuring adverse events and changes in cardiovascular and psychiatric responses from baseline.

Secondary:

1. To evaluate whether chronic daily treatment with disulfiram alters the pharmacokinetics of cocaine or its metabolites.

2. To evaluate whether changes in pharmacokinetics of cocaine or its metabolites induced by chronic daily treatment with disulfiram correlate with changes in plasma cholinesterase activity.

3. To evaluate the dose-relationship to the safety profile for a disulfiram-cocaine-ethanol three-way interaction.

4. To evaluate whether chronic daily treatment with disulfiram alters the subjective effects of cocaine (euphoria, craving) measured by Visual Analog Scale (VAS), Profile of Moods State (POMS) and modified Positive Syndrome Rating Scale (mPSRS) assessments.

5. To evaluate whether ethanol changes the subjective responses to cocaine in disulfiram-treated subjects as measured by VAS, POMS, mPSRS and Adjective Self-Assessment for disulfiram-ethanol reaction (DER) symptoms.

STUDY DESIGN: This is a two-site, double-blind, placebo-controlled inpatient study to determine the cardiovascular and psychiatric safety of alcohol use in cocaine-dependent subjects who had used cocaine after treatment with disulfiram. In this study, subjects will be screened for eligibility including initial screening for clinical tolerance to a cocaine infusion of 30 mg i.v. on day -3. Thereafter, baseline cardiovascular responses to i.v. cocaine and ethanol infusions (on days -2 and -1, respectively) will be established. In the previous version of this protocol, subjects were to be randomized on day 1 (after infusion #3) to one of three study groups (placebo, 250 mg and 500 mg of disulfiram). As of July 1, 2005, n=4 subjects have been tested with the 500 mg dose of disulfiram, but not all are evaluable and the design has changed so that no more subjects will be randomized to the 500 mg of disulfiram group. Thus, the current design is to complete a total of 16 subjects tested with either 250 mg disulfiram (n=8) or placebo (n=8). On the day of randomization (day 1), subjects will initiate oral dosage treatment with 250 mg disulfiram or placebo once a day for 7 days. Three days after initiation of daily treatment with either 250 mg disulfiram or placebo, all subjects will receive treatment infusions. On day 4, subjects will receive only i.v. saline; on day 5, 30 mg i.v. cocaine; on day 6, i.v. dose of ethanol;

and on day 7, 30 mg i.v. cocaine followed by i.v. ethanol 5 minutes later. After the day 7 dose of disulfiram/placebo, double-blind oral treatment will cease but subjects will remain in the hospital until discharge one week later on day 14. Subjects will be requested to return for safety follow-up approximately one and two weeks after the day of discharge. All infusions will be single blind and 'double-dummy', i.e. the cocaine infusion is blinded by a parallel saline infusion and the alcohol infusion is blinded by a parallel dextrose infusion. Study agent (disulfiram/placebo) will be administered double-blind.

STUDY DURATION: The study schedule consists of 30 days or less of outpatient screening, 4-17 days of inpatient screening (the UCLA site conducts most screening assessments in the inpatient unit), 14 days of inpatient research assessments, and follow-up visits on approximately days 21 and 28.

SAMPLE SIZE: 16 evaluable subjects will be enrolled in the 250 mg disulfiram (N=8) and placebo (N=8) dose groups..Each of the two sites will enroll 4 subjects in these two treatment groups.

POPULATION: Cocaine using research volunteers 18 to 50 years of age, who meet DSM-IV criteria for cocaine abuse or dependence and who are not seeking treatment. Volunteers must have a history of i.v. cocaine use and have used cocaine by the smoked or i.v. route on average at least twice per week and drink at least two drinks of alcohol on average at least twice per week for at least four of the past six weeks.

TREATMENTS: The additional subjects will be randomized (1:1, disulfiram/placebo) on day 1 to one of the following two arms:

Disulfiram 250 mg: 250 mg of disulfiram once a day on days 1 through 7.

Placebo: placebo once a day on days 1 through 7.

ASSESSMENTS: The primary study endpoint is safety. The safety of cocaine plus ethanol administration in disulfiram treated subjects will be determined by recording adverse events (AE), blood pressure (BP), heart rate (HR), and electrocardiogram (ECG). Secondary outcome measures include pharmacokinetic parameters, psychometric assessments and changes in activities of plasma cholinesterase and leukocyte aldehyde dehydrogenase. Pharmacokinetic analysis of cocaine and several of its metabolites (ecgonine methylester, benzoylecgonine, and norcocaine) as well as pharmacokinetic analysis of cocaethylene, a reinforcing metabolite of cocaine that is formed in the presence of ethanol, will be used to track the extent of changes in cocaine metabolism. Measurements of acetaldehyde levels will track the onset and time-course of this key ethanol metabolite associated with adverse disulfiram-ethanol reactions. The effect of disulfiram alone and its interaction with ethanol on subjective effects of cocaine (craving, euphoria) will be assessed by changes in VAS, POMS, mPSRS. Adjective Self-Assessment and physician observations will record the extent of disulfiram-ethanol reaction (DER) symptoms. Enzyme assays of plasma cholinesterase and leukocyte aldehyde dehydrogenase will determine the extent of enzymes inhibition by disulfiram.

4 INTRODUCTION AND RATIONALE

4.1 Therapeutic Strategies for Treating Cocaine Abuse

Despite 15 years of combating the problem of cocaine dependence, it remains a major medical, social, and legal concern, particularly for Americans who are living in urban areas and who are of ethnic minority backgrounds (SAMHSA, 1997). Since the beginning of the cocaine epidemic, intensive preclinical and clinical inquiry into medication candidates has been conducted, yet to date, an effective pharmacotherapy has eluded detection (Ling and Shoptaw, 1997). A variety of neuropharmacological strategies are being pursued in the search for an effective treatment for cocaine abuse. One approach has been to target the dopaminergic neurotransmitter system involved in the reward mechanism to interrupt the reinforcing action of cocaine and thus reduce its use and prevent relapse (Hyman and Nestler, 1995; Ling and Shoptaw, 1997; Mendelson and Mello, 1996). Cocaine is known to produce its major effects through dopaminergic mechanisms in the midbrain. Cocaine blocks the reuptake of dopamine; the consequent excess of dopamine stimulates the midbrain reward centers. To date there are not any effective pharmacological treatments for cocaine dependence.

4.2 Disulfiram as a Potential Medication to Treat Cocaine Dependence

Disulfiram is approved by FDA for the treatment of alcohol abuse and is marketed as Antabuse, an aversive therapy for alcohol use. The potential for disulfiram to be useful for induction of abstinence from cocaine use is based on observational data and clinical outpatient studies, indicating that multidrug abusing patients on disulfiram significantly reduced their use of cocaine (Grabowski *et al.,* 1991; Higgins *et al*., 1993, Carroll *et al*., 1998, George *et al*., 2000). Similarly for ethanol, disulfiram may act as an aversive therapy for cocaine use by enhancing cocaine-induced dysphoria as patients report increased dysphoria, anxiety, and paranoia after using cocaine in the presence of steady state disulfiram (Hameedi *et al*., 1994). A postulated mechanism is that disulfiram inhibits dopamine β-hydroxylase, resulting in higher dopamine concentrations by reducing the amount that is converted to norepinephrine. In addition to enhancing the aversive effects of cocaine, this increase in brain dopamine availability is hypothesized to reduce cocaine craving and hence use.

Clinical Trials. Three open-label trials have reported that disulfiram (Antabuse) reduced cocaine use in cocaine dependent outpatients with concomitant alcohol abuse. The first two studies (Grabowski *et al.,* 1991; Higgins *et al.,* 1993) suggested that disulfiram-mediated drinking reductions may have indirectly reduced associated patterns of cocaine use as well. The third non-blinded trial, randomized cocaine and alcohol dependent patients to different types of psychotherapy with or without disulfiram (Carrol *et al.,* 1998) and reproduced the effect of disulfiram on cocaine use. That study further suggested that disulfiram may work to inhibit the formation of cocaethylene, a reinforcing metabolite of cocaine that is formed in the presence of ethanol (McCance *et al*., 1995). Most recently, two double-blind trials (George *et al*., 2000; Petrakis *et al.,* 2000) showed disulfiram-induced reductions in cocaine use among opiate-dependent outpatients on opioid maintenance therapy. This suggests that the disulfiram effect on cocaine use may be direct and not mediated through a secondary mechanism of reductions in alcohol intake. Importantly, meta-analysis of data obtained in the trials mentioned above indicate that treatment with disulfiram results in a significantly higher level of cocaine-free

urines compared to placebo, i.e. 51% *versus* 35%, with no serious adverse events being reported (N=200).

Laboratory Studies of Disulfiram-Cocaine Interactions. Two laboratory studies (Hameedi *et al.,* 1995; McCance-Katz *et al*., 1998b) were conducted to assess the pharmacological interactions between disulfiram and cocaine. They reported that disulfiram may increase anxiety and other dysphoric effects of cocaine which thereby diminishes its euphorigenic potential. They also found that disulfiram increased cocaine plasma levels and but did not potentiate subjective or cardiovascular effects of cocaine. A seminal paper by McCance-Katz *et al*. (1998a) more thoroughly characterized the pharmacokinetic, subjective, and cardiovascular results of cocaine effects with and without pretreatment with disulfiram in five cocaine dependent subjects who also abused alcohol. The design was a double-blind, placebo-controlled, crossover study examining the factorial combinations of intranasal cocaine (0, 1, and 2 mg/kg) administration with one of three daily oral doses of disulfiram (0, 250, and 500 mg) pretreatment. Cocaine doses were given in an ascending series within a block of 3-5 days of disulfiram pretreatment and the disulfiram doses were random crossovers with a five-day washout between treatments. Disulfiram produced a dose-related inhibition of cocaine metabolism. The 500 mg dose of disulfiram produced: 1) a 3-fold increase in maximum plasma cocaine concentration; 2) a 2-fold increase in cocaine elimination half-life; 3) an increase in the time-to-maximum cocaine concentration; and 4) nearly a 6-fold increase in area-under-the-time/cocaine concentration curve. Pulse and pressor effects of cocaine were increased by disulfiram but not in a manner related to disulfiram dose. Mean disulfiram-induced heart rate increases of 10-15 bpm were maintained over a period of 6-8 hours post-cocaine dose as were mean systolic blood pressure increases of 10-15 mm Hg. Visual analog ratings of subjective effects were not significantly altered by disulfiram although two subjects dropped out of the study after experiencing "negative effects" of cocaine following disulfiram treatment.

4.3 Cocaine

Pharmacology. Cocaine inhibits the reuptake of norepinephrine, serotonin, and dopamine. The dopaminergic activity is thought to contribute to the reinforcing effects of cocaine, and actions at dopamine and norepinephrine terminals may contribute to its sympathomimetic effects.

Pharmacokinetics. Following i.v. administration, cocaine is eliminated with a $t_{1/2}$ of 80-90 minutes following administration of a single dose (Jeffcoat *et al*., 1989), though this may be prolonged to 2-3 hours following chronic dosing (Mendelson *et al*., 1999). In 6 subjects (Cone, 1995), peak plasma cocaine concentrations occurred within 5 minutes of administering a 25 mg dose, and declined rapidly over the next 12 hours. However, there were very significant differences in peak plasma concentrations (97.7 – 349.4 ng/mL) and elimination half-life (0.97 – 9.8 hr). Two subjects had half-lives of 9.1 and 9.8 hr compared to 0.97 to 1.6 hr in the other four subjects. The clearance of cocaine also differed significantly between the two groups. Despite intravenous administration, there were variations in time to reach peak concentration (1.2 – 4.8 min). Thus, substantial inter-individual variability in cocaine metabolism is possible. Another pharmacokinetic study in 5 subjects also reported rapid decline in plasma concentrations after intravenous administration of a 32 mg dose (Chow *et al*., 1985). However, the observed elimination half-lives (31 – 63 min) were shorter than those reported by Cone (1995). These data are more consistent with the rapid metabolism and elimination rates generally seen with

cocaine (Benowitz, 1993; Jeffcoat *et al.,* 1989). The study by Chow *et al.* (1985) reported that the peak chronotropic effect of i.v. cocaine occurred at 7.3 minutes after drug administration.

Metabolism. Cocaine is rapidly metabolized by plasma cholinesterases, liver esterases, and by liver microsomal enzymes. In humans, cocaine is metabolized to 1) ecgonine methyl ester (up to 50%) by plasma and hepatic cholinesterases, 2) benzoylecgonine (up to 45%) by spontaneous hydrolysis and hepatic carboxyesterase, and 3) norcocaine (up to 6%) by CYP3A4 (Benowitz, 1993; Dean *et al.,* 1991; Stewart *et al.,* 1977, 1978, 1979). In a study of cocaine metabolism in pigs (Kambam *et al.,* 1992), pharmacological inhibition of plasma cholinesterase was associated with a decrease in the active metabolite, ecgonine-methyl-ester, and an increase in the inactive metabolite, benzoylecgonine. This may explain why inhibition of plasma cholinesterase was actually associated with protective effects from cocaine-induced cardio-respiratory fatality in rats (Kambam *et al.,* 1990). It is also possible that between-individual variability in cocaine metabolism and/or toxicity may be accounted for by variation in the patients' plasma levels of cholinesterase activity (Hoffman *et al*., 1998). For the present study, it is important to determine levels of plasma cholinesterase activity and the extent of its inhibition by disulfiram to understand the relationship of these parameters to the changes in cocaine metabolism.

Safety and Dose Justification. In our prior laboratory investigations of effects of cocaine we have utilized safely, individual doses of 40 mg given i.v. Therefore, the proposed doses of 30 mg i.v. would be expected to provide a wider margin of safety. That is, were there to be an interaction with a study compound that increased the cardiovascular or subjective effects of the combination, it should be demonstrable yet safe in the laboratory.

The co-administration of cocaine with alcohol leads to the development of cocaethylene, a compound with pharmacological effects resembling cocaine, but that is eliminated considerably more slowly, with a terminal half-life of several hours. Thus, cocaine taken in the presence of alcohol could theoretically produce extended cardiovascular consequences and toxicities. Practically, however, the formation of cocaethylene occurs slowly and reaches a peak concentration that is less than 10% of that reached by cocaine. Thus, the formation of cocaethylene probably contributes little above cardiovascular effects produced by cocaine alone (Cami *et al*, 1998; Perez-Reyes and Jeffcoat, 1992).

In an interaction study with alcohol, Foltin and Fischman (1988) reported the cardiovascular effects in 9 subjects following intranasal administration of cocaine hydrochloride (4, 48, or 96 mg) 25 minutes after consuming an ethanol cocktail (0, 19.4, 38.7, or 58.1 mg). The two highest doses of cocaine with the highest dose of alcohol increased HR by 20 bpm. While performing a serial addition task, the combination of the highest cocaine dose and alcohol increased HR by 40 bpm, though only relatively small increases in BP were also observed under these conditions. Based on these data, Foltin and Fischman concluded that combinations of ethanol, cocaine and task performance produce greater increases in HR than BP, and, in addition, this increase in HR is greater than that observed following cocaine, ethanol, or task performance alone.

Cocaine Effects on Immune Function. Cocaine administration has been shown to produce activation of the hypothalamic-pituitary-adrenal (HPA) axis, with resulting elevations in cortisol. Concommitant with HPA activation, interleukin-6 (IL-6) is also released (Goebel *et al*., 2000). IL-6 is a member of the class of proinflammatory cytokines which activate several aspects of the

immune system (Horn *et al*., 2000). A recent article reports that cocaine administration may be associated with reduction in the IL-6 release, which is activated by i.v. cannula insertion (Halpern *et al.,* 2003). This suggests that cocaine administration may result in reduced proinflammatory activity, or put differently, immunosuppression. Indeed, it has been hypothesized that cocaine associated reductions in IL-6 may contribute to an increased prevalence of infections in cocaine-dependent patients.

Because cocaine dependence is thought to be a risk factor for infection, the effects of cocaine on immune parameters affecting vulnerability to infection are of great interest. In order to further investigate effects of cocaine on relevant immune parameters, we propose to measure cortisol and several cytokines and their receptors (IL-6, IL-6r, TNF, TNFr, and IL-1r) in blood. These cytokines were selected because they contribute both agonistically and antagonistically to the neuroimmune cascade trigerred by the physiological stress of i.v. insertion (Horn *et al*., 2000), such as may occur with i.v. cocaine administration.

4.4 Disulfiram

Pharmacology. Disulfiram is a relatively non-specific inhibitor of sulfhydril-containing enzymes. Among these, the inhibition of aldehyde dehydrogenase by disulfiram has been exploited for its use as an aversive medication in the treatment of alcoholics who are motivated to maintain abstinence (Goldfrank, 1994). In addition, disulfiram has been reported to inhibit the primary pathways for cocaine metabolism by inhibiting plasma cholinesterases and hepatic microsomal and plasma carboxylesterases (Faiman, 1979). Also pertinent to the current study is the finding that disulfiram inhibits dopamine β-hydroxylase, the enzyme catalyzing the conversion of dopamine to norephinephrine (Hameedi *et al.,* 1994). Although disulfiram is not metabolized by these isoenzymes, disulfiram and its primary metabolite, diethyldithiocarbamate, are inhibitors of CYP2E1 and CYP2C9 *in vivo* (Frye and Branch, 2002). These two isoenzymes are not involved in the metabolism of cocaine or ethanol and so any inhibitory effect of disulfiram on these enzymes should not affect the cocaine/ethanol interaction.

Pharmacokinetics. The pharmacokinetics of disulfiram are complex (Johansson, 1992; Faiman *et al*., 1984). After ingestion, disulfiram is rapidly converted, probably in the stomach, to its bis (diethyldithiocarbamato) copper complex resulting in the absorption and distribution of both the parent drug and its copper complex. In the blood, both compounds are rapidly degraded to form diethyldithiocarbamate (DDC), which is unstable and undergo's spontaneous degradation to form diethylamine, and carbon disulphide. DDC is also metabolized in the liver, which forms diethyldithiomethylcarbamate (Me-DDC) and the glucuronic acid of DDC. Me-DDC undergoes oxidative biotransformation to diethylthiomethylcarbamate (Me-DTC), which is further oxidized to its corresponding sulphoxide and sulphone metabolites. Both the disulfiram parent compound and most of these metabolites are biologically active although not all accumulate to a biologically significant extent. The elimination half-life ($t_{1/2}$) of the disulfiram parent compound as well as two of it most important metabolites (Me-DDC and Me-DTC) is approximately 7-11 hr. However, these values are not so relevant because the inhibition of aldehyde dehydrogenase is irreversible so that inhibition accumulates with repeated dosing and new enzyme must be generated upon cessation of dosing. With repeated disulfiram dosing, maximal enzyme inhibition is achieved within six days (Beyeler *et al*., 1985) and sensitivity to alcohol typically lasts for 1 week after the last dose of disulfiram (Faiman, 1979; Goldfrank, 1994). Depending on hepatic function, residual sensitivity may be present for as long as two weeks.

Interestingly, alcoholic liver damage impairs the formation of some of the disulfiram metabolites and the therapeutic effectiveness of disulfiram as an inhibitor of aldehyde dehydrogenase is diminished (Wicht *et al*., 1995).

Interactions with Alcohol. Disulfiram is approved by the FDA for the treatment of alcohol abuse and is marketed as Antabuse, an aversive therapy for alcohol use. The inhibition of aldehyde dehydrogenase by disulfiram produces a reaction when taken concurrently with alcohol. In the presence of disulfiram, blood alcohol levels of approximately 50 mg/dL will provoke a response (Goldfrank, 1994). However, patients may be sensitive to lower blood alcohol concentrations and idiosyncratic responders have been known to react to the topical application of alcohol containing products. The effects of alcohol in disulfiram-treated individuals have been well characterized. In patients who are at steady state levels of disulfiram, the characteristic physiologic response will typically occur within 15-30 minutes after oral alcohol ingestion. The most universally common and rapid onset symptoms include warmness and flushing of the skin, especially in the upper chest and face and related conjunctival injection of the eyes (Kristenson, 1995). Other symptoms include pruritus, decreased blood pressure, increased heart rate, nausea, vomiting, sweating, dizziness, headache, blurred vision, and confusion. The intensity of these reactions varies with each individual, but is generally proportional to the doses of disulfiram and alcohol ingested. The Disulfiram-Ethanol Reaction (DER) is caused by increased levels of the alcohol metabolite, acetaldehyde, and individual differences in the intensity of the DER are believed to be attributable to differences in acetaldehyde levels due to differential aldehyde dehydrogenase activity and its inhibition by disulfiram (Beyeler *et al*., 1985; Sauter *et al.,* 1977).

Several recent laboratory studies have examined the DER in alcoholics and research volunteers treated with disulfiram. Christensen *et al.* (1991) examined doses of 100-600 mg per day for 14 days in 52 volunteers challenged with 0.15 g/kg oral ethanol. They measured valid DER's in 92% of subjects given 200 mg disulfiram and 100% of subjects given 300 mg disulfiram. Alcohol challenge doses have been given to disulfiram treated individuals of up to 0.2 g/kg ethanol orally and 0.5 g/kg by the i.v. route (Johnsen *et al.,* 1992). Following oral ethanol dosing, acetaldehyde levels reach a peak at approximately 30 minutes and decline to baseline levels within 2-3 hours (Beyeler *et al*., 1985). In general, the common symptoms of the DER covary (i.e. rise and fall) with plasma levels of acetaldehyde. Although the flushing response is considered one of the most universally prevalent and earliest signs of a DER (Kristenson, 1995), heart rate increases and diastolic blood pressure decreases showed the best correlation with acetaldehyde plasma levels (Beyeler *et al*., 1985).

Following the oral administration of 40 g ethanol to 33 alcoholics treated with 500-3000 mg disulfiram, diastolic pressure decreases were said to range from 5-100 mm Hg and to average 45 mm Hg reaching peak at approximately 65 min after alcohol ingestion (Raby, 1953). In 13 alcoholics treated with 400 mg disulfiram and given oral alcohol challenges of 0.2 g/kg, diastolic pressure decreases of greater than 15% of baseline began to occur within 10 min and peaked at 30 min after alcohol dosing (Beyeler *et al.,* 1985). The mean % decline in diastolic pressure was 40-50% of baseline value but was adequately managed with reclining head position. Interestingly, the changes in systolic pressure were not as dramatic, not as related to acetaldehyde concentration, and were greater for subjects over the age of 40 years.

Interactions with Cocaine. Disulfiram has been investigated for treatment of cocaine abuse. In a pilot study, Carroll *et al.* (1998) found that disulfiram (250-500 mg/day) substantially reduced cocaine use in 35 of the 76 cocaine/alcohol-dependent subjects, was well tolerated, and resulted in these 35 individuals achieving 3 or more weeks of consecutive abstinence during treatment. Disulfiram binds to other sulfhydryl-containing enzymes including plasma cholinesterase and to a lesser extent, liver esterases (Zemaitis and Greene, 1976; Faiman, 1979), which are involved in cocaine metabolism. In the clinical laboratory study by McCance-Katz *et al.* (1998a, b) disulfiram substantially inhibited cocaine metabolism in 5 subjects. They reported increases in peak cocaine blood concentration, AUC, and elimination half-life. Even though disulfiram produced dose-related increases in plasma levels of cocaine, it did not significantly potentiate subjective effects of cocaine and the cardiovascular effects of cocaine were increased more by the lower (250 mg) than the higher (500 mg) disulfiram dose. These investigators reported there was no significant alteration in plasma cholinesterase function, however, the methodology for this assessment was not described. The proposed study of cocaine and disulfiram interactions will clarify these apparent discrepancies by more thoroughly characterizing the cardiac and cardiovascular effects of cocaine, the plasma levels cocaine and its metabolites, and how each of these relate to the extent of plasma cholinesterase inhibition using standardized methods.

In one study (Honjo and Netter, 1969), a single disulfiram dose of 0.2 g/kg administered to rats reduced plasma cholinesterase activities at 24 hrs post drug administration by about 25%. A higher dose of 1.0 g/kg resulted in about 50% reduction at the same time point (Zemaitis and Greene, 1976). These effects of disulfiram on cholinesterase activity could explain the changes in cocaine metabolism but may not be the only explanation for possible therapeutic effects against cocaine dependence. It has been suggested that as with alcohol, disulfiram may act as an aversive therapy for cocaine use, since some individuals report increased anxiety, dysphoria, and paranoia after using cocaine in the presence of disulfiram (Hameedi *et al.,* 1994). A postulated mechanism is that disulfiram inhibits the sulfhydryl-containing dopamine β-hydroxylase, which would increase dopamine concentrations by reducing the amount that is converted to norepinephrine.

Two new studies examining the use of disulfiram for the treatment of cocaine dependence have suggested there may be a need to increase the dose of disulfiram from 250 to 500 mg. One study, presented at the American College of Neuro-Psychopharmacology (ACNP) (Oliveto *et al.,* 2004), examined the treatment of cocaine-dependent methadone maintenance patients with placebo *versus* one of three disulfiram doses (62.5, 125, or 250 mg). In that study, the lower two doses of disulfiram (62.5 and 125 mg) significantly increased cocaine use above that observed for placebo. Although the 250 mg dose of disulfiram was not better than placebo, there was evidence that subjects with minimal dopamine beta hydroxylase (DBH) activity had a greater severity of cocaine dependence that was more resistant to treatment relative to subjects with low to normal DBH activity. Within the group of subjects having low to normal DBH activity, those with higher DBH activity appeared to be less responsive to disulfiram at 250 mg than those with lower DBH activity. In a second study presented to the College on Problems of Drug Dependence (Schottenfeld *et al.,* 2004), buprenorphine-maintained subjects with cocaine dependence were treated with 250 mg disulfiram vs. placebo. Overall, disulfiram treatment was superior to placebo on self-report measures but not urine drug screen results. However, there was evidence that the effects of disulfiram 250 mg daily were most pronounced for subjects who had the "T-allele" genotype of the #1021C>T polymorphism of the DBH. These data suggest

that the disulfiram dose may need to be increased for subjects with higher DBH activity. Among subjects with continued high severity cocaine use during the buprenorphine induction period, disulfiram was superior to placebo on self-report and urine drug screen results for those who had the "T-allele" genotype of the #1021C>T polymorphism of the DBH. Subjects who did not have the T-allele did not show a response to disulfiram 250 mg daily on urine screen results. Collectively, these data led the authors to speculate that subjects with more severe forms of cocaine dependence or individuals with the #1021-C>T polymorphism may require doses of disulfiram higher than 250 mg per day. Furthermore, there may be a risk that doses of disulfiram which are too low, may actually exacerbate patterns of cocaine use, perhaps due to changes in cocaine metabolism that may occur more sensitively at the lower doses of disulfiram.

Based upon these data, future clinical trials with disulfiram may need to test doses higher than the 250 mg doses previously tested. A previous laboratory study comparing 250 and 500 mg doses of disulfiram showed that its effects on cocaine were dose related and that 500 mg dose was tolerated well (McCance-Katz *et al*., 1998). One of the previous cocaine-dependence treatment studies allowed flexible doses between 250 and 500 mg disulfiram given three times a week and the modal dose was 261.5 mg (Carroll *et al*., 1998). In one study administering challenge doses of alcohol after disulfiram treatment at doses of 200-300 mg produced an Antabuse reaction in only approximately one-half of the patients (Brewer, 1984). In the U.S.A., the maximum recommended daily dose of disulfiram for alcoholism treatment is 500 mg (Brewer, 1984) although higher doses may be required for effectiveness in some subjects (Kitson, 1977).

5 STUDY DESIGN

This is a two-site, double-blind, placebo-controlled inpatient study to determine the cardiovascular and psychiatric safety of alcohol use in cocaine-dependent subjects who had used cocaine after treatment with disulfiram. In this study, subjects will be screened for eligibility including initial screening for clinical tolerance to a cocaine infusion of 30 mg i.v. on day -3. Thereafter, baseline cardiovascular responses to i.v. cocaine and ethanol infusions (on days -2 and -1, respectively) will be established. In the previous version of this protocol, subjects were to be randomized on day 1 (after infusion #3) to one of three study groups (placebo, 250 mg and 500 mg of disulfiram). As of July 1, 2005, n=4 subjects have been tested with the 500 mg dose of disulfiram, but not all are evaluable and the design has changed so that no more subjects will be randomized to the 500 mg of disulfiram group. Thus, the current design is to complete a total of 16 subjects tested with either 250 mg disulfiram (n=8) or placebo (n=8). On the day of randomization (day 1), subjects will initiate oral dosage treatment with 250 mg disulfiram or placebo once a day for 7 days. Three days after initiation of daily treatment with either 250 mg disulfiram or placebo, all subjects will receive treatment infusions. On day 4, subjects will receive only i.v. saline; on day 5, 30 mg i.v. cocaine; on day 6, i.v. dose of ethanol; and on day 7, 30 mg i.v. cocaine followed by i.v. ethanol 5 minutes later. After the day 7 dose of disulfiram/placebo, double-blind oral treatment will cease but subjects will remain in the hospital until discharge one week later on day 14. Subjects will be requested to return for safety follow-up approximately one and two weeks after the day of discharge. All infusions will be single blind and 'double-dummy', i.e. the cocaine infusion is blinded by a parallel saline infusion and the alcohol infusion is blinded by a parallel dextrose infusion. Study agent (disulfiram/placebo) will be administered double-blind.

The study will assess subjective and physiological responses to cocaine and the pharmacokinetics of cocaine and its major metabolites upon administration of disulfiram or disufiram plus ethanol. A combination between-subjects and within-subjects analysis will be performed. A between-subjects analysis will be used to assess the effects of disulfiram 250 mg vs. placebo pretreatment on the effects of doses of cocaine, ethanol, and cocaine plus ethanol. A combined between-subjects and within-subjects analysis will allow for a pharmacodynamic assessment of cocaine's effects before and after initiating treatment with disulfiram. The cardiovascular safety of ethanol administrations in disulfiram-treated cocaine dependent individuals will be assessed by within-subject contrasts.

Subjects will be discharged from the hospital 7 days after the last doses of disulfiram, cocaine, and ethanol. This is to optimize medical monitoring for adverse events and to allow time for *de novo* regeneration of liver dehydrogenase levels so that subjects can safely return to the outpatient environment. Subjects will be asked to return twice for follow-up approximately 1 and 2 weeks after hospital discharge to monitor their well-being.

6 STUDY OBJECTIVES

6.1 Primary

The primary objective of this study is to determine safety of alcohol use in cocaine-dependent subjects that used cocaine after treatment with disulfiram. This will be achieved by measuring adverse events and changes in cardiovascular and psychiatric responses from baseline.

6.2 Secondary

Secondary objectives include:

1. To evaluate whether chronic daily treatment with disulfiram alters the pharmacokinetics of cocaine or its metabolites.

2. To evaluate whether changes in pharmacokinetics of cocaine or its metabolites induced by chronic daily treatment with disulfiram correlate with changes in plasma cholinesterase activity.

3. To evaluate the dose-relationship to the safety profile for a disulfiram-cocaine-ethanol three-way interaction

4. To evaluate whether chronic daily treatment with disulfiram alters the subjective effects of cocaine (euphoria, craving) measured by Visual Analog Scale (VAS), Profile of Moods State (POMS) and modified Positive Syndrome Rating Scale (mPSRS) assessments.

5. To evaluate whether ethanol changes the subjective responses to cocaine in disulfiram-treated subjects as measured by VAS, POMS, mPSRS and Adjective Self-Assessment for disulfiram-ethanol reaction (DER) symptoms.

7 STUDY SITES

This study will be conducted at two sites. The sites will be the University Clinical Psychopharmacology Laboratory (UCPL) of the University of Texas Health Science Center in San Antonio (UTHSCSA) and at the General Clinical Research Center (GCRC) of the Center for Health Sciences at the University of California at Los Angeles (UCLA).

8 SUBJECT POPULATION

8.1 Inclusion Criteria

In order to participate in the study, subjects must:

1. Be volunteers who meet DSM-IV criteria for cocaine abuse or dependence and are not seeking treatment at time of study.

2. Be between 18 and 50 years of age.

3. Be able to verbalize understanding of consent form, able to provide written informed consent, and verbalize willingness to complete study procedures.

4. Use cocaine by the smoked or i.v. route and drink at least two drinks of alcohol on average at least twice per week for at least four of the past six weeks.

5. Have a history and physical examination that demonstrate no clinically significant contraindication for participating in the study, in the judgment of the admitting physician and the site investigators.

6. Have a body mass index (BMI) $\leq$ 28.

7. Have resting vital signs as follows: heart rate between 50 and 90 bpm, systolic BP below 150 mm Hg and diastolic BP below 90 mm Hg.

8. Have electrolytes (Na, K, Cl, HCO_3) and hematocrit that is clinically normal (+/- 10% of laboratory limits).

9. Have liver function tests (total bilirubin, ALT, AST, and alkaline phosphatase) less than three times the upper limit of normal.

10. Have kidney function tests (creatinine and BUN) less than twice the upper limit of normal.

11. Have an ECG performed that demonstrates no clinically significant arrhythmia or deviations from a normal sinus rhythm and conduction.

12. Be male or be female and have a negative pregnancy test and be postmenopausal or have had a hysterectomy or have been sterilized, or agree to use one of the following methods of birth control:

a. oral contraceptives
b. barrier (diaphragm or condom) with spermicide,or condom only
c. intrauterine progesterone,or non-hormonal contraceptive system
d. levonorgestrel implant

e. medroxyprogesterone acetate contraceptive injection
f. complete abstinence from sexual intercourse

8.2 Exclusion criteria

In order to participate in the study, subjects must not:

1. Have a current or past history of seizure disorder, including alcohol- or stimulant-induced seizure, febrile seizure, or significant family history of idiopathic seizure disorder.

2. Have a history of head trauma that resulted in neurological sequellae (e.g., loss of memory for greater than 5 minutes or that required hospitalization).

3. Have a physiological dependence on alcohol, sedative-hypnotics (e.g., benzodiazepine, barbiturates) or opiates that requires medical detoxification based on the clinical signs of withdrawal in the presence of negative alcohol breath samples and negative drug urine samples.

4. Have any previous medically serious adverse reaction to cocaine or Antabuse™ including loss of consciousness, chest pain, seizure, or psychosis resulting in hospitalization.

5. Meet the diagnostic criteria for the following Axis I disorders: psychosis, bipolar I disorder, organic brain disease, dementia, major depression, schizoaffective disorder, or schizophrenia.

6. Have any evidence of clinically significant heart disease, hypertension, or other significant medical illness, including diabetes.

7. Be pregnant or nursing.

8. Have a diagnosis of adult asthma, including a history of acute asthma within the past two years, or current or recent (past 2 years) treatment with inhaled or oral beta-agonist or steroid therapy (due to potential serious adverse interactions with cocaine).

9. Be actively using albuterol or other beta agonist medications, regardless of formal diagnosis of asthma. (Inhalers are sometimes used by cocaine addicts to enhance cocaine delivery to the lungs.) If respiratory disease is excluded and the subject will consent to discontinue agonist use, s/he may be considered for inclusion.

10. For subjects suspect for asthma but without formal diagnosis, 1) have a history of coughing and/or wheezing, 2) have a history of asthma and/or asthma treatment two or more years before, 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): a detailed history and physical exam, pulmonary consult, and pulmonary function tests should be performed prior to including or excluding from the study or 5) have an FEV_1 <70 %.

11. Have any illness, condition, and/or use of medications that in the opinion of the site investigator and the admitting physician would preclude safe and/or successful completion of the study. Excluded medications include any which affect the CNS, are psychoactive, affect the cardiovascular system, or produce pharmacological interactions with cocaine, alcohol, or disulfiram.

12. Have active syphilis that has not been treated or refuse treatment for syphilis (see note).

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

14. Have AIDS according to the current CDC criteria for AIDS - MMWR 1999; 48 (no. RR-13: 29-31).

15. Have peripheral neuropathy or other significant neurological disorders.

16. Have a history of alllergic responses to rubber or latex products.

17. Be using disulfiram or any medication that could interact adversely with disulfiram, within the following times of beginning of administration of disulfiram based on the longest time interval of A, B, or C, below or as otherwise specified:

    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:

    a. Disulfiram (Antabuse™) used during the past 30 days
    b. Antidepressants including monoamine oxidase (MAO) inhibitors (GlaxoSmithKlein recommends 14 days after stopping MAO inhibitors)
    c. Neuroleptics
    d. Anticoagulants, i.e. coumadin
    e. Phenytoin
    f. Psychotropics
    g. Systemic corticosteroids
    h. Xanthines, i.e., theophilline, theophilline sodium glycinate and aminophylline
    i. Drugs that lower seizure threshold

Notes on inclusion/exclusion criteria: Although AIDS is an exclusion criteria, a positive antibody titer to HIV is not. Prospective subjects will be offered HIV testing during screening but may not have the test performed until after enrollment. This test is offered as a courtesy to the prospective subject along with HIV education.

Prospective subjects who are positive for syphilis by the RPR test will have a fluorescent treponemal antibody absorbant 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 to be enrolled on the study or provide evidence of previous successful treatment for syphilis.

The infectious disease panel for hepatitis is performed as an aid to determine if the prospective subject has been exposed to a hepatitis virus. Positive hepatitis antibody results do not exclude a prospective subject from participation unless there is an indication of active liver disease or infection (positive for antigen). Similarly, a positive tuberculin (PPD) result does not exclude a prospective subject from participation, but if diagnostic tests (e.g. chest x-ray) indicate that active disease is present, subjects may be excluded from participation.

If any test results are positive, subjects will be notified of positive and confirmatory test results and will be referred for treatment.

History of cocaine-induced psychosis does not exclude a prospective participant from the study; however, the presence of current psychosis will exclude a prospective participant from the study.

9 INVESTIGATIONAL AGENTS

9.1 Disulfiram

The research pharmacist will prepare medication by cutting 250 mg disulfiram tablets in half and putting them into two Size-0 opaque gelatin capsules backfilled with cornstarch. Identically appearing gelatin capsules will be filled with cornstarch only to produce matching placebo.

9.2 Cocaine

The 30 mg unit doses of sterile i.v. human use cocaine HCl will be prepared from 2 mL ampules (20 mg/mL) provided by NIDA. Sterile physiological saline will serve as the "placebo" control for the cocaine injections. The Research Pharmacist shall provide prefilled syringes to the research physician containing single-blind labeled cocaine diluted to 30 mg/2 mL or saline (0.9% w/v NaCl, 2 mL) for study administration. Standard narcotics control procedures will govern access to and recording of all drug supplies. Any unused drug will be disposed according to standard practices.

9.3 Ethanol

A commercially available 10% w/v ethanol solution in 5% dextrose will be used as the study agent. 5% dextrose alone will serve as the alcohol "placebo". The 500 mL of either of these solutions will be provided in a single-blind labeled i.v. bag for attachment to a standard intravenous line-pump.

10 TREATMENT PLAN

Disulfiram or Placebo: Capsules containing disulfiram 250 mg, or placebo will be administered orally under double-blind conditions, once daily at 8:00 a.m. for 7 days (study days

1 through 7). Disulfiram/placebo capsules will be given at the same time each day and should be given 2 hours before the planned time for infusions. Subjects assigned to the placebo group will receive matching placebo on the same schedule as the disulfiram group.

Cocaine or Saline: Single-blind cocaine (30 mg/2mL) or saline (2 mL) will be administered i.v. over a 60 sec period by study physicians using continuous infusion pumps. Saline will be given on days -3, -2, 4, and 6 while cocaine will be given on days -3, -1, 5, and 7. Per Study Design, day -3 will include both saline and cocaine infusions, while all other infusion sessions will include either cocaine or saline.

Ethanol: The 500 mL bags of single-blind 10% w/v ethanol or dextrose will be connected to an arm vein through a standard intravenous line infusion pump. Dextrose will be given on days -1, 4, and 5 while ethanol will be given on days -2, 6, and 7. The dose for infusion will be 0.4 g/kg of ethanol in a 10% by volume solution. The infusion pump flow rate will be set at 30 mL/min, and a 70 kg person will receive 280 mL infusion over 9.3 minutes. The female ethanol dose for infusion will be 85% of the male dose. All infusions will be stopped when any of the stop-point criteria listed in section 11.4.4 are reached.

Note: One multivitamin tablet will be dispensed every morning to all subjects during the in-patient phase of the study.

11 STUDY PROCEDURES

Appendix I provides a summary of the schedule of study activities.

11.1 Screening (Study Days -30 to -4)

People who use cocaine and drink alcohol and are willing to stay in the hospital for 17 days will be recruited by newsprint advertising. Interested candidates between the ages of 18 and 50 who respond will be asked if they are interested in receiving treatment for drug or alcohol problems. Those responding in the affirmative will be referred for a treatment program. Those responding in the negative will be asked a few additional questions about their use of medications, drugs, and alcohol, and their interest in staying in the hospital for at least 17 days will be confirmed. Those respondents who appear to have used cocaine by the smoked or i.v. route at least twice per week and drank at least two drinks of alcohol on average at least twice per week will be invited to the screening facility for written informed consent. If still interested after receiving an explanation of the study, the candidate will be given an opportunity to review, inquire about, and sign the study informed consent form approved by the site's IRB. Screening assessments to establish eligibility will be scheduled after obtaining witnessed, signed consent.

Depending upon the site procedures, some of the screening assessments can and will be completed while subjects are outpatients and some may be completed after hospital admission. Assessments performed before hospital admission include collection of demographic information and completion of a timeline follow-back for cocaine use for the prior 6 weeks, quantity frequency interview, urine drug screen, a 12-lead ECG, and vital signs (HR and BP). For women of reproductive potential a urine pregnancy test will be performed. The remaining screening assessments may or may not be completed after hospital admission including: a physical exam,

medical history, laboratory analyses including hematology, blood chemistries, an infectious disease panel, an HIV antibody test (optional), and SCID for DSM-IV Axis I Disorders.

All screening procedures must be conducted within 30 days of randomization whether in the inpatient or outpatient setting. Adverse events will be recorded at each visit starting the day of the completion of the informed consent process.

11.2 Inpatient Screening on Day -3

Subjects admitted to the hospital, and meeting all previous inclusion criteria and none of the exclusion criteria will receive the final screening assessment of clinical tolerance to a 30 mg i.v. dose of cocaine. This will be conducted on day -3 of the study. Only subjects completing this day without exceeding the medical stop-point criteria specified in Section 11.4.4 will be considered to have completed all eligibility criteria and will be "Enrolled" in the study and allowed to continue. Note: If a standard hematology and blood chemistry panel test has not been done during the inpatient hospitalization, it will be conducted before commencing with the infusions on day -3.

11.3 Randomization

If the prospective subject meets all of the study inclusion and does not meet any of the exclusion criteria (including clinical tolerance to a 30 mg i.v. dose of cocaine on day -3), then the subject can be randomized into the study. Subjects will be randomized centrally using an interactive voice response system (IVRS). The research pharmacist will place a call to the IVRS to obtain the treatment assignment for each subject to either the disulfiram or placebo arm. Subjects will receive their randomized treatment, first on the morning of day 1. The research pharmacist at each site will maintain the list of subject treatment assignments and will prepare all investigational agents in a blind-coded manner. Subsequent to the change in the study design, subjects will be randomized into one of the two treatment arms (250 mg disulfiram or placebo) using a blocked randomization schema stratifying subjects by clinical site and replacing all non-evaluable subjects so that each site completes 4 subjects for each of these two dosage group. Subjects not receiving the ethanol infusion on day 7 of the study will be replaced as drop-outs.

11.4 Cocaine and Ethanol Infusion Sessions

11.4.1 Schedule

Intravenous (i.v.) cocaine and ethanol sessions will be conducted according to the schedule shown in Table 1. The series of infusions will consist of one screening session (day -3) and two baseline sessions (days -2 and -1) prior to randomization on day 1. Randomized treatment with disulfiram or placebo will be administered for one week (on days 1 to 7) and four successive infusion sessions will be implemented on days 4, 5, 6, and 7. All infusions will be single blind and 'double-dummy', i.e. the cocaine infusion is blinded by a "dummy" saline infusion and the alcohol infusion is blinded by a "dummy" dextrose infusion.

Table 1. Schedule of Days, Dosing, and Blood Draws

Day #			Session #	1st i.v. at 1000 h	2nd i.v. at 1005 h	Disulfiram or Placebo	Blood Draws
-4	M	T	Admission				
-3	T	W	Screening Infusion Session #1	saline*	30 mg cocaine*		
-2	W	R	Baseline Infusion Session #2	saline	ethanol		Acetaldehyde
-1	R	F	Baseline Infusion Session #3	30 mg cocaine	dextrose		Enz, Cocaine, Immune Parameters
1	F	**St**				X	
2	**St**	**Sn**				X	
3	**Sn**	M				X	
4	M	T	Treatment Infusion Session #4	saline	dextrose	X	
5	T	W	Treatment Infusion Session #5	30 mg cocaine	dextrose	X	Enz, Cocaine, Immune Parameters
6	W	R	Treatment Infusion Session #6	saline	ethanol	X	Acetaldehyde
7	R	F	Treatment Infusion Session #7	30 mg cocaine	ethanol	X	Enz, Cocaine, Acetaldehyde
8	F	**St**					
9	**St**	**Sn**					
10	**Sn**	M					
11	M	T					
12	T	W					
13	W	R					
14	R	F	Discharge				
21			Follow-up				
28			Follow-up				

The 1st infusion of cocaine or saline is sustained for 1 min; the 2nd i.v. procedure is a slow titrating infusion of ethanol or saline for up to 23 minutes. All i.v. infusions will be single-blind and double-dummy. All oral medications (Disulfiram/Placebo capsules) will be double-blind. * On study day -3 only, the times actually will be saline i.v. at 1000 h; then 30 mg cocaine i.v. at 1100 h. "ENZ" indicates one blood draw (15 mL) for assay of enzyme activity. "Cocaine" indicates repeated blood draws for PK analyses of cocaine metabolites (5 mL each). "Acetaldehyde" indicates repeated blood draws for PK analyses of acetaldehyde (5 mL each). "Immune Parameters" indicates three blood draws (4 mL each) for analyses of neuromodulators of immune function (cortisol, IL-6, IL-6r, TNF, TNFr, and IL-1r).

During the baseline sessions, the subject's responses to cocaine or ethanol without concomitant disulfiram or placebo administration will be assessed. The baseline sessions will acclimate subjects to the experimental conditions and ensure that volunteers are responsive to and safely tolerate the cocaine and ethanol test doses. The baseline sessions determine the physiological and psychometric responses to cocaine and ethanol in the absence of disulfiram and allow determination of baseline cocaine and acetaldehyde pharmacokinetics (PK). Data from baseline sessions will be used for within-subjects analyses. Only subjects responsive to (in the judgment of the investigator) and safely tolerating the test doses of cocaine and ethanol will continue in the study.

Thereafter, daily disulfiram or placebo treatment will be administered for seven days (days 1-7). At a time when disulfiram levels have achieved steady state and at a time when substantial enzyme (aldehyde dehydrogenase) inhibition has been established (see Section 3.5), the subject's responses to cocaine and ethanol alone and in combination will be tested (days 5-7). A "dose run-up" approach has been utilized beginning with a placebo (saline/dextrose) session (day 4), then a repeat cocaine alone session (day 5) followed by ethanol alone (day 6) before finally achieving the combination cocaine plus ethanol treatment (day 7). At each step, there are well-defined medical "stop-points" that are used to determine whether infusions are terminated or whether subjects will continue in the study. In this way, problems arising from cocaine or ethanol alone can preclude further escalation into cocaine plus ethanol combination, etc. The initial placebo (saline/dextrose) session (day 4), will accommodate subjects to the procedures, and assess expectational effects of the i.v. ethanol/dextrose procedure. Delaying ethanol exposure to the last two days (days 6 and 7) reduces the likelihood that the previous experience with the disulfiram-ethanol reaction will affect cocaine assessments. The fact that previous disulfiram-ethanol experience may carryover into the final assessment of the cocaine-ethanol interaction, is an unavoidable compromise designed to maximize subject safety.

11.4.2 Conduct of Cocaine/Ethanol Infusion Sessions

There are seven i.v. infusion session days in the protocol (see Table 1). Each session will consist of two i.v. infusions, the 1st one (cocaine or saline) being sustained for 1 minute and the 2nd (ethanol or dextrose) is a slow titrating infusion for up to 23 minutes. All infusions will be administered by a study physician. The cocaine or ethanol infusion will occur at approximately 10 a.m.; the timing of the infusion session should be scheduled to occur as close to 2 hours after the morning dose of disulfiram/placebo as possible. The timing of the dosing of the disulfiram/placebo and cocaine/ethanol infusions should remain the same for each series of sessions for an individual. All infusions will be single blind and 'double-dummy', i.e., the cocaine infusion is blinded by a parallel saline infusion and the ethanol infusion is blinded by a parallel dextrose infusion. During all infusions, subjects will have oxygen delivered via nasal canula at a rate of 2 L/min from -30 min to 75 min after infusion. If additional oxygen delivery is deemed clinically necessary by monitoring physician, flow rate and delivery method (i.e., facemask) to increase delivery will also be available.

Before the first infusion session (day -3), study subjects must have had a drug toxicology screening that shows negative urine drug/metabolite levels for drugs of abuse (except marijuana). On day -3, i.v. saline infusion will be followed 1 hour later by 30 mg cocaine i.v. (Table 2a). A 12-lead ECG will be measured before and at 15 min after infusion, and continuous (5-lead) ECG

and blood pressure will be monitored every 2 minutes for 15 minutes before and through at least 20 minutes after infusion (see Table 2a for details).

Table 2a. Saline and Cocaine Infusions on Day -3

Actual Time	Relative Time	Dose	BP/ HR	ECG	BAL	VAS	Adj	DER	Other
730		* breakfast							
800	-120		X						UDS
930	-30	insert i.v.		X					POMS
945	-15		q.		X	X	X	X	
1000	0	Saline, i.v.	2						
	4		min			X	X		
	6				X			X	
	8					X			
	12					X	X		
	15			X					
	16					X	X		
	18				X			X	
	20					X	X		
1030	30		X			X	X		
	45 (-15)		q.			X	X		
1100	60 (0)	Cocaine, i.v.	2						
	(+4)		min			X	X		
	(+6)								
	(+8)					X			
	(+12)					X	X		
1115	75 (+15)			X					
	(+16)					X	X		
	(+20)					X	X		
1130	90 (+30)					X	X		
	(+40)		X						
	(+45)					X	X		
	(+50)		X						
1200	120 (+60)		X			X	X		
1215	(+75)								mPSRS
1230	(+90)		X	X		X			
1300	180 (+120)	* lunch	X			X			
1400	240 (+180)		X			X			
1600	360		X						POMS
1800	480	* dinner							
2000	600	* snack							

Saline i.v. = 1 min infusion at 1000h
Cocaine i.v. = 1 min infusion at 1100h
ECG = 12-lead and rhythm strip
BAL = Breath Alcohol Level
VAS = Visual Analog Scale
Adj = Adjective self-rating for DER symptoms
UDS = Urine Drug Screen
DER= clinically rated signs of disulfiram reaction
mPSRS = modified positive symptom rating scale
POMS = Profile of Mood States

BP/HR blood pressure and heart rate reading or q. 2 min. Continuous ECG also during q. 2 min.
* food after other procedures

On days -2 and -1 the subject will receive baseline i.v. infusions of ethanol and cocaine, respectively, under monitored conditions. Thus, on day -2, the subject will receive saline infusion followed 5 minutes later by ethanol infusion; on day -1, the subject will receive 30 mg cocaine infusion followed 5 minutes later by a dextrose infusion. On days -2 and -1, the subject will have two intravenous catheters placed and will be monitored non-invasively for blood pressure, heart rate, electrocardiogram, and pulse rate, while breathing through a t-tube fitted with a mouthpiece that allows inspiration of ambient air and exhalation through a one-way valve into a breathalyzer.

On day 4, the subject will receive an i.v. saline followed by i.v. dextrose 5 minutes later. BP and HR will be monitored during and after infusions (Table 2). On day 5, the subject will receive an i.v. dose of cocaine 30 mg, followed 5 minutes later by i.v. dextrose as described for the cocaine administration session on day -1. BP and HR will be monitored during and after infusions (Table 2). On day 6, the subject will receive an i.v. saline followed 5 minutes later by i.v. ethanol while monitoring exhaled alcohol concentration by breathalyzer, as described on day -2. Subjects will be monitored (BP and HR) during and after infusions (Table 2); they will be also monitored for symptoms of disulfiram-ethanol reaction (DER).

On day 7, the subject will receive 30 mg cocaine i.v. over 1 minute, followed 5 minutes later by ethanol i.v. administration using the same stop-point criteria, and all monitoring will be conducted as in previous sessions.

Subjects will receive a hospital meal (breakfast) prior to infusion session initiation, but will not be allowed to eat within the hour prior to the infusion. Cigarette-smoking subjects may not smoke from 1-hour prior to session initiation until 90 minutes after the infusion. Smoking is not permitted within 15 minutes of scheduled vital sign measurements. Only decaffeinated coffee or tea and caffeine-free beverages will be allowed for participant consumption throughout the inpatient period of residential stay.

11.4.3 Safety Precautions

Cocaine administration may accentuate cardiovascular effects of the disulfram-ethanol interaction. This has been anticipated, and the potential effects for each participant of the disulfram-ethanol interaction will be known ahead of time based on the earlier infusion (session #6). The dose of cocaine selected, 30 mg, is below that generally utilized in studies of this type, allowing for potentially exaggerated effects.

A physician (ACLS certified) will perform the infusions and will be present at least 60 minutes after the infusion and will remain until vital signs are stabilized. The physician may leave the room, if the subject's vital signs are stabilized, but will remain nearby and available by pager for prompt response, if needed, for at least four hours post-injection. If a subject demonstrates a significant adverse reaction to cocaine or ethanol, the cocaine or ethanol administration will be halted, appropriate medical response will be implemented (see Appendix III), and the subject will be discontinued from the remainder of the study.

11.4.4 Stopping Criteria for Further Cocaine or Ethanol Administration

Cocaine administration will be discontinued if any of the following events occurs:

1. Systolic BP > 165 mm;
2. Diastolic BP > 100 mm;
3. HR > 130 bpm;
4. Behavioral manifestation of cocaine toxicity, e.g., agitation, psychosis, inability to comply with study procedures.

Ethanol administration will be discontinued if any of the following events occurs:

1. $\geq$ 15% decrease in diastolic BP from pre-cocaine baseline;
2. Diastolic BP of $\leq$ 60 mm;
3. Subject reported distress or unwillingness to continue;
4. Development of DER (see Note).

Note: The development of the DER will be assessed during all treatment infusion sessions and will consist of assessment of subjects' symptoms, assessment of physician observable signs, and assessment of cardiovascular indices.

Subjects will be instructed to report "any noteworthy complaints or difficulties that develop over the course of this session. Please inform us if you develop notable nausea, headache or other symptom that is different from earlier in the day".

We are particularly interested in symptoms attributable to the DER, such as nausea and pruritus. These will be noted as expected drug related events, and the time of onset relative to start of any drug administration procedures will be noted as will their resolution.

The development of the DER will be assessed as described in Section 12.5.2.4 and will be defined as the development of a *bona fide* subjective complaint, by a rating of 2 or greater on the flushing scale, or of changes in cardiovascular indices (noted above). The physician must interpret the subject's complaint as physiologically consistent; for example, the complaint of itching before the onset of drug delivery would be discounted. This is intended to reduce the impact of the "infectious itch" phenomenon, in which thinking about a symptom can facilitate its occurrence. Drug administration may be halted in between 2-minute observation periods if an obvious DER develops by subjective complaint or physician observation, and such actual time of cessation will be noted in the CRF, and such actual time of cessation will be noted in the CRF.

11.4.5 Stopping Criteria for Further Study Participation

Subject participation will be terminated if any of the following events occur:

1. Stopping criteria for further cocaine or ethanol administration do not return to acceptable limits within appropriate time frames (e.g., 30 minutes);
2. Stopping criteria for further cocaine or ethanol administration are met for a second time within the protocol;
3. Systolic BP > 180 mm Hg sustained for 5 minutes or more;
4. Diastolic BP > 120 mm Hg sustained for 5 minutes or more;

5. Heart rate > (220 – age x 0.85) bpm sustained for 5 minutes or more;
6. After clinic intake and before the first cocaine infusion session, study subjects have a positive drug toxicology screening (except for marijuana) before conduct of the infusion session.

11.4.6 Disulfiram Safety Concerns

Although serious toxicities are relatively rare, investigators should be aware of and monitor for the adverse effects associated with disulfiram in the absence of ethanol. Diethyldithiocarbamate and carbon disulfide are metabolites of disulfiram and share the enzyme inhibiting effects of the parent compound. Carbon disulfide also causes pruritus and rash, garlic or sulfur odor on the breath. These are common early treatment effects. Peripheral neuropathies, optic neuritis, and polyneuritis have been associated with disulfiram and its metabolites, due to inhibition of multiple enzymes and pyridoxine deficiency. Time and dose-related central neurologic effects, including headache, drowsiness, irritability, ataxia, impotence, paranoia and disorientation are also described (Goldfrank, 1994). Liver toxicity is relatively rare but is not dose-related. A cholestatic presentation is characteristic (elevation of alkaline phosphatase and bilirubin); progression to fulminant hepatitis may also occur. Disulfiram and its metabolites also inhibit the metabolism of multiple other drugs via the mixed function oxidase system. The pharmacokinetics of benzodiazepines, phenytoin, isoniazid, coumadin, tricyclic antidepressants, phenothiazines, and acetaminophen have been reported to be affected (Watson, 2001).

Subjects will not be allowed to take concomitant medications, whether prescription or over the counter (OTC), without the permission of the site investigator. Specific medications that will be excluded are:

- Antidepressants including MAO inhibitors
- Neuroleptics
- Psychotropics
- Systemic corticosteroids
- Xanthines (i.e., theophilline, theophilline sodium glycinate and aminophylline)
- Medications that interfere with cocaine detection in urine samples (e.g. ephedrine and pseudoephedrine)

11.4.7 Volunteer Discontinuation

Subjects will be excluded or discharged if their behavior is disruptive, noncompliant with study procedures, or otherwise not consistent with remaining in the hospital. Subjects will be excluded if urine toxicology indicates illicit use of illegal or legal drugs that are not allowed on this study during participation in this protocol.

11.4.8 Off-unit Passes

Subjects will reside full-time in the clinic throughout their study participation. In extraordinary cases, subjects may be allowed a pass for the shortest period feasible at the site investigator's discretion with an escort. Subjects must agree to provide urine for toxicology upon return. Subjects will be excluded from the remainder of the study, if there is evidence that they used drugs during the off-unit period.

11.4.9 Subject Payment

Subject payment will be determined by local site IRB requirements and will be combinations of cash and vouchers. A daily rate of compensation will be determined by the local IRB for the inpatient portion of the study. A completion bonus is included to encourage subjects to complete the study and to remain for the full duration of safety monitoring. Subjects who drop out or are excluded after initiating the protocol will be paid on a prorated basis according to the number of days that they participated, but will not receive the completion bonus.

12 CLINICAL AND LABORATORY EVALUATIONS

A table summarizing the timing of the clinical and laboratory assessments to be conducted over the entire study period is shown in Appendix I.

12.1 Screening

Screening evaluations will be performed initially before clinic intake with some assessments conducted after intake in the inpatient setting.

Screening Assessments. The following evaluations will be performed during screening:

1. Informed consent;
2. Demographics information;
3. Timeline follow-back for cocaine use for prior 6 weeks;
4. Quantity frequency interview;
5. Qualitative urine drug toxicology (positive for cocaine at study inclusion, but negative for other drugs, and daily for during the study monitoring);
6. 12-lead ECG;
7. Adverse events;
8. Pregnancy test for women of reproductive potential;
9. Physical exam and medical history;
10. Vital signs (BP and HR);
11. Hematology;
12. Blood chemistries;
13. SCID for DSM-IV Axis I Disorders and cocaine and alcohol abuse/dependence;
14. Quantity Frequency Interview;
15. POMS;
16. Infectious disease panel;
17. HIV test (optional).

Note: If a standard hematology and blood chemistry panel test has not been done during the inpatient hospitalization, it will be conducted before commencing with the infusions on day -3.

12.2 Evaluations Performed Daily During Inpatient Phase of Study

1. Illicit drug use will be monitored once daily (8 a.m.), as documented by a daily qualitative urine test.
2. POMS will be conducted once daily (9:30 a.m.) on non-infusion days and twice (i.e., pre- and post-infusion) on infusion days;

3. Adverse events will be monitored daily starting after intake.
4. Vital signs (daily).

12.3 Evaluations Performed During Infusion Sessions

Table 2b shows the series of activities that occur during infusion sessions #2-7. Refer to Table 1 for the timing of the infusion sessions according to the study day and to Table 2a for specific variations in the timing of infusion session #1 on Day -3.

All subjects will be fitted with a nasal oxygen tube maintained for 15 minutes before infusion until 60 minutes post infusion. Before and after each i.v. session, the subject's physiologic responses will be closely monitored using repeated HR, BP, and ECG readings. As shown in Table 2b for sessions #2-7, BP and HR will be taken at -30 and -15 minutes before infusion, and then monitored continuously every 2 minutes until 30 minutes post-infusion, and then again at 45, 60, 90, 120, 180, 240, and 360 minutes following infusion. ECG (5-lead) will be monitored continuously from 15 minutes before to 60 minutes after each infusion with a 12-lead ECG and rhythm strip recorded 30 minutes before and 15, 25 and 45 minutes after cocaine infusion. Oxygen, blood pressure, and ECG monitoring will be added as clinically indicated.

Table 2b. Daily Schedule for Cocaine/Ethanol Infusion Sessions #2-7
(all activities occur at each infusion session, unless otherwise noted)

Actual Time	Relative Time	Dose	BP/ HR	ECG	BAL	VAS	Adj	DER	Coc	Acet	Other
730		* breakfast									
800	-120	disulfiram, p.o.	X				X				UDS
930	-30	insert i.v.		X					X	X	ENZ, POMS
945	-15		q. 2 min		X	X	X	X			Immune
1000	0	Cocaine, i.v.									
	2				X			X			
	3								X	X	
	4				X	X	X	X			
1005	5	Ethanol, i.v. (slow infusion at a rate of 30 mL/min)									
	6				X			X	X	X	
	8				X		X	X			
	10				X	X		X			
	12				X		X	X			
	14				X			X			
	15			X					X	X	
	16				X		X	X			
	18				X			X			
	20				X	X	X	X			
	22				X			X			
	25			X							
1030	30		X		X	X	X	X	X	X	
	45		X	X	X	X	X	X	X	X	
1100	60		X		X	X	X	X	X	X	
	75										mPSRS
	90		X		X	X					
1200	120		X		X	X			X	X	Immune
1300	180	* lunch	X		X	X			X	X	
1400	240		X			X			X		Immune
1600	360		X			X			X		POMS
1800	480	* dinner				X			X		
2000	600	* snack							X		
2200	720								X		
0930	1410								X		

Cocaine i.v. = 1 min infusion
Ethanol i.v. = 23 min infusion
ECG = 12-lead and rhythm strip
BAL = Breath Alcohol Level
VAS = Visual Analog Scale
Adj = Adjective self-rating for DER symptoms
mPSRS = modified positive symptom rating scale
ENZ = Enzyme Activity on days -1, 5 and 7.
Coc = Cocaine Metabolites on days -1, 5 and 7.
Acet = Acetaldehyde levels on days –2, 6 and 7.
UDS = Urine Drug Screen
POMS = Profile of Mood States
DER = clinically rated signs of disulfiram reaction
BP/HR = blood pressure and heart rate reading or at q. 2 min. Continuous ECG also during q. 2 min.
Immune = cortisol, IL-6, IL-6r, TNF, TNFr, and IL-1r levels on days -1 and 5.
* food after other procedures

12.4 Evaluations at Discharge and Follow-up

The following evaluations will be performed at time of discharge (day 14). The same evaluations will be performed in the case of early study discontinuation.

1. Vital signs;
2. Hematology;
3. Blood chemistries;
4. 12-lead ECG;
5. Qualitative urine drug toxicology;
6. POMS;
7. AEs;
8. Pregnancy test for women of reproductive potential.

The following evaluations will be performed during the follow-up visits on days 21 and 28:
1. AEs;
2. Vital Signs;
3. Qualitative urine drug toxicology.

12.5 Clinical and Laboratory Assessment Methods

12.5.1 Screening Assessments

A variety of standardized psychosocial assessments and information will be collected during screening in order to describe fully the characteristics of participants and in order to facilitate future contact for follow-up. Study personnel who will administer the questionnaires and interviews are extensively trained and experienced in working with a drug abusing population.

12.5.1.1 Timeline Follow-back

Detailed histories of cocaine and alcohol use over the past 6 weeks prior to screening 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).

12.5.1.2 Quantity Frequency Interview

A quantity frequency interview will be used to establish the subject's history of cocaine, alcohol and other drug use. This instrument collects data on the amount and frequency of use over the lifetime of the subject. This interview will be conducted during screening.

12.5.1.3 Structured Clinical Interview for the DSM-IV (SCID)

A SCID (Spitzer *et al.,* 1995) will be conducted during screening by a staff member experienced in conducting the SCID and who has at least a Master's degree. The SCID serves to determine whether the subject meets the DSM-IV criteria for cocaine or alcohol dependence and to rule out any major psychiatric disorders (e.g., affective disorders, schizophrenia).

12.5.2 Medical Assessments

12.5.2.1 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 will be performed during screening. Height and weight will be recorded. A forced expiratory volume in 1 second (FEV_1) pulmonary function test should be performed during screening at the discretion of the investigator on any subject that is suspected of having asthma but without a formal diagnosis (an $FEV_1 < 70$ % will exclude a potential subject from study participation).

12.5.2.2 Medical History

To monitor the health of all potential study subjects, health profiles and medical history will be collected during screening.

12.5.2.3 Vital Signs

Vital signs to be assessed during screening and discharge include oral temperature, sitting blood pressure, heart rate, and respiratory rate. In addition, vital signs will be taken daily after clinic intake.

12.5.2.4 Disulfiram Ethanol Reaction (DER)

Clinical signs of early DER include conjunctival injection, flushing; more extensive reactions include vomiting, headache, etc. A scale documenting the extent of the DER has been developed by Johnsen *et al*., (1992) and will be used in a modified form in this protocol:

0= no change from baseline
1= localized flushing around the eyes or conjunctival injection
2= extensive facial flushing
3= flushing extending to the neck and upper thorax
4= flushing extending to the back and arms

The physician will ensure that the subject's face is clearly visible and well lit. S/he will examine the eyes, face and neck from the front and rate it as 1 when clear and distinct changes from baseline are apparent. The physician will utilize this scale to rate the participant at 2-minute intervals from prior to initiation of the ethanol/dextrose solution until administration is halted due to the development of the DER or when other stopping parameters are reached, which will be noted on an appropriate CRF.

12.5.3 Eligibility Checklist

The Eligibility Checklist must be completed prior to randomization and enrollment. This information will be used to determine whether the patient may be enrolled in the study. This form will document final eligibility and, if applicable, the reason the subject was not enrolled in the study.

12.5.4 Daily Surveys

Qualitative analysis for urine toxicology will be performed daily, and personality and mood state assessments will be performed every day starting at intake for the duration of the inpatient phase of the study.

12.5.4.1 Profile of Mood States (POMS)

The POMS is a questionnaire that measures dimensions of affect or mood. It consists of 65 adjectives to which the client responds according to a 5-point scale ranging from "not at all" to "extremely". Subjects will start the measure after clinic intake and will complete this questionnaire every day until the end of the study, once daily on non-infusion days and twice a day (i.e. pre- and post-infusion) on infusion days

12.5.4.2 Urine Drug Toxicology

Urine toxicology for marijuana, opiates, and cocaine will be monitored once daily (8:00 a.m.) using on-site qualitative urine test cup.

The onsite test indicates the presence/absence of all those abused drugs at once using a non-quantitative antibody test. There are circumstances (use of over the counter drugs or carryover after cocaine infusions) that lead to false positives. Therefore, cocaine positive tests can be sent to analytical lab for chemical determination of the amount of drug present if the investigator suspects that the subject has used cocaine outside of infusion sessions. Quantitative tests for cocaine will not be performed routinely as the subjects are receiving cocaine as one of the investigational agents.

12.5.5 Modified Positive Symptom Rating Scale (mPSRS)

PSRS is a psychiatric assessment that has been modified from a longer form of the BPRS (Brief Psychiatric Rating Scale) to fit the needs of the current study to assess temporal paranoia or agitation that may be seen in this study. The mPSRS consists of a 4-item Positive Symptom Rating Scale (1. Suspiciousness; 2. Unusual Thought Content; 3. Hallucinations; 4. Conceptual Disorganization). It is an interviewer-administered assessment. The responses for the Positive Symptom Rating Scale are rated on a 7-point scale (1. Not Present; 2. Very Mild; 3. Mild; 4. Moderate; 5. Moderately Severe; 6. Severe; 7. Extremely Severe). The mPSRS will be administered 75 minutes after each infusion session (#1-7).

12.5.6 Laboratory Tests

12.5.6.1 Hematology

Blood will be collected in anticoagulant containing vacutainer tubes for hematologic assessments. Analysis of hemoglobin, hematocrit, mean corpuscular volume, white blood cell count, differential white blood cell count and platelet count will be performed. Analyses will be performed in the institutions clinical laboratory. The laboratory 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. Hematologic assessments will occur during screening, on day 8 and at discharge. Note: If a hematology test has not been done

during the inpatient hospitalization, it will be conducted before commencing with the infusions on day -3.

12.5.6.2 Blood Chemistries

Blood will be collected in serum separation vacutainer tubes and serum separated according to standard procedures. Quantitative analysis will be performed for the following analytes: creatinine, blood urea nitrogen (BUN), glucose, creatinine phosphokinase (CPK), lactate dehyrodrogenase (LDH), electrolytes (Na, K, Cl, HCO_3), and liver function tests [total bilirubin, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), and alkaline phosphatase]. 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. Blood chemistry assessments will occur during screening, on day 8 and at discharge. Note: If blood chemistries test has not been done during the inpatient hospitalization, it will be conducted before commencing with the infusions on day -3.

12.5.6.3 Enzymatic Assays

The activity of two enzymes that are important to this study and its objectives will be conducted on days -1, 5 and 7, i.e. plasma cholinesterase and leucocyte aldehyde dehydrogenase assays.

Pseudocholinesterase is a plasma enzyme that metabolizes a significant portion (approximately 30%) of the administered dose of cocaine and generates ecgonine methylester, an active and potentially toxic metabolite of cocaine. Disulfiram is known to inhibit this enzyme and its inhibition may account for a substantial portion of the interaction between disulfiram and cocaine (both beneficial as well as toxic).

Plasma Cholinesterase Assay. Cholinesterase activity will be determined spectrophotometrically using a modification of the method described by Dietz *et al.* (1973). The method is based on a colorimetric determination of the rate of production of thiocholine from butyryl-thiocholine substrate catalyzed by cholinesterase using a color-producing reagent. Cholinesterase activity is measured as a change in absorbance at 405 nm and expressed in units/L. A 5 mL sample of blood will be processed to separate the plasma that will be frozen for later shipment to the central lab for analysis.

Aldehyde dehydrogenase is a hepatic enzyme responsible for the metabolism of the ethanol metabolite acetaldehyde. Its inhibition by disulfiram is assumed to be responsible for the disulfiram-ethanol reaction. Aldehyde dehydrogenase is found in other organs beside the liver; in particular, it is present in leucocytes. Whereas this study will measure the levels of acetaldehyde, measurement of the activity of leucocyte aldehyde dehydrogenase will provide information about the extent of its inhibition by disulfiram and thus may explain substantial between-subject variability in risk.

Leucocyte Aldehyde Dehydrogenase Assay. Aldehyde dehydrogenase activity will be determined according to the method of Helander *et al*. (1988) by following the disappearance of aldehyde substrate (DOPAL) and formation of its metabolite (DOPAC) by high performance liquid chromatography. A 10 mL of whole blood will be rapidly processed (within 2 hours) to obtain the mononuclear cell preparation that will be frozen for later shipment to the central lab for analysis.

12.5.6.4 Pregnancy Test

A urine-based pregnancy test designed to measure human chorionic gonadotropin will be used during outpatient screening, during inpatient screening, within 72 hours prior to the first dose of disulfiram, and at discharge.

12.5.6.5 HIV Test

All subjects will be offered the opportunity to have an HIV test performed during screening. This test is not requisite for study participation. Subjects may be tested at the clinical site or may be referred to another clinic for testing and education on HIV risk-behaviors. If the test is to be performed by the clinical site, a separate HIV test informed consent must be obtained before collecting blood for this test. An HIV antibody test will be performed on a serum sample collected from the subject after the HIV informed consent form is signed.

12.5.6.6 Infectious Disease Panel

During screening, blood will be collected in a serum separation evacuated venous blood collection tubes (e.g., Vacutainer^{TM}) 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 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, an FTA-abs and MHA-TP confirmatory test will be performed.

12.5.6.7 Assessment of Immune Parameters

On days -1 and 5, six neuromodulators of immune function (cortisol, IL-6, IL-6r, TNF, TNFr, and IL-1r) will be assayed for their time related increase following i.v. cannula insertion. Based on past experience working with these neuroimmune parameters, we propose to sample 300 mcL of plasma per hormone/cytokine at each of 3 time points: before (approximately -15 minutes) and 120 minutes and 240 minutes following cocaine administration. Each of these neuromodulators of immune function will be assayed on day -1 (baseline infusion, session #3) and also on day 5 (treatment infusion, session #5). These days were selected to assess the time-related changes in immune parameters with cocaine administration before and after treatment with disulfiram or placebo.

12.5.7 Monitoring and Assessments During Cocaine/Ethanol Infusion Sessions

12.5.7.1 Blood Sample Collections

A schedule of blood collections and volumes is provided in Appendix II including collection of samples for cocaine and acetaldehyde pharmacokinetics, plasma cholinesterase and leucocyte aldehyde dehydrogenase levels, and hematology and blood chemistry assays. Blood samples collected for cocaine and acetaldehyde pharmacokinetic analysis will be prepared and shipped according to the instructions in the Manual of Operating Procedures.

An intravenous catheter will be inserted for each infusion session, and maintained in place for the duration of the entire test, if the subject wishes. Two intravenous catheters will be placed for

infusion sessions that involve repeated blood draws: one will be for cocaine or ethanol administration, the other for blood sample collection.

Samples will be collected for assessment of cocaine pharmacokinetics at baseline (infusion session #3) and after treatment with disulfiram (infusion sessions #5 and #7). Samples will be collected for assessment of acetaldehyde pharmacokinetics at baseline (infusion session #2) and after treatment with disulfiram (infusion sessions #6 and #7). Samples will be collected for enzymatic assays of plasma cholinesterase and leucocyte aldehyde dehydrogenase at baseline (infusion session #3) and after treatment with disulfiram (infusion sessions #5 and #7).

On day -1 (infusion session #3) and day 5 (infusion session #5), six neuromodulators of immune function (cortisol, IL-6, IL-6r, TNF, TNFr, and IL-1r) will be assayed for their time related increase following i.v. cannula insertion at the following time points: approximately 15 minutes before and 120 minutes and 240 minutes following cocaine administration. Total blood loss during the study will be approximately 489 mL (Appendix II).

12.5.7.2 Physiology

Before and after each i.v. infusion, the subject's physiologic response will be closely monitored using repeated HR, BP, and ECG readings. BP, HR, and ECG will be measured using a "Spacelabs PC Scout" telemetry unit or a "Spacelabs Ultraview 1050 Medical Monitor". BP and HR will be taken at 120 minutes before infusion, every 2 minutes from 15 minutes before until 22 minutes following infusion, and at 30, 45, 60, 90, 120, 180, 240, and 360 minutes following infusion; additional time points (480, 600, 720 and 1410 minutes after infusion) will be added when clinically indicated. ECG (5-lead) will be monitored continuously from 15 minutes before to 60 minutes after each infusion; 12-lead ECG and rhythm strip will be performed at 30 minutes before and 15, 25, and 45 minutes after each infusion.

12.5.7.3 Subjective Responses (VAS and Adjective Self-Assessment for DER Symptoms)

During and after the infusions, subject's subjective response to the cocaine or ethanol will be closely monitored. The Visual Analog Scale (VAS) is a paper and pencil form used on infusion days to rate cocaine and ethanol effects important to abuse liability assessment. Seven individual items are rated on a 100 mm line labeled at the left and right-hand extremes with "not at all" to "extremely", respectively. Subjects are requested to place a vertical slash along the line to indicate the extent to which: "Right Now, I…FEEL EFFECTS of the drug; LIKE the DRUG effects that I feel; feel REALLY GOOD; feel a COCAINE HIGH; feel an ALCOHOL BUZZ; CRAVE COCAINE; WANT COCAINE. VAS will be administered 15 minutes before and 4, 10, 20, 30, 45, 60, 90,120, 180, 240, 360, and 480 minutes after each infusion.

On days -3, -2, -1, 4, 5, 6 and 7, subjects will complete the Adjective Self-Assessment to rate nine items potentially related to an adverse disulfiram-ethanol reaction (DER). Subjects are requested to circle a number on a 5-point scale (scored 0-4) to indicate how they feel "Right Now…" The items: "I Feel Good"; "I Feel Bad"; "I Feel Nauseous"; "My Face Feels Hot or Flushed"; "I Feel Dizzy"; "My Heart is Racing"; "I Feel Short of Breath"; "I Have a Headache"; and "I Feel Sick" are each rated and there is a composite score which sums the individual items ("I Feel Good" is reverse scored). The Adjective Self-Assessment for DER symptoms will be administered 120 and 15 minutes before and 4, 8, 12, 16, 20, 30, 45, and 60 minutes after infusions #1-7.

12.5.8 Adverse Events (AEs)

AEs will be assessed starting as soon as the subject completes the informed consent process and then daily after clinic intake by an investigative staff nurse or physician. If an AE is reported to a nurse that requires medical attention, it should be reported to a study physician immediately. The investigator or study physician will assess subjects for any medical or psychiatric side effects.

12.5.9 Concomitant Medications

Concomitant medications will be assessed once per week by an investigative staff member. Any medications to be taken during the study must be approved by the site investigator/study physician.

12.5.10 Discharge Form

The Discharge CRF will document all data relevant to subject discharge: reason for discharge (note that more than one answer can be selected), date of discharge, and study day of discharge.

13 REGULATORY AND REPORTING REQUIREMENTS

13.1 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.

13.2 FDA Form 1572

The investigator agrees to sign and submit a Statement of Investigator (FDA Form 1572) prior to initiating this study.

13.3 IRB Approval

Prior to initiating the study, the site investigator will obtain written Institutional Review Board (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 given to the subject. Annual reports and progress reports will be submitted to the IRB annually or at a frequency requested by the IRB.

The site investigator will ensure that a duly constituted IRB at the study site that conforms to FDA regulations (21 CFR part 56) will review the protocol and the volunteer informed consent form. Each investigator will follow IRB and FDA guidance regarding reporting of AEs. Each investigator will promptly report to the IRB all changes in 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. Following procedures outlined by the IRB, each investigator will describe the study, its risks and benefits, to each subject and ensure that each subject understands the study prior to obtaining the subject's signature. A copy of the consent form will be given to the subject.

13.4 Informed Consent

All potential candidates for the study will be given a current copy of the Informed Consent Form to read. The investigator or other study physician 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. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice. Subjects who request treatment for addiction at anytime during the study will be dropped from the study and referred to a treatment center.

13.5 Risks and Benefit Assessment

The primary risks of this study are those of possible adverse reactions to the study drugs, cocaine, ethanol, and disulfiram. We have extensive experience administering cocaine safely in the laboratory. The ethanol/disulfram interaction is well characterized and generally well tolerated but unpleasant. Effects of the combination of ethanol, cocaine and disulfram can be estimated from effects of pair-wise combinations, but have not been evaluated. The FDA is requiring this kind of Phase I assessment of the triple drug interaction under carefully controlled and monitored conditions in the hospital before disulfiram treatment trials for cocaine dependence can be approved. The doses of cocaine and ethanol used are modest, the safety screening and monitoring procedures are careful, and there have been no significant prior serious adverse events with these procedures.

Disulfiram is a marketed product with which there is extensive experience and little indication of significant risk. However, it is possible that the dopaminergic activities of both cocaine and disulfiram might be additive or greater when they are given together.

There is the risk of a breach of confidentiality regarding study records, but this is unlikely, since staff is well trained and experienced in this area.

The study does not offer direct therapeutic benefit to participants. However, because it is directed toward the identification and development of effective treatment for cocaine abuse and dependence, it does offer the potential of future benefit to this same population group.

Overall, the risks are modest, and appropriate safety precautions have been taken. Since there is a potential societal health benefit, we believe the risk/benefit ratio is favorable.

13.6 Drug Accountability

Upon receipt, the investigator/pharmacist or a licensed designate 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(s) shall be disposed of appropriately.

13.7 Safety Monitoring

Safety data will be reviewed via regular conference calls between study sites' physicians and NIDA Medical Monitor on a case by case basis. In case of disagreement between any of these three parties, an independent medical Monitor will be consulted.

Medical Monitor: An independent medical monitor will be appointed for the study. The medical monitor will be responsible for establishing concurrence with the investigator on the severity of any SAEs, the relatedness to the study treatments, and for determining if the SAE should be reported to the FDA in a 7 or 15 day expedited report or an annual report. The medical monitor will also be responsible for tracking and assessing trends in the SAEs reported.

Clinical Monitors: All investigators will allow representatives of the sponsor to periodically audit, at mutually convenient times during and after the study, all source documents for each subject. 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 compliance with good clinical practice guidelines and FDA regulations, confirm receipt of study supplies, and assure that acceptable facilities are available to conduct the study.

Routine monitoring visits by the sponsor's representatives will be scheduled at appropriate intervals but more frequently at the beginning of the study. At these visits, the monitors will verify that study procedures are being conducted according to the protocol guidelines. At the end of the study, they will advise on storage of study records and return of unused study medication. The site should anticipate visits by NIDA and the FDA.

13.8 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 site investigator or sub-investigators 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 potential subject completes the informed consent process.

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 medication-related 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 Form. The AE Form is also used to record follow-up information for unresolved events reported on previous visits.

Each week, a study investigator must review the AE Form 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 should be reported up to 4 weeks following completion of, or termination from treatment.

13.9 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 investigator-sponsor (IND Holder) as follows:

NIDA Medical Monitor: Ann Anderson, M.D.
NIDA Project Officer: Jurij Mojsiak. M.S.
Investigator-Sponsor: John Roache, M.D. 210/562-5401

The telephone report is to be followed 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 IRB 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 investigator-sponsor.

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 follow-up 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 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 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.

14 ANALYTICAL PLAN

14.1 Outcome Measures

14.1.1 Primary Outcome Measures

The primary outcome measures to address the safety of disulfiram treatment are adverse events, changes in cardiac (ECG) and cardiovascular responses (HR, BP) and observations of significant negative psychiatric effects (mPSRS, as well as POMS and self-rated DER) from disulfiram, ethanol and cocaine.

14.1.2 Secondary Outcome Measures

Secondary outcome measures are intended to satisfy the secondary objectives to understand the character and possible mechanism for the effects of disulfiram treatment on cocaine effects alone, and in combination with ethanol. The following secondary outcome measures will be used to satisfy these objectives:

1. Blood pharmacokinetic parameters of cocaine and its metabolites including Cmax, Tmax, AUC, apparent $t_{½}$, and CL, V, and λ_Z will be used to better characterize how disulfiram alters cocaine metabolism.
2. Plasma cholinesterase and leukocyte aldehyde dehydrogenase enzyme activities and plasma acetaldehyde levels will be examined to assess the relationship between the inhibitory activities of disulfiram and its effects on the cocaine response.

3. Subjective mood, symptom, and psychometric assessments will determine how disulfiram alters euphoric and craving responses to cocaine (VAS), as well as positive mood (POMS) and well being (mPSRS and Adjective Self-Assessment for DER symptoms) in response to cocaine or ethanol exposure.

14.2 Analysis Plan

14.2.1 Basic Analytic Approach

Both the primary and secondary objectives of this study require examination the effects of disulfiram on the cocaine response with and without concurrent ethanol exposure. The design of the study makes this analysis principally a within-subject comparison of cocaine effects before vs. after disulfiram treatment and with vs. without concurrent ethanol administration. However, there is only a limited sample size (N=8 in the 250 mg disulfiram dose group) to achieve this objective and thus statistical analyses will be primarily descriptive. Raw data will be descriptively analyzed accounting for disulfiram/placebo randomization, study-day/dose administered, and repeated time-point within a day. Data reduction steps will be applied to the repeated time-point data within a study day to calculate pharmacokinetic parameters and peak effects observed, etc., and post-infusion effects can be adjusted for the pre-infusion observations. Because certain effects of ethanol, cocaine, and disulfiram are hypothesized to be large enough to be detected with inferential statistics, even with these small sample sizes, repeated measures ANOVA models will be used for several of the primary and secondary hypothesis tests. Population demographics will be compiled for both treatment arms and presented in tabular form.

Cocaine Response will be monitored with repeated measures of cardiac, cardiovascular, subjective, and pharmacokinetic parameters before and at pertinent timepoints after single-blind cocaine infusion. Day -3 provides a screening demonstration of cocaine vs. placebo response differential and initial clinical tolerance. However, it is the day 4 (placebo) vs. day 5 (cocaine) contrast that provides a post-randomized treatment statistical demonstration of cocaine effects. Repeated measure ANOVA models acounting for Day should demonstrate significant “Day” effects and “Day x Time” interactions.

Disulfiram Effects on Cocaine Response will be determined by within-subject contrasts between day -1 and day 5 for the 8 subjects randomized to the 250 mg disulfiram group. A repeated measures ANOVA will determine whether the “Day” factor is significant.

Disulfiram-Ethanol Responses (DER) will be determined first by within-subject contrasts between day -2 and day 6 and then by observations of the expected large between-group disulfiram/placebo treatment differences on day 6. Expected DERs should be large enough to be detected by significant “Day” effects in an ANOVA conducted on the 8 subjects randomized to the 250 mg disulfiram group.

Disulfiram-Ethanol Response (DER) effects on the Disulfiram-Cocaine Response will be determined by within-subject contrasts between Day 5 and Day 7 for the 8 subjects randomized to the 250 mg disulfiram group. A repeated measures ANOVA will determine whether the “Day” factor is significant. Interpretation of apparent effects of DER from these analyses will be weighted by between-subject comparisons with the comparable data for three dosage groups.

14.2.2 Primary Objectives

The primary study objective is assess the "safety" of disulfiram as a putative cocaine treatment agent by increasing our understanding of how disulfiram alters the cocaine response and how the addition of small doses of ethanol may alter this cocaine response. Satisfaction of this objective is required before the FDA will consider approval of further clinical trials with disulfiram treatment for cocaine dependence.

Primary safety assessments will include Adverse Events reports, cardiographic (ECG) and cardiovascular (heart rate and blood pressure) changes, and psychatric disturbances (mPSRS, POMS, and self-assessment of DER). A thorough characterization of these assessments for the above-specified ***Disulfiram Effect on Cocaine Response*** addresses basic disulfiram safety issues and the analyses for the ***Disulfiram-Ethanol Response (DER) effects on the Disulfiram-Cocaine Response*** will address the safety of low dose ethanol challenges in cocaine-using populations treated with disulfiram.

14.2.3 Secondary Objectives

The secondary objectives use the same data analytic approaches as described above, but seek to better characterize the responses and thereby understand possible mechanisms:

1. Plasma concentration-time profiles of cocaine and its metabolites after cocaine (day -1, day 5) and cocaine/ethanol (day 7) infusions will be analyzed to obtain pharmacokinetic parameter estimates (Cmax, Tmax, AUC, apparent $t_{½}$, CL, V, and λ_Z) for each analyte by individual subject and means computed by treatment group. Confidence intervals (90%) for each parameter will be determined. Disulfiram-induced changes in cocaine metabolism will be revealed by day -1 vs. day 5 contrasts and ethanol effects will compare day 7 vs. day 5 contrasts.

2. The enzymatic activities of plasma cholinesterase and leucocyte aldehyde dehydrogenase will be assessed on days -1, 5, and 7. Treatment group differences and/or day-related decreases in the disulfiram group should be demonstrable by ANOVA. This will determine the extent to which disulfiram inhibited the enzymes believed to be mechanistically important to the observed effects. Individual differences in enzyme inhibition also may account for individual differences in the observed effects of cocaine and ethanol on the other outcome measures.

3. The extent to which disulfiram alters cocaine's effects on craving and euphoria (VAS), mood (POMS), and possible psychiatric disturbance (mPSRS) will be determined as described above for the ***Disulfiram Effects on Cocaine Response***.

4. The extent to which ethanol changes cocaine's effects on craving and euphoria (VAS), mood (POMS), and possible psychiatric disturbance (mPSRS) in disulfiram treated individuals will be determined as described for the ***Disulfiram-Ethanol Response (DER) effects on the Disulfiram-Cocaine Response***.

14.3 Sample Size

No formal sample size analysis was performed. The number of subjects in each group (N=8) is hypothesized to provide an indication of the safety and potential interactions between disulfiram,

cocaine, and ethanol. The evaluable subject population is defined as the subjects who are randomized, meet all of the inclusion/exclusion criteria, and have completed study procedures up to midnight of study day 7.

14.4 Control of Bias/Randomization

The remaining subjects to beenrolled will be randomized into one of the two treatment arms using a blocked randomization method stratifying subjects by clinical site and replacing all non-evaluable subjects so that each site completes 4 subjects for each dosage group. Given the small sample size it is important to control site differences that could contribute to assessment outcome.

15 DATA MANAGEMENT AND CASE REPORT FORMS

Data management activities and statistical analytical support will be coordinated through the KAI, data coordinating center.

15.2 Data Collection

Data will be collected at the study sites on source documents which will be entered at the site into electronic case report forms (eCRFs). The eCRFs will be supplied by KAI, data coordinating center. eCRFs are to be completed on an ongoing basis during the study. The medical chart and the source documents are the source of verification of data. eCRFs 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.

15.3 Data Editing and Control

Data are edited for out of range values, internal consistency and data entry errors as they are entered into the computer and resolved at the site by the coordinator/PI. Prior to his/her visit, the monitor will review the eCRF, identify any obvious inconsistencies, and request changes be made at the site prior to his/her visit. At the monitoring visit, any inconsistencies between source and eCRF will be resolved by the coordinator. If any data problems are found in the data analysis process, the site will be notified and will respond by modifying the eCRF or annotating it electronically to explain the discrepancy. NIDA/DTR&D and the participating sites will receive reports at least monthly regarding the quality and quantity of data submitted to KAI, data coordinating center.

The site principal investigator agrees to routine data audits by the KAI staff and by NIDA's programmatic staff. The 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 agents 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 KAI procedures.

15.4 Data Entry, Processing, and Analyses

Data will be collected at the study sites on source documents that will be entered into eCRFs. When the study is completed and all data have been entered into the clinical database and the database has been checked by Quality Assurance and is locked, statistical analysis of the data will be performed by KAI's statisticians in accordance with the analytical plan section of this protocol. Periodically, during the investigation, data sets will be submitted to the NIDA DTR&D central data repository according to procedures specified in the study operations manual.

15.5 Study Documentation and Records Retention

Study documentation includes all eCRFs, data correction forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence and regulatory documents (e.g., signed protocol and amendments, IRB correspondence and approved consent form and signed subject consent forms, Statement of Investigator (FDA Form 1572), and clinical supplies receipt and distribution records).

Source documents include all 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, patient diaries, biopsy reports, ultrasound photographs, patient 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 an 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 the NDA.

15.6 CONFIDENTIALITY

15.6.3 Confidentiality of Data

Particular attention is drawn to the regulations promulgated by the FDA under the Freedom of Information Act providing, in part, that proprietary information furnished to clinical investigators and IRBs will be kept confidential by the FDA 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.

15.6.4 Confidentiality of Patient Records

To maintain subject confidentiality, all laboratory specimens, eCRFs, reports and other records will be identified by a coded study subject number only. Research and clinical records will be stored in a locked cabinet. Only research staff and NIDA program officials will have access to the records. Subject information will not be released without written permission, except as necessary for monitoring by the FDA, KAI or NIDA. Upon approval of the study by an IRB, an application will be filed with NIDA for a certificate of confidentiality.

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 case report form data.

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

16 PUBLICATIONS OF THE STUDY RESULTS

NIDA and the investigator agree that the study database will be made available to principal investigator to encourage other publications provided that: manuscripts based on the use of disulfiram for the treatment for cocaine dependence may not be submitted for publication until the main findings of the study have been published and this study has been accepted by the FDA for filing to the IND or NDA.

17 SIGNATURES

NIDA REPRESENTATIVES

Typed Name	Signature	Date
Jurij Mojsiak, M.S. Project Manager	_____	_____
Ann Anderson, M.D. Medical Monitor	_____	_____
Nora Chiang, Ph.D. NIDA Investigator	_____	_____
Ahmed Elkashef, M.D. NIDA Investigator	_____	_____
Roberta Kahn, M.D. NIDA Investigator	_____	_____

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 13.8 of this protocol.

Typed Name	Signature	Date
John D. Roache, Ph.D. Lead Investigator	_____	_____
Thomas K. Newton, M.D. Site Principal Investigator	_____	_____
Christopher L. Wallace, M.D. Site Sub-Investigator	_____	_____
Francis Lam, Pharm.D. Site Sub-Investigator	_____	_____

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Appendix I: Time and Events Schedule

Study Phase	Screening and Intake	Screening Infusion	Baseline Infusions		Days	Infusion Days						Discharge	Follow-up
Study Day	**-30 to 0**	**-3**	**-2**	**-1**	**1-3**	**4**	**5**	**6**	**7**	**8**	**9-13**	**14**	**21 & 28**
Informed Consent	X												
Quantity Frequency Interview/Demographics	X												
Cocaine use by timeline follow-back	X												
Physical Exam/Medical History	X												
12-lead ECG	X											X	
SCID	X												
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology and Blood Chemistries	X	X[a]								X		X	
Infectious Disease Panel	X												
Pregnancy Test	X											X	
HIV test (optional)	X												
Urine Toxicology Screen	X	X	X	X	X	X	X	X	X	X	X	X	X
POMS	X	X	X	X	X	X	X	X	X	X	X	X	
mPSRS		X	X	X		X	X	X	X				
Disulfiram or Placebo					X	X	X	X	X				
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Infusion Sessions, #		**1**	**2**	**3**		**4**	**5**	**6**	**7**				
Saline/30 mg Cocaine i.v.		X											
Saline/Ethanol i.v.			X										
30 mg Cocaine/Dextrose i.v.				X									
Saline/Dextrose i.v.						X							
30 mg Cocaine/Dextrose i.v.							X						
Saline/Ethanol i.v.								X					
30 mg Cocaine/Ethanol i.v.									X				
VAS		X	X	X		X	X	X	X				
Adjective Self-Assessment for DER		X	X	X		X	X	X	X				
Continuous BP, HR, ECG		X	X	X		X	X	X	X				
Cocaine Blood PK				X			X		X				
Acetaldehyde Blood PK			X					X	X				
Enzyme Activity				X			X		X				
Immune Parameters				X			X						

X[a] - If a standard hematology and blood chemistry panel test has not been done during the inpatient hospitalization, it will be conducted before commencing with the infusions on day -3.

APPENDIX II: Schedule of Blood Collections

Analysis	Volume Per Sample	Type[a]	7-8 a.m.	Minutes Relative to Infusion															Total volume
				-30	-15	3	6	15	30	45	60	120	180	240	360	480	600	720	1410	
Screening, days 8 and 14																				
Hematology	10 mL	P	X																	30 mL
Chemistry	10 mL	S	X																	30 mL
Days -1, 5, 7																				
Cocaine PK	5 mL	P		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	225 mL
Days –2, 6 & 7																				
Acetaldehyde PK	5 mL	P		X		X	X	X	X	X	X	X	X							135 mL
Days -1, 5, 7																				
Cholinesterase activity	5 mL	P		X																15 mL
Aldehyde dehydrogenase activity	10 mL	S		X																30 mL
Days -1 and 5																				
Immune parameters	4 mL	P			X							X		X						24 mL
Total Volume of Blood Collected																				**489 mL**

[a]Sample type is P = plasma; S = serum.

APPENDIX III: Standard Operating Procedure for the Detection and Treatment of Adverse Event and Adverse Drug Reactions

ADVERSE EVENT MONITORING:

A: Equipment - Medications

1) Equipment availability - the Infusion Unit shall have available one resuscitation bag, suction apparatus, oxygen outlets, compressed air outlets, and one bedside monitor for ECG, blood pressure and transcutaneous oxygen saturation.

2) Medications will be located in the locked medication cabinets and crash cart with external pacemaker and intubation tray.

B: Safety and Maintenance

1) General safety rules throughout the hospital shall apply in the Unit.

2) Electrical preventive maintenance and safety program and medical equipment maintenance will be conducted according to the Hospital Acute Care Unit Policy and Procedure Manual.

CRITERIA FOR INTERVENTION AND METHODS

(I) Change in Heart Rhythm

1) Ventricular Fibrillation
   a) Recognition: Clinical cardiac arrest with ventricular fibrillation on ECG and absence of carotid pulse.
   b) Procedure: stop study drug/ethanol/cocaine administration.

   1) If arrest witnessed, apply a precordial thump then check pulse and ECG rhythm.
   2) If no pulse, begin CPR.
   3) Defibrillate (unsynchronized) at 200 joules and check pulse and ECG rhythm. If no change, repeat defibrillation at 300 joules. Check pulse rhythm. If still no change, defibrillate at 360 joules. Check pulse and rhythm.
   4) If above not successful in generating pulse, continue CPR
   5) Give Epinephrine 1 mg I.V. push.
   6) Repeat defibrillation at 360 joules. Check pulse and rhythm.
   7) Give Lidocaine 1 mg/kg I.V. push.
   8) Draw arterial blood gases.

2) Sustained Ventricular Tachycardia
   a) Recognition:

   1) Ventricular tachycardia on ECG.

   b) Procedure: stop study drug/alcohol/cocaine administration.

   1) Apply oxygen at 100%

2) Apply synchronized cardioversion, start with 50 joules (J). If no response, go to 100 J, if still no response go to 200 J.
3) May give amiodarone 150mg IV over 10 minutes if thought secondary to cocaine; if needed, lidocaine 1 mg/kg I.V. bolus, followed by Lidocaine drip 2 mg/min.

3) Ventricular Extrasystoles
a) Recognition: Ventricular extrasystoles, single or multiple, unifocal or multifocal
b) Procedure: Discontinue study drug/ cocaine, ethanol or cocaine/ethanol infusion if frequent or repeated (three or more in 1 minute). If extrasystoles remain frequent or repeated, give lidocaine 100 mg IV followed by infusion of 2 mg/min.

4) Bradycardia-Severe
a) Recognition: Pulse rate and ventricular rate under 40 associated with fall in BP below 90/60, change in mental status, chest pain, or dyspnea.
b) Procedure: stop study drug/ cocaine, ethanol or cocaine/ethanol infusion. Give Atropine 1 mg I.V. push and obtain ECG rhythm strip.

5) Ventricular Asystole
a) Recognition: Clinical cardiac arrest by ECG in two leads and absence of carotid pulse.
b) Procedure: stop study drug/ cocaine, ethanol or cocaine/ethanol infusion.

1) Begin cardiopulmonary resuscitation (CPR)
2) Give Epinephrine 1 mg I.V. push.
3) Continue resuscitation until effective heart action returns.
4) Draw arterial blood gases.

6) Sinus Tachycardia
a) Recognition: From continuous pulse monitoring, pulse elevated over 160 BPM.
b) Procedure: immediately stop study drug/ cocaine, ethanol or cocaine/ethanol infusion, monitor rate. If patient symptomatic or if rate does not lower below 160 after 1 minute, treat as hypertensive crisis, below.

(II) Hypertensive Crises

a) Recognition: From continuous blood pressure monitoring: elevated BP levels (Diastolic > 120, Systolic > 180) or elevated BP associated with encephalopathy, acute aortic dissection, acute left ventricular failure, stroke or myocardial ischemia will be deemed hypertensive emergencies.

b) Procedure: stop study drug/ethanol/cocaine administration. Give Lorazepam 2 mg I.V. Push followed by reduction of BP with combined alpha and beta adrenergic receptor antagonist, labetolol, 20 mg IV over 5 minutes with repeat injections every 20 minutes if necessary. Subsequent doses should be calculated on the basis of the diastolic response.

(III) Seizures

a) Recognition: observed seizure activity.

b) Procedure: Stop study drug/ cocaine, ethanol or cocaine/ethanol infusion. Establish an airway and maintain adequate oxygenation. Since, benzodiazepines rapidly enter the brain and control seizures give: Diazepam 10-15 mg IV at 4 mg/min or Lorazepam 2 mg at 5 min intervals to 10 mg.

(IV) Chest Pain

a) Recognition: By complaint
b) Procedure: Discontinue study drug/ cocaine, ethanol or cocaine/ethanol infusion. Note heart rate and blood pressure and treat with Labetolol if significantly elevated (parameters above). Give sublingual nitroglycerine 0.4 mg and Lorazepam 2 mg IV Push and review 12 lead ECG for evidence of myocardial ischemia. If chest pain persists give Verapamil 5 mg IV over 3 minutes; may repeat sublingual nitroglycerine 0.4mg up to 3 times.

(V) Hypotension

a) Recognition: Drop in blood pressure to below 90/50 or subjective complaints of dizziness or fatigue associated with drop in blood pressure from baseline.
b) Procedure: Discontinue study drug/ cocaine, ethanol or cocaine/ethanol infusion. Maintain patient in supine position. If symptoms and signs continue, give normal saline bolus of 500 cc over 20 minutes, I.V.

(VI) Disulfram-Ethanol Reaction (DER)

a) Recognition of typical DER: flushing, conjunctival injection, urticaria and tachycardia may be observed and generalized warmth, headache, pruritus, diaphoresis, nausea, palpitations, dyspnea, and lightheadedness may be reported.

Rescue procedures needed for hypotension (90/50), tachycardia (160 bpm) or severe subjective distress.

b) Procedures:

1) Discontinue study drug/ cocaine, ethanol or cocaine/ethanol infusion. Maintain patient in supine position.
2) Administer supplemental inspired O2 sufficient to maintain transcutaneous oxygen saturation (SpO2) at $\geq$ 94%.
3) Administer diphenhydramine 50mg IV
4) If tachycardia or hypotension continue or are severe, intravenous fluid loading with 0.9% saline or balanced crystalloid solution (lactated Ringer's, Normosol) at approximately 100 ml every 5-10 minutes. Up to 500 mL may be administered in 20-30 minutes if necessary.
5) Fomepizole (Antizol) 1.5 gm (1.5 mL vial) diluted in 100 mL: Loading dose 15 mg/kg.
6) If tachycardia or hypotension are unresponsive to above, Phenylephrine (Neo-synephrine) 1 mg diluted in 10 mL (0.1 mg/mL), administered as 0.05- 0.1 mg intravenous push every 10 minutes. Effect will be sustained for 5-10 min. May substitute Ephedrine 25 mg diluted in 10 mL (2.5 mg/mL) administered as 2.5 mg intravenous push; may repeat every 10 minutes.

(VII) Other symptoms

a) Recognition: Bronchospasm, nausea and vomiting
b) Procedure: bronchospasm**:** Albuterol aerosol, 2 inhalations repeated every 4 hours
For nausea and vomiting: Metoclopramide (Reglan) 20 mg I.V.

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

A. GENERAL INSTRUCTIONS

1. AEs will be reported as soon as the subject signs the informed consent.

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

3. 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 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 V: 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 participants. 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. Jacqueline R. Porter
NIDA Certificate of Confidentiality Coordinator
or
Ms. Sandra Solomon,
Certificate of Confidentiality Assistant

Office of Extramural Affairs
6001 Executive Boulevard, Room 3158, MSC 9547
Bethesda, Maryland 20852-9547
Rockville, MD 20852 (courier or express mail)
TEL: 301-443-2755
FAX: 301-443-0538
E-MAIL: jporter@nida.nih.gov or ssolomo1@nida.nih.gov

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 participants. The investigator must use the authority of the Certificate to resist compulsory disclosure of individually identifiable research data.

The study participants 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 participants 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.