NIDA-CTO-0010

DOUBLE-BLIND, PLACEBO-CONTROLLED ASSESSMENT OF POTENTIAL INTERACTIONS BETWEEN INTRAVENOUS METHAMPHETAMINE AND ORAL BUPROPION

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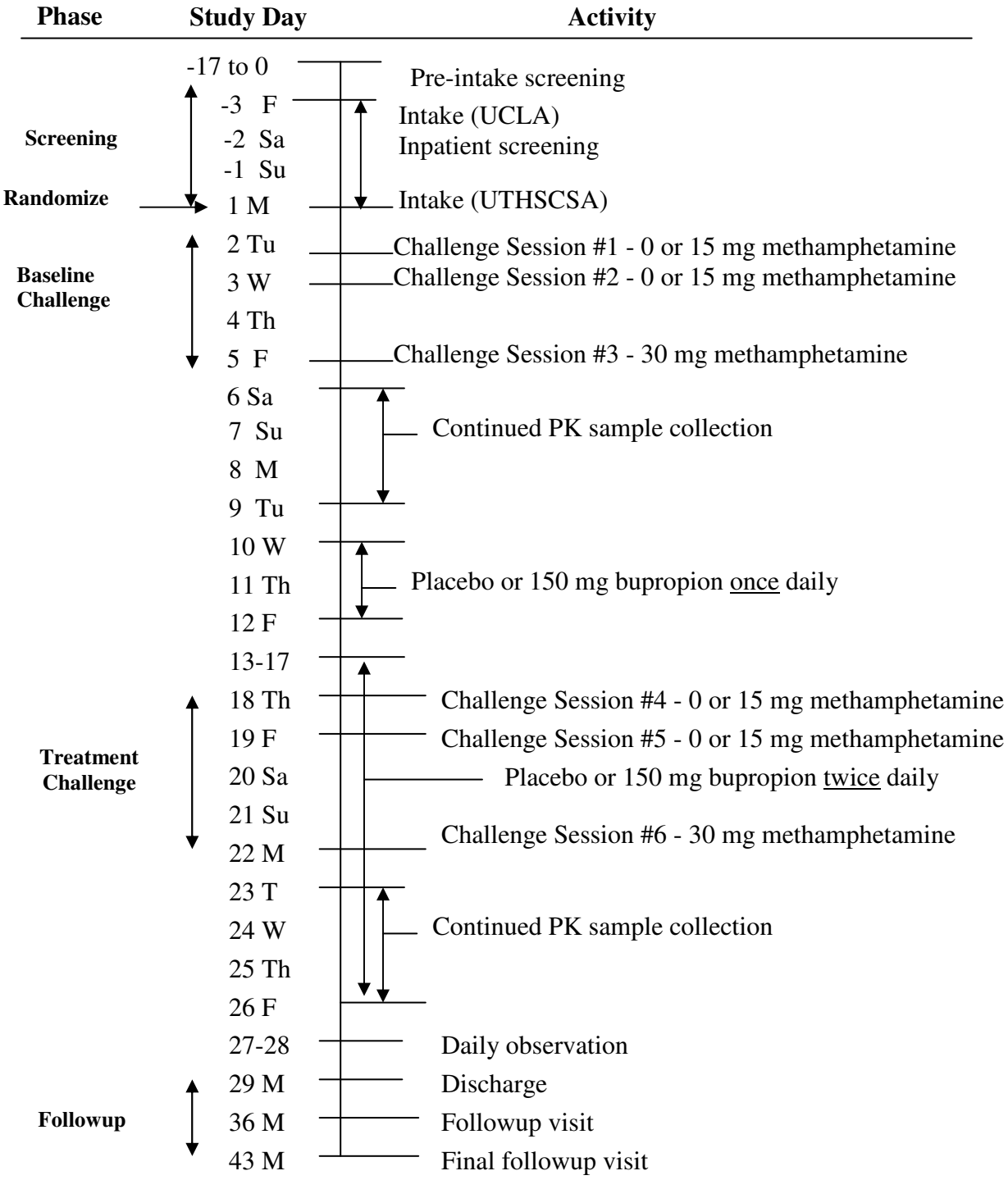
TABLE OF CONTENTS

1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADD	Attention Deficit Disorder
ADHD	Attention Deficit Hyperactivity Disorder
AE	adverse event
ALP	alkaline phosphatase
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvic transaminase
ANOVA	analysis of variance
ARCI	Addiction Research Center Inventory
ASI-Lite	Addiction Severity Index-Lite
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminse
AUC	area under the plasma concentration time curve
BDI	Beck Depression Inventory
b.i.d.	twice per day
BP	Blood Pressure
bpm	beats per minute
BPRS	Brief Psychiatric Rating Scale
BSI	Brief Symptom Inventory
BUN	blood urea nitrogen
CAP	College of American Pathologists
CLIA	Clinical Laboratory Improvement Amendment of 1988
COC	cocaine
CRF	Case Report Form
CPK	creatinine phosphokinase
CYP2D6	cytochrome P 450 2D6
CYP2B6	cytochrome P450IIB6
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
FHN	family history negative
FHP	family history positive
GCRC	General Clinical Research Center (UCLA site)
GSI	General Severity Index (GSI)
GGT	gamma glutamyltranspeptidase
HD	high density
HIV	human immunodeficiency virus
HR	heart rate
HRBS	HIV Risk-Taking Behavior Scale
IRB	Institutional Review Board
i.v.	intravenous(ly)
LDH	lactate dehydrogenase

Abbreviation	Definition
mAMP	methamphetamine
mg	milligrams
mL	milliliter
MAO	monoamine oxidase
NIDA	National Institute on Drug Abuse
OPI	opiates
PCR	polymerase chain reaction
PK	pharmacokinetic
POMS	Profile of Moods States
PSDI	Positive Symptom Distress Index
PST	Positive Symptom Total
SAE	serious adverse event
SCID	structured clinical interview for DSM-IV
SR	sustained release
SSRIs	selective serotonin reuptake inhibitors
THC	tetrahydrocannabinol
UCLA	University of California at Los Angeles
UCPL	University Clinical Psycopharmacology Laboratory (UTHSCSA site)
UTHSCSA	University of Texas Health Science Center at San Antonio
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 methamphetamine challenge and treatment with oral sustained-release (SR) bupropion.

Primary: To assess safety prior to undertaking an outpatient clinical trial of bupropion for the treatment of methamphetamine dependence.

Secondary:

1. To determine plasma levels of bupropion and its metabolites during chronic daily treatment with bupropion and the effects of methamphetamine on bupropion pharmacokinetics.

2. To evaluate whether administration of bupropion alters the pharmacokinetics of d-methamphetamine or its metabolites.

3. To evaluate whether bupropion treatment alters the subjective or cardiovascular response to methamphetamine.

4. To assess the effects of bupropion on craving for methamphetamine, assessed using a laboratory cue exposure paradigm.

5. To assess the effects of bupropion on mood and personality assessments [Brief Symptom Inventory (BSI), Beck Depression Inventory (BDI), and Profile of Moods State (POMS)], other psychological parameters [visual analog scales (VAS), Addiction Research Center Inventory (ARCI), and Adjective Scales)], and a targeted neuropsychiatric battery.

STUDY DESIGN: This is a double-blind inpatient study in which, after establishing eligibility, subjects will be randomized (stratified by site) into one of two treatment groups [placebo (n = 10) or bupropion (n = 10)]. All subjects will undergo one series (baseline challenges) of intravenous (i.v.) methamphetamine challenges (0, 15, and 30 mg) before placebo or bupropion administration and a second methamphetamine challenge series (0, 15, and 30 mg) starting 6 days after the initiation of the twice daily placebo or bupropion administration (treatment challenges). The order of the 0 and 15 mg challenge sessions will be randomly assigned. Thus, the investigator will only be unblind to the 30 mg methamphetamine challenge. The 30 mg challenge will always follow the 0 and 15 mg challenge. After clinic discharge, all subjects will be asked to return weekly for 2-weeks for safety follow-up.

STUDY DURATION: The study schedule consists of 17 days or less of outpatient/inpatient screening (some screening assessments will be performed after clinic intake at UCLA), 29 days of inpatient treatment and assessments, and two weeks of follow-up after discharge. Study completion is anticipated to be twelve months with 2 subjects being enrolled every 29 to 32 days.

SAMPLE SIZE: 20 subjects total (10 at each site); subjects dropping out before completion of study procedures up to midnight of study day 22 (after discussions with the NIDA Investigator) will be replaced.

POPULATION: Volunteer experienced methamphetamine users, 18 to 45 years of age, who have used methamphetamine by the smoked or i.v. route on average at least twice per week for at least four of the past six weeks.

TREATMENTS: Subjects will be randomized on day 1 to one of the following arms:

Bupropion: Subjects will take 150 mg once daily on days 10 through 12 and twice daily (b.i.d.) on days 13 through 25, and once in the morning on day 26.

Placebo: Subjects will take a placebo tablet once daily on days 10 through 12 and two tablets daily (b.i.d.) on days 13 through 25, and one tablet once in the morning on day 26.

ASSESSMENTS: Safety of methamphetamine administration in bupropion dosed subjects will be determined by monitoring adverse events (AE), blood pressure (BP), heart rate (HR), and electrocardiograph (ECG) readings. Interactions between methamphetamine and bupropion will be assessed by pharmacokinetic studies using a between- and within-subjects design. The effect of bupropion on methamphetamine craving will be assessed by a laboratory cue exposure paradigm and changes in VAS, adjective scales, and ARCI. Other psychological assessments include Profile of Moods State (POMS), Brief Symptom Inventory (BSI), Brief Psychiatric Rating Scale (BPRS), and Beck Depression Inventory (BDI). A targeted neuropsychiatric battery will be used to characterize the study population and determine the effects of bupropion and methamphetamine on neuropsychiatric parameters.

4 INTRODUCTION AND RATIONALE

4.1 Therapeutic Strategies for Treating Methamphetamine Abuse

A variety of neuropharmacological strategies are being pursued in the search for an effective treatment for methamphetamine abuse. One approach has been to target the dopaminergic neurotransmitter system involved in the reward mechanism to interrupt the reinforcing action of methamphetamine and thus reduce its use and prevent relapse (Hyman and Nestler, 1995; Ling and Shoptaw, 1997; Mendelson and Mello, 1996). Methamphetamine is known to produce its major effects through dopaminergic mechanisms in the midbrain. Methamphetamine causes dopamine release and blocks the reuptake of dopamine; the consequent excess of dopamine stimulates the midbrain reward centers. One therapeutic strategy is to develop and test dopamine antagonists, to see if blocking dopamine can reduce methamphetamine abuse. A second, and diametrically opposed therapeutic strategy, is to develop and test dopamine agonists - agents that increase dopamine release or dopaminergic activity to determine whether methamphetamine abuse can be reduced. This second strategy is based on a combination of theory and data suggesting that chronic methamphetamine use depletes brain dopamine and that this depletion is

experienced as methamphetamine craving; the aim is to reduce methamphetamine craving and use by restoring the depleted dopamine system to normality.

4.2 Methamphetamine

Pharmacology. (d-)Methamphetamine inhibits the reuptake and causes release of norepinephrine, serotonin, and dopamine. The dopaminergic activity is thought to contribute to the reinforcing effects of methamphetamine, and actions at dopamine and norepinephrine terminals may contribute to its sympathomimetic effects.

Pharmacokinetics. Following i.v. administration, methamphetamine is eliminated with a $t_{1/2}$ of 12 $\pm$ 3.2 hours.

Metabolism. Methamphetamine is metabolized by N-demethylation to amphetamine (Lin *et al.,* 1997) and by hydroxylation to 4-OH methamphetamine (Lin *et al.,* 1995). Both of these reactions are catalyzed by cytochrome P 450 2D6 (CYP2D6). Approximately 38% of the administered dose is excreted in the urine unchanged (Mendelson *et al.,* 1995). Methamphetamine and amphetamine also inhibit CYP2D6 with an apparent ki of 25 μM and 26.5 μM, respectively (Wu *et al.,* 1997). This could shift metabolism during chronic administration towards urinary excretion of the parent compound.

Safety. Intravenous (i.v.) methamphetamine administration spanning the doses proposed for use in this study have been previously investigated in human laboratory clinical trials. Mendelson and colleagues (personal communication) have employed i.v. methamphetamine doses from 15 mg to 0.5 mg/kg (about 45 mg maximally). These doses were administered safely over 1 to 10 minutes in subjects with prior experience with i.v. methamphetamine use. In these studies, the immediate subjective effects of a 15 mg dose were minimal, almost indistinguishable from placebo. However, after about 10 minutes all subjects were able to distinguish when methamphetamine was administered as compared to placebo. The cardiovascular effects of the 15 mg dose were also minimal.

In a pharmacokinetic and interaction study with alcohol, Mendelson *et al.,* (1995) reported the cardiovascular effects in 8 subjects following i.v. administration of 30 mg of methamphetamine. Blood pressure peaked at 2 minutes and heart rate peaked at 10 minutes. Both measures returned from peak values to a plateau level (20 mm Hg above and about 15 bpm above pre-methamphetamine baseline) 15 minutes following i.v. administration. The plateau levels slowly returned to baseline levels over the rest of the day. Heart rate and blood pressure responses were dramatic in some individuals (50 mm Hg elevations in systolic blood pressure occurred). A few subjects exhibited a baroreceptor reflex response with a brief, relative bradycardia with heart rates of 55 to 60. All subjects had a robust, predictable response to the 30 mg dose with immediate intoxication ratings of about 50 (0=none, 100=max). In the interaction part of this study, methamphetamine (30 mg i.v.) was administered in combination with ethanol (1 gm/kg). Methamphetamine pharmacokinetics were not altered by the concurrent administration of ethanol, with the exception of lowering the apparent volume of distribution at steady state for methamphetamine. Based on these data, Mendelson concluded that doses around 30 mg produced at least half maximal acute subjective and cardiovascular responses.

Methamphetamine Dose Justification. Peak plasma concentrations of 140 ng/mL are observed after i.v. administration of 30 mg doses of methamphetamine in humans (Mendelson, *et al.,* 1995). Thirty mg doses of methamphetamine translate to an effective dose of 21 mg when delivered by the smoked route (Cook, 1991). A peak plasma concentration of 44 ng/ml was observed after 30 mg of methamphetamine was administered by smoking (Cook, 1991). Logan *et al.* (1998) quantitated methamphetamine levels in the postmortem blood of individuals involved in traffic fatalities that had detectable levels of methamphetamine. Levels ranged from 50 to 2,600 ng/mL (median 350 ng/mL). Thus, the highest dose of methamphetamine to be used in this study is representative of the levels in blood of methamphetamine users while at the same time being a safe dose to administer in the human laboratory setting.

4.3 Bupropion

Pharmacology. Bupropion is a weak inhibitor of serotonin, norepinephrine and dopamine reuptake. It is efficacious as an antidepressant and as an aid in smoking cessation, although the mechanisms are unknown. Action at the monoaminergic transporters is assumed.

The results of animal studies designed to test the ability of bupropion to block effects of methamphetamine support clinical use for the treatment of methamphetamine dependence (Kim *et al.,* 2000). Bupropion provided complete protection against methamphetamine-induced decreases in dopamine uptake in striatum in an *in vitro* model of methamphetamine-induced dopamine nerve terminal toxicity.

Pharmacokinetics. Following oral administration of bupropion (Zyban formulation), peak plasma concentrations were reached within 3 hours. The mean peak concentration (C_{max}) values were 91 and 143 ng/mL from two single-dose (150-mg) studies. At steady state, the mean C_{max} following a 150 mg dose every 12 hours was 136 ng/mL. In a single-dose study, food increased the C_{max} of bupropion by 11% and the extent of absorption as defined by area under the plasma concentration time curve (AUC) by 17%. The mean time to peak concentration (t_{max}) was prolonged by 1 hour. Bupropion follows biphasic pharmacokinetics best described by a two-compartment model. The terminal phase has a mean $t_{1/2}$ of about 21 hours while the distribution phase has a mean $t_{1/2}$ of 3 to 4 hours (PDR, 2000).

We propose to dose bupropion (Zyban formulation) at a dose of 150 mg given orally every 12 hours. We propose to time challenge studies to the t_{max} of approximately 3 hours. Because food has a minor effect on measures, we propose to dose bupropion 1 hour prior to breakfast.

Metabolism. Bupropion is extensively metabolized in humans. There are three active metabolites: hydroxybupropion and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, which are formed via hydroxylation of the tertiary-butyl group of bupropion and/or reduction of the carbonyl group. Oxidation of the bupropion side chain results in the formation of a glycine conjugate of meta-chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency and toxicity of the metabolites relative to bupropion have not been fully characterized; however, it has been demonstrated in mice that hydroxybupropion is comparable in potency to bupropion, while the other metabolites are one tenth to one half as potent. This may be of clinical importance because the plasma concentrations of the metabolites are higher than those of bupropion.

In vitro findings suggest that cytochrome P450IIB6 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion, while cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion. CYP2B6 participates in the metabolism of orphenadrine and cyclophosphamide, but not methamphetamine.

Although bupropion is not metabolized by this isoenzyme, bupropion and hydroxybupropion are inhibitors of the CYP2D6 isoenzyme *in vitro*. In a study of 15 male subjects (ages 19 to 35 years) who were extensive metabolizers, daily doses of bupropion given as 150 mg twice daily followed by a single dose of 50 mg desipramine increased the C_{max}, AUC, and $t_{1/2}$ of desipramine by an average of approximately two-, five- and two-fold, respectively. The effect was present for at least 7 days after the last dose of bupropion.

Safety of Bupropion in Humans. Bupropion has been proved to be effective for treatment of nicotine dependence (Hurt *et al.,* 1997; Goldstein, 1998) and is FDA-approved and marketed as Zyban, a non-nicotine aid to smoking cessation. Dose response clinical trials of Zyban showed that 300 mg/day was the most effective dose for increasing the quit rate amongst smokers (36% 4-week quit rate for bupropion treated subjects versus 17% 4-week quit rate for placebo controls) (PDR, 2000). Adverse events that occurred in over 5% of the subjects were in order of frequency, insomnia (40%), dizziness (10%), dry mouth (10%), nausea (9%), disturbed concentration (9%), and anxiety (8%). Symptoms of insomnia were sufficiently severe to require discontinuation of Zyban in 0.6% of 243 subjects treated with 300 mg/day.

Bupropion has been investigated for treatment of cocaine abuse. In a pilot study, Margolin *et al.* (1991) found that bupropion (300 mg/day), administered to five cocaine-dependent methadone-maintenance patients substantially reduced cocaine use in four of the five, was well tolerated, and reduced self-reported craving for cocaine. A multicenter placebo-controlled double-blind clinical trial of bupropion for cocaine dependence in methadone-maintenance patients indicated efficacy of bupropion for the subgroup of patients with depression at study entry (Margolin *et al.,* 1995).

Potential drug-drug interactions. Methamphetamine would not be expected to alter the peak concentration or disposition of bupropion. Bupropion inhibits CYP2D6, which is responsible for 4-hydroxylation and N-demethylation reactions. Thus, treatment with bupropion may result in higher methamphetamine plasma concentrations and possibly greater cardiovascular effects.

Methamphetamine is a substrate for CYP2D6, (Lin *et al.,* 1997) so that its inhibition by bupropion may affect the pharmacokinetics of methamphetamine. Preclinical evidence supports the contention that inhibition of the rat equivalent of 2D6 may be behaviorally relevant (Tomkins *et al.,* 1997). In the rat, however, hepatic metabolism is of much greater significance than in the human. It remains unclear from the published literature whether inhibition of 2D6 will have meaningful effects on cardiovascular and subjective effects of experimentally administered methamphetamine. Clinical experience of the Principal Investigator (Dr. Newton) and many others giving bupropion to patients who subsequently used relatively large doses of methamphetamine suggests that pharmacodynamic effects are unlikely to be dramatic. These data support the need for careful studies of the interaction of methamphetamine and bupropion,

to determine the pharmacodynamic effects of cotreatment with bupropion and methamphetamine.

5 STUDY DESIGN

This is a randomized (stratified by site), double-blind, placebo-controlled, two-arm study (10 subjects per arm) designed to evaluate the safety of bupropion treatment, compared to placebo treatment, concurrent with i.v. methamphetamine challenges. All subjects will undergo one series (baseline challenges) of i.v. methamphetamine challenges (0, 15, and 30 mg) before placebo or bupropion administration and a second series of methamphetamine challenges (0, 15, and 30 mg) starting 6 days after the initiation of the twice daily placebo or bupropion administration (treatment challenges). The order of the 0 and 15 mg challenge sessions will be randomly assigned. Thus, the investigator will be unblind to the 30 mg methamphetamine challenge. The 30 mg challenge will always follow the 0 and 15 mg challenge for safety.

After clinic discharge, all subjects will be asked to return weekly for 2 weeks for safety follow-up. The study will assess the subjective and physiological response to methamphetamine, the pharmacokinetics of methamphetamine and its major metabolites, and the blood levels of bupropion and its metabolites. A combination between-subjects and within-subjects analysis will be performed. A between-subjects analysis will be used to assess the effects of bupropion pretreatment on subjective effects of two doses of methamphetamine. A combined between-subjects and within-subjects analysis will allow for a pharmacodynamic assessment of methamphetamine's effects before and after initiating treatment with bupropion.

Subjects will be discharged from the hospital 2 days after the last doses of bupropion and methamphetamine. This is to optimize medical monitoring for adverse events and to reduce the likelihood that methamphetamine administration in an experimental paradigm might increase craving and increase illicit use. Subjects will be asked to return twice for payment and follow-up at 1 and 2 weeks after clinic discharge to ascertain whether adverse events have occurred.

6 STUDY OBJECTIVES

6.1 Primary

The primary objective of this study is to determine the safety of bupropion concurrent with d-methamphetamine challenges of 15 mg and 30 mg i.v., with the focus being on cardiovascular responses (HR, BP) to the i.v. methamphetamine challenges.

6.2 Secondary

Secondary objectives include:

1. Determining plasma levels of bupropion and its metabolites during chronic daily treatment with bupropion and the effects of methamphetamine on bupropion pharmacokinetics.
2. Evaluating whether administration of bupropion alters the pharmacokinetics of d-methamphetamine or its metabolites.

3. Evaluating whether bupropion treatment alters the subjective or cardiovascular response to methamphetamine.
4. Assessing the effects of bupropion on craving for methamphetamine assessed using a laboratory cue exposure paradigm.
5. Assessing the effects of bupropion on mood and personality assessments (BSI, BDI, and POMS), other psychological parameters (VAS, ARCI, and Adjective Scales), and a targeted neuropsychiatric battery.

7 STUDY SITES

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

8 SUBJECT IDENTIFICATION

8.1 Inclusion Criteria

In order to participate in the study, subjects must:

1. Be volunteers who meet DSM-IV criteria for methamphetamine abuse or dependence and are non-treatment seeking at time of study.

2. Be between 18 and 45 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 methamphetamine by the smoked or i.v. route on average at least twice per week for at least four of the past six weeks, as assessed by self report and a positive urine test during screening.

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 investigator.

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

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

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

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

10. Have an ECG performed that demonstrates normal sinus rhythm, normal conduction, and no clinically significant arrhythmias.

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

    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

NOTE: Recent intermittent alcohol or other illicit drug use without physical dependence is allowable (however an opiate and benzodiazepine-free urine should be produced to document absence of recent use).

8.2 Exclusion criteria

In order to participate in the study, subjects must <u>not</u>:

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

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

3. Have physiological dependence on alcohol or a sedative-hypnotic, (e.g., a benzodiazepine) that requires medical detoxification.

4. Have any previous medically serious adverse reaction to methamphetamine including loss of consciousness, chest pain, or epileptic seizure 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 significant medical illness.

7. If female, be pregnant or nursing.

8. Have a significant family history of early cardiovascular morbidity or mortality.

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

10. Be actively using albuterol or other beta agonist medications, regardless of formal diagnosis of asthma. (Inhalers are sometimes used by methamphetamine addicts to enhance methamphetamine 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.

11. 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 %.

12. 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.

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

14. Be undergoing HIV treatment with antiviral and non-antiviral therapy.

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

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

17. Have neurological disorders including Parkinson's disease.

18. Be using bupropion or any medication that could interact adversely with bupropion, within the following times of beginning of administration of bupropion 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. Bupropion (Wellbutrin®, Zyban®) used during the past 30 days

b. Antidepressants including monoamine oxidase (MAO) inhibitors (GlaxoSmithKlein recommends 14 days after stopping MAO inhibitors)
c. Neuroleptics
d. Psychotropics
e. Systemic corticosteroids
f. Xanthines, i.e., theophilline, theophilline sodium glycinate and aminophylline
g. Nicotine replacement therapy for patients undergoing smoking cessation treatment
h. Drugs that lower seizure threshold

Notes on inclusion/exclusion criterion: 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 results do not exclude a prospective subject from participation unless there is an indication of active liver disease. 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 subject will be notified of positive and confirmatory test results and will be referred for treatment.

History of Methamphetamine 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 until clinically stabilized.

9 INVESTIGATIONAL AGENTS

9.1 Bupropion

The research pharmacist will prepare double-blind medication as single size gelatin capsule containing either 150 mg bupropion SR or placebo.

9.2 Methamphetamine

Sterile i.v. human use methamphetamine HCl at 10 mg/mL in 1 mL ampules will be provided by NIDA. The compound will be stored in the pharmacy vault. Standard narcotics control procedures will govern access to the drug. Aliquots of 0, 15 or 30 mg will be drawn into a syringe for i.v. administration. Methamphetamine will be administered by i.v. infusion over 2

minutes by the study physician. Any unused drug will be disposed according to standard practices.

10 TREATMENT PLAN

Bupropion or Placebo: Bupropion or placebo tablets will be administered once daily for 3 days (study days 10 through 12), b.i.d. for 13 days (study days 13 through 25), and once in the morning on study day 26. Bupropion will be given at the same time each day and should be given 3 hours before the planned time for infusions and again at 5 p.m. as appropriate to the dosing schedule with the once daily dose being given 3 hours before the planned time for infusions. Subjects assigned to the placebo group will receive matched placebo on the same schedule as the bupropion group.

Methamphetamine or Saline (All Subjects):

Saline i.v. or 15 mg methamphetamine i.v.: Study days 2, or 3, and, 18, or 19 (random assignment)

30 mg methamphetamine i.v.: Study days 5 and 22

11 STUDY PROCEDURES

Appendix I provides a detailed table of the timing of study activities.

11.1 Screening (Study Days –17 to 0)

Interested candidates between the ages of 18 and 45 who have been determined to have used methamphetamine by the smoked or i.v. route on average at least twice per week for at least four of the past six weeks, are not seeking treatment, and are available to participate in an inpatient study for 29 to 32 days will meet with the investigator and receive an explanation of the study purpose and requirements. If still interested after receiving an explanation of the study, the candidate will be given an opportunity to review, inquire about, and sign the study informed consent form approved by the site's IRB. All subjects will be counseled by the site investigator regarding the option of receiving treatment before, and at the conclusion of the study.

Screening of subjects to establish eligibility will occur initially before clinic intake. Some assessments will be completed after intake at UCLA. Assessments performed before intake at both UCLA and UTHSCSA include collection of demographic information and completion of a subject intake form, subject locator form, a timeline followback for methamphetamine use for the prior 6 weeks, drug use and treatment history, quantity frequency interview, urine test for methamphetamine (will be repeated until a positive test is obtained within 17 days prior to intake), a 12-lead ECG, and vital signs (HR and BP). For women of reproductive potential a urine pregnancy test will be performed. Adverse events will be recorded as soon as the potential subject completes the informed consent process.

All drug-abusing applicants for study participation will receive counseling about drug dependence and be advised that treatment for drug abuse is indicated and available. Applicants

not participating in the study will receive treatment referral information as appropriate. At the completion of their participation, study participants will again be advised that treatment is indicated and available, and will be given treatment referral information and assistance.

11.2 Inpatient/Additional Outpatient Screening

Potential candidates at the UCLA site, whose results of screening assessments conducted prior to intake do not exclude them from study participation, will complete intake procedures and reside full-time at the GCRC starting on a Friday and continuing until discharge or completion of the study. Additional screening procedures conducted at the UTHSCSA site will be conducted in the outpatient setting. The remaining screening procedures must be conducted within 3 days of randomization whether in the inpatient or outpatient setting. The rest of the screening assessments include a physical exam including vital signs, medical history, family history of drug or alcohol abuse/dependence, laboratory analyses including hematology, blood chemistries, an infectious disease panel, an HIV antibody test (optional), urine drug toxicology tests, a pregnancy test for women of reproductive potential, SCID for DSM-IV diagnosis of methamphetamine dependence and Axis I Disorders, BDI, BSI, POMS, HRBS, Attention Deficit Disorder (ADD) interview, and ASI-Lite assessment. Adverse events will be recorded at each visit starting the day of the completion of the informed consent process.

To ensure abstinence by documenting declining methamphetamine levels and to assess individual methamphetamine elimination characteristics, the following evaluations will be performed on subjects admitted to the inpatient unit of GCRC at the UCLA site and with urine test positive for methamphetamine on study days –3, –2 and –1:

1. Quantitative blood methamphetamine test twice a day at 8 a.m. and 8 p.m.
2. Quantitative methamphetamine test on all of the urine output from each subject collected in 8 hour blocks (7 a.m.-3 p.m.; 3 p.m.-11 p.m.; 11 p.m.-7 a.m.).

11.3 Randomization and Enrollment

If the prospective subject meets all of the study inclusion and does not meet the exclusion criteria (a checklist will be provided with the CRFs), then the subject can be enrolled onto the study. If the subject is enrolling at the UTHSCSA site, the subject will complete intake procedures and reside at the UCPL for the duration of the study. Subjects at the UCLA site will have already competed intake procedures. The site investigator or a study coordinator will contact the research pharmacist for randomization and enrollment. Two randomizations will be performed. The first will be for the schedule of administration of the 0 and 15 mg doses of methamphetamine for the challenge sessions. The second randomization will apply to the assignment to the bupropion or placebo arm. The NIDA data-coordinating center will create a set of envelopes containing randomized treatment assignments for study participants. A blocked randomization schema will be used and subjects will be stratified by site. The research pharmacist will maintain the envelopes and list of subject treatment assignments and will prepare all investigational agents in a blind-coded manner. If subjects are terminated before completing all of the methamphetamine challenge sessions and methamphetamine PK sample collection up to midnight of day 22, replacement subjects (after discussions with the NIDA Investigator) will be included until 10 subjects from both treatment arms have completed the study.

11.4 Methamphetamine Challenge Sessions

11.4.1 Schedule

Intravenous (i.v.) methamphetamine challenge sessions will be conducted according to the schedule shown in Table 1. Each series of repeated administrations will consist of three challenge sessions in one week. Each challenge session will be on different days and there will be one day off in between the second and the third challenge sessions to assure a one-day break between methamphetamine challenges. The fixed ascending sequence of methamphetamine challenges each week is a safety precaution.

During the baseline challenge session, the subject's responses to methamphetamine without concomitant bupropion or placebo administration will be assessed. The baseline series of challenges (sessions 1, 2, and 3) are for training and adaptation purposes and to ensure that volunteers are responsive to (in the judgment of the investigator) and safely tolerate the methamphetamine test doses. The baseline series of challenges are also for a determination of physiological and psychological responses to methamphetamine challenge in the absence of bupropion and for the determination of methamphetamine PK (session 3). Data from baseline challenge sessions will be used for within-subjects analyses. Only subjects responsive to and safely tolerating both test doses of methamphetamine will continue in the study.

During the bupropion treatment phase, the subject's responses to methamphetamine with concomitant bupropion or placebo administration will be assessed. This data will be used for both between-subject and within-subject analyses.

Table 1. Methamphetamine Challenge Session Schedule

Study Phase	Session Number	Study Day	Challenge
Baseline	Session 1	2	0 or 15 mg methamphetamine
Baseline	Session 2	3	0 or 15 mg methamphetamine
Baseline	Session 3	5	30 mg methamphetamine
Treatment	Session 4	18	0 or 15 mg methamphetamine
Treatment	Session 5	19	0 or 15 mg methamphetamine
Treatment	Session 6	22	30 mg methamphetamine

11.4.2 Conduct of Methamphetamine/Saline Challenge Sessions

Each intravenous challenge dose will be administered over a 2-minute duration by a study physician. The methamphetamine or saline injection will occur between 10 a.m. and noon, depending on scheduling constraints. The timing of the challenge session should be scheduled to occur as close to 3 hours after the morning dose of bupropion/placebo as possible. The timing of the dosing of the bupropion/placebo and methamphetamine infusions should remain the same for each series of sessions for an individual.

Before the first challenge session, study subjects must have had a drug toxicology screening that shows negative urine drug/metabolite levels for drugs of abuse (except marijuana) on day 2 before conduct of the challenge session. Subjects with positive urine drug toxicologies will be discharged and replaced.

Subjects will receive a hospital meal prior to test session initiation, but will not be allowed to eat within the hour prior to the infusion until after the entire session. 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.

Before and after each i.v. challenge, the subject's physiologic responses will be closely monitored using repeated HR, BP, and ECG readings. BP and HR will be taken at –25 and – 15 minutes before, and 3, 6, 9, 12, 15, 20, 30, 45, 60, 90, 180, 210, 240, 300, 360, 420, 480 minutes and 10 and 12 hours following methamphetamine/saline administration. ECG and HR will be monitored continuously for the first 60 minutes after methamphetamine infusion.

11.4.3 Safety Precautions

A physician 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 methamphetamine, the methamphetamine 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 Methamphetamine Infusion

Methamphetamine i.v. 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 methamphetamine toxicity, e.g., agitation, psychosis, inability to comply with study procedures.

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 methamphetamine infusion do not return to acceptable limits within appropriate time frames (e.g., 30 minutes);
2. Stopping criteria for further methamphetamine infusion 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 methamphetamine infusion session, study subjects have a positive drug toxicology screening (except for marijuana) before conduct of the infusion session.

11.4.6 Bupropion Safety Concerns

One of the potentially most serious adverse effects of bupropion is reduction in the seizure threshold (Johnston *et al.,* 1992, Settle, 1998, Storow, 1994). Bupropion is contraindicated in patients with a seizure disorder or a predisposing factor for seizures (e.g., cranial trauma history, current seizure disorder, concomitant use of drugs that lower seizure threshold). However, the relative risk of seizures with various antidepressants, including bupropion, has not been clearly defined. The incidence of seizures at doses of 400 mg daily as sustained-release tablets increases to 0.4%.

The incidence of seizures with bupropion depends on dose. Minimizing the risk of seizures includes restriction of total dosage to 400 mg daily as sustained-release. Administration of the daily dose in divided doses up to 150 mg twice daily, at least 8 hours apart, should minimize the risk of seizure.

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 methamphetamine detection in urine samples (e.g. ephedrine and pseudoephedrine)

11.4.7 Subjective Response

During and after infusions, subject's subjective responses will be closely monitored. Computerized VAS will be administered 15 minutes before, and 3, 6, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420, and 480 minutes after each infusion.

11.4.8 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.

11.4.9 Off-unit Passes

Subjects will normally 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. 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.

11.4.10 Subject Payment

Subject payment will be determined by local site IRB requirements, which can change and will be combinations of cash and vouchers. We currently plan to reimburse subjects $20 for the initial screen, $30 to complete the medical screening, including ECG, labwork, and baseline assessments and a completion bonus of $50. 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.

Subjects will not receive the entire payment at once but in increments paid over two weeks. Subjects will return to the hospital for a one- and two-week follow up visit following completion of the residential phase of the study. These visits will permit monitoring of safety outcomes and provide therapeutic support that should reduce the likelihood of immediate relapse to methamphetamine abuse.

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 at UCLA.

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

1. Informed consent;
2. Locator form;
3. Intake form;
4. Demographics information;
5. Timeline followback for methamphetamine use for prior 6 weeks;
6. Drug use and treatment history;
7. Qualitative urine drug toxicology (this test will be repeated until a methamphetamine positive test is obtained within 17 days prior to intake);
8. 12-lead ECG and vital signs (HR and BP);
9. Adverse events;
10. For women of reproductive potential, a urine pregnancy test will be performed.
11. Physical exam and medical history;
12. Vital signs;
13. Hematology;
14. Blood chemistries;
15. SCID for DSM-IV Axis I Disorders and methamphetamine abuse/dependence;
16. Family history of drug/alcohol abuse;
17. Quantity Frequency Interview;
18. Qualitative urine drug toxicology (daily after intake);

19. 12-lead ECG;
20. Pregnancy test for women of reproductive potential;
21. Adverse events;
22. BDI, BSI, and POMS (every other day after intake);
23. ADD interview;
24. HRBS;
25. ASI-Lite;
26. Timeline followback for methamphetamine use for interval between first assessment and study start;
27. HIV test (optional);
28. Infectious disease panel.

Note: Screening assessments performed on subjects admitted to the inpatient unit of GCRC at the UCLA site and with urine test positive for methamphetamine on study days –3, –2 and –1 will also include:

1. Quantitative blood methamphetamine test twice a day at 8 a.m. and 8 p.m.
2. Quantitative methamphetamine test on all of the urine output from each subject collected in 8 hour blocks (7 a.m.-3 p.m.; 3 p.m.-11 p.m.; 11 p.m.-7 a.m.).

12.2 Evaluations Performed Daily or Every Other Day 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. BSI, BDI, POMS will be conducted every other day.
3. Adverse events will be monitored daily starting after intake.
4. Vital signs (daily).

12.3 Evaluations Performed During Challenge Sessions

Table 2 shows the series of activities that occur during methamphetamine challenge sessions. This is also depicted diagrammatically in Appendix IV. Refer to Table 1 for the timing of the challenge sessions according to the study day. All activities occur at each challenge session, unless otherwise noted. Urine collections for methamphetamine elimination pharmacokinetics are shown in Table 3.

Table 2. Methamphetamine Challenge Sessions Daily Schedule

Time point	Activity (occurs at all sessions unless otherwise noted)
Before 7 a.m.	Insert catheters if multiple blood draws will be made Draw blood for trough bupropion assay (sessions 4, 5, & 6) Vital signs
7 a.m. (see note)	Administer bupropion or placebo (sessions 4, 5, & 6) Note: Bupropion administration should be scheduled to occur 3 hours before the time planned to start the methamphetamine infusion.
7 a.m. – 8 a.m.	BSI, BDI, POMS
8 a.m.	Urine Drug Toxicology
10 a.m. (see note)	Draw blood for peak bupropion levels (sessions 4, 5, & 6) Note: Timing of the blood collection should be 2 hours after bupropion

Time point	Activity (occurs at all sessions unless otherwise noted)
	administration.
The following should start at approximately 10 a.m. Times shown are relative to the start of methamphetamine administration	
-30 min	Insert catheters (catheter for blood may already be in place)
-25 min	BP, HR, oral temperature
-20 min	Cue-Induced Assessments (sessions 1, 2, 4, & 5)
-15 min	VAS, ARCI, Adj Scale, BP, HR, and start continuous monitoring of ECG and HR (HR is recorded every two minutes)
- 5 min	Draw blood for peak bupropion assay (sessions 4, 5, & 6) Draw baseline blood for methamphetamine assay
Time 0	Inject methamphetamine or saline 2 min i.v. infusion
2 min	Draw blood for methamphetamine assay
3 min	VAS, BP
5 min	Draw blood for methamphetamine assay
6 min	VAS, BP
9 min	BP
10 min	VAS
12 min	BP
15 min	VAS, BP Draw blood for methamphetamine assay
20 min	BP
30 min	VAS, BP, Draw blood for methamphetamine, ARCI, Adj Scale, oral temperature, stop continuous monitoring of ECG and HR
45 min	VAS, BP, HR
60 min	BP, HR, VAS, BPRS, Draw blood for methamphetamine assay, oral temperature
90 min	BP, HR, VAS, Draw blood for methamphetamine assay
120 min	Draw blood for methamphetamine assay VAS
180 min	VAS, BP, HR, Draw blood for methamphetamine assay
210 min	BP, HR
240 min	VAS, BP, HR, Draw blood for methamphetamine assay Neuropsychiatric measures (sessions 3 & 6)
300 min	VAS, BP, HR
360 min	VAS, BP, HR, Draw blood for methamphetamine assay
420 min	VAS, BP, HR
480 min	VAS, BP, HR, Draw blood for methamphetamine assay
5 p.m.	Administer bupropion or placebo (sessions 4 through 6)
10 hr	BP, HR
12 hr	BP, HR, Draw blood for methamphetamine assay
24 hr	Draw blood for methamphetamine assay
36 hr	Draw blood for methamphetamine assay (sessions 3 & 6)
48 hr	Draw blood for methamphetamine assay (sessions 3 & 6)
60 hr	Draw blood for methamphetamine assay (sessions 3 & 6)

Time point	Activity (occurs at all sessions unless otherwise noted)
72 hr	Draw blood for methamphetamine assay (sessions 3 & 6)

Table 3. Schedule for Collection of Urine Specimens for Methamphetamine Elimination Pharmacokinetics

Sample #	Time Relative to Infusion
1	-3 to 0 hours
2	0 to 6 hours
3	6 to 12 hours
4	12 to 24 hours
5	24 to 30 hours
6	30 to 36 hours
7	36 to 48 hours
8	48 to 54 hours
9	54 to 60 hours
10	60 to 72 hours
11	72 to 84 hours
12	84 to 96 hours

*Urine is collected during challenge session 3 and 6.

12.4 Evaluations at Discharge

The following evaluations will be performed at time of discharge. The same evaluations will be performed in the case of early study discontinuation. No further evaluations following completion of the residential phase are planned.

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

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 Intake Form

At time of clinic intake or before at UTHSCSA, subjects will be asked a variety of questions with respect to their family, medical, psychiatric, and substance use histories. This information will be used to determine eligibility.

12.5.1.2 Follow-up Locator Form

A locator form developed by Dr. Douglas Anglin's group at the UCLA Drug Abuse Research Center (1996) and altered for use with substance using populations, will be used to assist in finding participants at follow-up. This form asks participants to give consent for follow-up and to provide names, addresses, and phone numbers of several friends and family members. This information is essential and will be collected at enrollment, and will be updated throughout the study as necessary.

12.5.1.3 Addiction Severity Index (ASI)-Lite CF Version

The ASI-Lite CF version will be administered by a research staff member having at least a bachelor's degree in the social sciences or equivalent training and experience as determined by the site investigator. The ASI-Lite is the interviewer's estimate of the severity of the subject's status in seven areas (medical, employment, drug use, alcohol use, legal, family/social, and psychological). Composite scores will be calculated according to the procedures described by McGahan *et al*. (1982) and Carroll *et al*. (1994). The Lite version is a shorter version of the ASI that still retains all questions used to calculate the ASI composite scores. The ASI-Lite will be completed during screening.

12.5.1.4 Timeline Followback

Detailed histories of methamphetamine use over the past 6 weeks prior to screening will be obtained using the timeline followback method. The timeline followback 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).

12.5.1.5 Quantity Frequency Interview

A quantity frequency interview will be used to establish the subject's history of methamphetamine 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.

12.5.1.6 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 methamphetamine dependence and to rule out any major psychiatric disorders (e.g., affective disorders, schizophrenia).

12.5.1.7 Attention Deficit Disorder (ADD) Interview

An interview from the DSM-IV criteria for childhood attention deficit hyperactivity disorder (ADHD) has been adapted to diagnose adult ADD. This interview assesses the subject's inattention, hyperactivity, and impulsivity both as the childhood history and as current adult behaviors. This interview will be conducted during screening.

12.5.1.8 HIV Risk-Taking Behavior Scale (HRBS)

The HRBS is a brief 12-item instrument that examines the behavior of intravenous drug users in both drug injection behavior and sexual behavior and will be collected during screening.

12.5.1.9 CYP2D6 Genotyping

Thirty ml of blood will be collected into standard EST tubes. The white blood cells (WBC) will be centrifuged and separated from the plasma. WBC will be re-suspended and lysed in a phenol/chloroform/aqueous mixture. The lysate will be shipped to the University of Texas Health Science Center for analysis (except for the samples collected at this site which will be put into storage locally for analysis). The DNA separates into the aqueous phase and will be purified through two phenol/chloroform/aqueous extractions and overnight exposure to proteinase K. The DNA will be precipitated by suspension in ethanol and then re-suspension in TE-buffer wherein it can be stored indefinitely. DNA samples will be stored at - 40°C until the time of analyses. DNA samples will be coded for storage without patient identifying information. Genotyping will be performed by the polymerase chain reaction (PCR) method described by Schur *et al.* (2001).

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.

12.5.3 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 and Every Other Day Surveys

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

12.5.4.1 Beck Depression Inventory (BDI)

The BDI is a 21-item self-report inventory that focuses on the subject's subjective feelings of depression and is sensitive to changes in feeling status (Beck *et al*., 1961). Subjects will start the measure after clinic intake and continue to complete this questionnaire on an every other day basis, until the end of the study.

12.5.4.2 Brief Symptom Inventory (BSI)

The BSI is a 53-item self-report inventory that assesses the psychological symptomatology of psychiatric and medically ill individuals on nine primary dimensions: (1) somatization, (2) obsessive-compulsive, (3) interpersonal sensitivity, (4) depression, (5) anxiety, (6) hostility, (7) phobic anxiety, (8) paranoid ideation, and (9) psychoticism (Derogatis and Melisaratos, 1983). Each item is rated on a 5-point Likert scale of distress, which ranges from "not at all' to "extremely." The measure also includes three global indices of distress: the General Severity Index (GSI), the Positive Symptom Distress Index (PSDI), and the Positive Symptom Total (PST). The GSI reflects the number of symptoms experienced and their intensity. The PSDI reflects the intensity of the reported symptoms while the PST is a count of the symptoms that participants experience. Variables of interest include GSI, PSDI, PST, and scores for each of the subscales. Subjects will start the measure after clinic intake and continue to complete this questionnaire on an every other day basis, until the end of the study.

12.5.4.3 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 continue to complete this questionnaire on an every other day basis, until the end of the study.

12.5.4.4 Urine Drug Toxicology

Urine toxicology for marijuana, opiates, cocaine, and methamphetamine will be monitored once daily (8 a.m.) except on study days 3 and 19, using an onsite qualitative urine test cup. If the qualitative urine test indicates the presence of a drug of abuse, quantitative tests may be performed to monitor the level.

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 methamphetamine infusions) that lead to false positives. Therefore, methamphetamine 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 methamphetamine outside of infusion sessions. Quantitative tests for methamphetamine will not be performed routinely as the subjects are receiving methamphetamine as one of the investigational agents.

12.5.5 Laboratory Tests

12.5.5.1 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 study day 18, and at discharge.

12.5.5.2 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 study day 18 and at discharge.

12.5.5.3 Pregnancy Test

A blood or urine-based pregnancy test designed to measure human chorionic gonodotropin will be used during screening, once during the study between the baseline challenge and the start of bupropion administration, at the time of discharge, and once during follow-up.

12.5.5.4 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.

12.5.5.5 Infectious Disease Panel

During screening, blood will be collected in a serum separation evacuated venous blood collection tubes (e.g., Vacutainer™) 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 Neuropsychiatric Assessments

Subjects will undergo repeated neuropsychiatric assessments during the study. These tests will be conducted 4 hours after methamphetamine administration or at the same time of day on days when methamphetamine is not administered. An extensive baseline evaluation will be performed

on day 9, consisting of the measures listed below. Other assessments will be performed before and during bupropion/placebo treatment, on days 5 and 22. These assessments will include the Simple Reaction Time Test, Covert Orienting Test, n-back tests, Apathy Inventory, and all thought disorder assessments. In addition, on day 26, the following will be readministered: Rey Auditory Verbal Learning Test, Wechsler Memory Scale Letter-Number and Visual Spans, verbal and nonverbal fluency, Stroop, Trailmaking tests A and B, and Symbol Digit Modalities Test.

Domain	**Measures**
Mood/Emotional Function	Apathy Inventory
Thought Disorder	Young Mania Rating Scale Schedule of Assessment of Negative Symptoms Schedule of Assessment of Positive Symptoms Brief Psychiatric Rating Scale Hillside Akathisia Scale
Attention/Psychomotor Speed	Trailmaking Test-Part A, Symbol Digit Modalities Test, Simple Reaction Time Test, Degraded Stimulus Continuous Performance Test
Verbal Learning and Memory	Rey Auditory Verbal Learning Test
Executive Systems Function	Wechsler Memory Scale-III Letter-Number Sequencing, Visual Memory Span, Verbal Fluency, Nonverbal Fluency, Trailmaking Test-Part B, Stroop Color/Word, Choice Reaction Time, n-back reaction time tests, Cognitive Failures Questionnaire

Apathy Inventory. (Neuropsychiatric Inventory (Cummings *et al.* 1994). This scale is a modified version of the measure included in the Neuropsychiatric Inventory. Only the wording of the items, not the content, was modified. The seven-item scale is presented in a yes/no format and is similar to the items on the Apathy Evaluation Scale (Marin, 1990), the only other apathy scale that has been published in the literature. The apathy scale of the Neuropsychiatric Inventory operationally defines apathy as a lack of motivation, decreased initiative, diminished interest in one's environment, and affective flattening and specifically excluded items that were related to depression.

Hillside Akathisia Scale. The modified Hillside Akathisia Scale will be used to assess this particular aversive effect (Fleischhacker *et al.,* 1989). This scale includes two items that assess the subjective effects of inner restless and the urge to move. The objective scale includes three items assessing the rater's impression of Akathisia in the head, trunk, arms, hands, legs, and feet. These five items are completed while the examinee is sitting, standing, and lying down.

Schedule for the Assessment of Negative Symptoms/Schedule for the Assessment of Positive Symptoms. (Andreasen and Olsen, 1982). Positive schizophrenia is characterized by prominent delusions, hallucinations, positive formal thought disorder, and persistently bizarre behavior; negative schizophrenia, by affective flattening, alogia, avolition, anhedonia, and attentional impairment. When symptoms are defined by objective behavioral indices, they have excellent interrater reliability.

Young Mania Rating Scale. The Young Mania Rating Scale is an eleven item clinician-administered measure (Young *et al.,* 1978). Initial validation studies revealed high levels of interrater reliability. Elevated, expansive, or irritable mood, hyperactivity, and rapid or pressured speech contribute most strongly to a diagnostic classification of mania. Grandiosity and flight of ideas were related to this classification, but did not contribute as much as the previous factors.

Degraded Stimuli Continuous Performance Test. This computerized sustained attention task requires participants to press a button when the number "0" appears on the screen. Each of the 480 stimuli appear for 50 milliseconds (ms) and are degraded so that they blend into a similar background. Variables of interest include mean reaction time across the 480 trials and sensitivity, the capacity to respond to the appropriate target (i.e., "0") and ignore extraneous targets (i.e., "1" to "9").

Symbol Digit Modalities Test. (Smith, 1982). The Symbol Digit Modalities Test is a sensitive measure of attention/psychomotor speed. The written version of this test is considered to be a more difficult analog of the WAIS-III Digit Symbol subtest. The test requires the learning of new associations between numbers and symbols. The variable of interest is the number of numbers correctly written within 90 seconds.

Trailmaking Tests Part A and Part B. The Trail Making tests assess attention, sequencing, psychomotor speed, and mental flexibility. Trail Making part A requires the participant to connect 25 numbers, randomly arranged on a page, in proper order by drawing lines between them. Part B consists of 25 alternating letters and numbers. The participant connects the items (e.g. 1,A,2,B,3,C) by drawing lines. The dependent measure is time (Spreen, 1998; Reitan, 1958; Giovagnoli, 1996).

Simple Reaction Time. This computerized sustained attention task requires participants to press a button when a letter appears on the screen on each of the 24 trials. Each of the 480 stimuli appears for 200 ms. The variable of interest includes median reaction time.

Rey Auditory Verbal Learning Test. (Rey, 1964). This test is a verbal learning and memory task with six parallel forms. Participants attempt to learn and recall 15 words over five trials, complete an interference task, immediately recall the initial list, and recall the list after a 20-minute delay period. Variables of interest include number of words recalled across the five learning trials and recall of the initial list following the 20-minute delay.

Stroop Color Word Interference Test. (Spreen, 1998; Stroop, 1935). This measure of selective attention and cognitive flexibility consists of three parts. In Part One, the participant reads color

names (blue, green, red) printed in black ink. In Part Two, the participant names the color of squares (blue, green, red). In Part Three, the participant names the color in which the color names are printed and disregards their verbal content. The variables of interest include time to complete each subtest.

Wechsler Memory Scale-III. (Wechsler 1997). This package includes auditory (Letter-Number Sequencing) and visuospatial (Visual Memory Span) working memory tests. The Letter-Number Task presents progressively longer strings of alternating letters and numbers to participants and requires them to: (1) hold the numbers and letter on-line, (2) reorder them according to a specific of rules, and (3) state the new order to the examiner. The variable of interest is number spans correctly recalled. Spatial span, which is analogous to the Corsi Block Tapping Test, requires participants to observe and then tap from memory a specified sequence on a series of blocks arranged in a standardized manner. The variable of interest is the number of sequences correctly tapped.

Choice Reaction Time. This computerized executive systems function task requires participants to press a button when the same letter appears consecutively on the screen (e.g., A—A), but to not press a button when two different letters appear in succession (e.g., A—X). This test includes 25 trials in which subjects should respond by pressing a button (e.g., A—A) and 75 when they should not. Variables of interest include median reaction time across the 25 trials in which a response is appropriate and sensitivity, which quantifies the number of accurate and inaccurate responses in a single index.

N-back Test. This computerized executive systems function task requires participants to respond when the same letter appears twice with a different intervening letter (e.g., A—X—A; B—R–B), but to not respond other any other conditions (e.g., A—X—R; B—R—A; B—B—B). This test includes 25 trials in which subjects should respond and 75 when they should not. Variables of interest include median reaction time across the 25 trials in which a response is appropriate and sensitivity, which quantifies the number of accurate and inaccurate responses in a single index.

Cognitive Failures Questionnaire. (Broadbent, 1982). The Cognitive Failures Questionnaire is a 25-item measure in which participants report the frequency with which they experience attention, memory, and frontal lobe problems. Each item is rated on a scale from zero to four with zero indicating no difficulty with the item and four indicating frequent difficulty with that item.

12.5.7 Monitoring and Assessments During Methamphetamine Challenge 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 methamphetamine pharmacokinetics, bupropion blood levels, CYP2D6 genotyping, and hematology and blood chemistry assays. Blood samples collected for methamphetamine and bupropion pharmacokinetic analysis will be prepared and shipped according to the instructions in Appendix V.

An intravenous catheter will be inserted for each challenge session, and maintained in place for the duration of the entire test, if the subject wishes. Two intravenous catheters will be placed for challenge sessions that involve repeated blood draws: one will be for methamphetamine or saline administration, the other for blood sample collection.

Samples will be collected for assessment of methamphetamine pharmacokinetics at baseline and treatment challenge sessions and for bupropion peak and trough levels. Total blood loss during the study is 640 mL.

12.5.7.2 Physiology

Before and after each i.v. challenge, 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 -25 and -15 minutes before, and 3, 6, 9, 12, 15, 20, 30, 45, 60, 90, 180, 210, 240, 300, 360, 420, 480 minutes, and 10 and 12 hours following the methamphetamine/saline administration. ECG and HR will be monitored continuously for the first 60 minutes after methamphetamine infusion.

12.5.7.3 Subjective Responses (VAS, ARCI, and Adjective Scales)

During and after the infusions, subject's subjective response to the methamphetamine will be closely monitored. Computerized VAS will be administered 15 minutes before, and 3, 6, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420, and 480 minutes after each infusion. An ARCI and Adjective Scales will be administered 15 minutes before and at 30 minutes after the infusion. For the VAS scales, subjects will report the degree to which they feel "any drug effect", "high", "good effects", "bad effects", "like methamphetamine", "desire for methamphetamine", "depressed", "anxious", "stimulated", and "likely to use" on a continuous scale digitized between 0 to 100 for computing a score. In addition, they will be asked to answer the question: How much would you pay for this drug? The ARCI consists of 49 statements in a true/false format and the Adjective Scale contains 22 adjectives on which a response on a scale of 0-4 is required, ranging from "not at all" to "extremely".

12.5.8 Assessment of Cue-Induced Craving

On days 2, 3, 18, and 19 (prior to the challenge sessions) subjects will view videotapes depicting actors handling and using methamphetamine (active cues). Subjects will be shown a neutral video that shows scenes unrelated to drug use, on day 1. Before and following exposure to the cues, subjects will rate their using the "general craving scale" and the "within session rating scale". These two instruments assess mood states and the degree to which subjects report craving.

Immediately following the craving and subjective ratings of the Cue Procedure cue, subjects will complete the Multiple Choice Questionnaire (MCQ). The MCQ is a paper and pencil questionnaire assessing the choice preference for or motivation to use a drug by asking subjects to respond to a series of choices between receiving a drug or a designated amount of money. The subjects are to record their preference for receiving either additional injections or varying amounts of money. This exercise is to be implemented for each 70 items on the MCQ.

12.5.9 Brief Psychiatric Rating Scale (BPRS)

The BPRS is a psychiatrist-administered interview that may be conducted either by remote video or in face-to-face format to evaluate the severity of subject's psychopathology, including anxiety, depression and symptoms of schizophrenia. The BPRS may be dichotomized into subjective items based on patients' verbal reports and objective items based on visual observation of patients' behavior. The BPRS total score ratings serve as indicators of psychiatric comorbidity in drug-dependent subjects and as predictors of mental health services utilization. This scale will be measured 60-minutes after methamphetamine infusions.

12.5.10 Urine Collections for Methamphetamine Elimination Pharmacokinetics

To ensure abstinence by documenting declining methamphetamine levels and to assess individual methamphetamine elimination characteristics, a quantitative methamphetamine test will be performed at screening on days –3, –2, and –1 on subjects admitted to GCRC at the UCLA site with urine test positive for methamphetamine. For that purpose, all of the urine output from each subject with urine test positive for methamphetamine will be collected in 8 hour blocks (7 a.m.-3 p.m.; 3 p.m.-11 p.m.; 11 p.m.-7 a.m.).

Also, all of the urine output from each subject will be collected after methamphetamine infusion sessions 3 and 6 at the intervals shown in Table 3. Urine will be collected and pooled for each time interval and the total volume recorded. At the end of each time period the subject will be asked to void into collection bottles. Non-voided urine will be collected during the next time period. Two 20 ml aliquots from each timed specimen will be frozen at -20ºC until analyzed.

12.5.11 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.

12.5.12 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.

12.5.13 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, methamphetamine and bupropion. Our collaborators, Reese Jones, M.D. and John Mendelson, M.D., from UCSF developed these methamphetamine challenge procedures and they have extensive experience with them. The procedures have been safely performed many times without significant adverse effects. The doses of methamphetamine used are modest, the safety

screening and monitoring are careful, and there have been no significant prior adverse events with these procedures.

Bupropion 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 methamphetamine and bupropion might be additive or greater when they are given together. The ascending order of methamphetamine doses (the 15 mg dose will always precede the 30 mg dose) during the treatment challenge is one protection against this risk.

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 methamphetamine abuse, it does offer the potential of future benefit to this same population group.

Overall, we believe that the risks are modest, that appropriate precautions have been taken, that there is potential societal health benefit, and that therefore 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(s). 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 Outside Monitoring

Data and Safety Monitoring Board: Safety data will be reviewed by a data and safety monitoring board that will meet quarterly during the first year of study recruitment. Additional meetings after that will be held on an *ad hoc* basis. The board will be blinded to subjects' actual treatment assignments for the safety data. Reports from the DSMB will be sent to the site investigator for transmission to the appropriate IRB, in accordance with NIH policy.

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 VI. 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 2 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: Roberta Kahn, M.D. 301/443-2281

NIDA Project Officer: Jurij Mojsiak, M.S., 301/443-9804

Investigator-Sponsor: Thomas Newton, M.D. 310/267-0159

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 objective of this study is to determine the safety of the bupropion concurrent with d-methamphetamine challenges of 15 mg and 30 mg i.v. The primary outcome measures are cardiovascular responses (HR, BP) to the i.v. methamphetamine challenges.

14.1.2 Secondary Outcome Measures

Secondary outcome measures are intended to further explore the safety of bupropion administration in combination with methamphetamine, to determine if there are any changes in bupropion or methamphetamine pharmacokinetics and to assess the effects of bupropion on a variety of biological and neuropsychological measures. Secondary outcome measures include:

1. Peak and trough plasma levels of bupropion and its metabolites during chronic daily treatment with bupropion.
2. Change in plasma levels of bupropion after methamphetamine administration.
3. Blood pharmacokinetic parameters of d-methamphetamine including Cmax, Tmax, AUC, apparent $t_{½}$, and CL, F, V, and k.
4. Urine pharmacokinetic parameters of d-methamphetamine including renal clearance (CL_R), elimination half-life, and fraction excreted unchanged in urine (*fe*).
5. ECG effects.
6. Craving for methamphetamine, assessed using a laboratory cue exposure paradigm.
7. Mood and personality assessments (BSI, BDI, and POMS).
8. Psychological measures including VAS, ARCI, and Adjective Scales.
9. Repeated neuropsychiatric measures.
10. Adverse events.

In addition, CYP26D genotyping will be performed for scientific purposes. Methamphetamine is metabolized by CYP2D6 and bupropion is an inhibitor of CYP2D6. An abnormality in CYP2D6 that is present in 3 to 10% of the population results in deficient metabolism of certain drugs. Thus, individuals with this abnormality may have altered methamphetamine pharmacokinetics that could confound the interpretation of possible interactions.

14.2 Analysis Plan

14.2.1 Primary Outcome Measures

Baseline (pre-methamphetamine) resting HR and BP measures will be compared to HR and BP after each methamphetamine injection (saline, 15 mg and 30 mg doses). Changes (from baseline) in HR and BP induced by methamphetamine injection along with bupropion will be compared to those without bupropion, by methamphetamine dose level (saline, 15 mg and 30 mg doses), using repeated measures ANOVA in a between-subjects analysis.

14.2.2 Secondary Outcome Measures

Plasma concentration-time profiles of d-methamphetamine after each methamphetamine injection will be analyzed to obtain pharmacokinetic parameter estimates of methamphetamine (Cmax, Tmax, AUC, apparent $t_{½}$, CL, F, V, and k) by individual and means computed by group. Urine elimination pharmacokinetic parameters will also be computed using plasma data in combination with urine data to calculate renal clearance. Comparisons of pharmacokinetic parameter estimates of d-methamphetamine between the placebo control and bupropion arms will be performed for both the 15 and the 30 mg methamphetamine dose level using t-tests. Comparison of the pharmacokinetic parameters within subjects will be also be compared using the data collected during the baseline series of challenges as compared to that collected during the treatment challenges. Confidence intervals (90%) for each parameter will be determined.

Peak and trough levels of bupropion and metabolites will be compared between the saline and 15 and 30 mg dose administrations of methamphetamine using repeated measure ANOVA.

Changes in bupropion concentration before methamphetamine challenge (baseline) and 2 hours after methamphetamine challenge will be compared using a between-subjects analysis by t-test.

Changes in ECG parameters will be reported as summary statistics. Psychological outcome measures (including VAS and cue craving) obtained in the control phase will be compared, by methamphetamine dose level, to those in the bupropion phase to determine the extent to which these measures are modified by the administration of bupropion using repeated measures ANOVA.

Changes in BSI, BDI, and POMS scores will be compared before and after bupropion administration using repeated measures ANOVA.

Adverse events data will be compiled and presented as summary statistics.
Neuropsychological tests results will be presented for each test at each time point as summary statistics and changes in repeated measures will be compared using a between-subjects analysis t-test.

Population demographics will be compiled for both treatment arms and presented in tabular form.

14.3 Sample Size

No formal sample size analysis was performed. The number of subjects in each group, 10, is hypothesized to provide an indication of the safety and potential interactions between bupropion and methamphetamine. 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 22 .

14.4 Control of Bias/Randomization

Subjects will be randomized into one of the two treatment arms and with the order of administration of the 0 and 15 mg dose of methamphetamine an additional randomization using a blocked randomization schema stratifying subjects by clinical site. 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 NIDA data coordinating center.

15.1 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 the NIDA 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.

15.2 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 her visit, the monitor will review the eCRF, identify any obvious inconsistencies, and request changes be made at the site prior to 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 the data coordinating center.

The site principal investigator agrees to routine data audits by the staff of the NIDA data-coordinating center 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 the data coordinating center procedures.

15.3 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 the data coordinating center'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.

15.4 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.

15.5 CONFIDENTIALITY

15.5.1 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.

15.5.2 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, NIDA monitoring contractor 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 VII.

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 bupropion for the treatment for methamphetamine 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. NIDA Project Officer	_____	_____
Edwina Smith, RN, BC, M.S. NIDA Project Manager	_____	_____
Ahmed Elkashef, M.D. CMB, Branch Chief	_____	_____

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
Thomas Newton, M.D. Coordinating Center Principal Investigator	_____	_____
John Roache, Ph.D. Site-Principal Investigator	_____	_____

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Appendix I: Time and Events Schedule

Study Phase	**Screening***		**Baseline Challenges**													
Study day	**-17 to 0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Informed Consent	X														
Locator Form	X														
Intake Form	X														
Demographics	X														
Timeline Followback	X														
Drug Use and Treatment History	X														
Quantity Frequency Interview	X														
12-lead ECG	X														
SCID	X	**R**													
Medical History	X	**A**													
Physical Exam	X	**N**													
ASI-Lite, HRBS, ADD	X	**D**													
Vital Signs	X	**O**	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Chemistries	X	**M**													
Hematology	X	**I**													
Pregnancy Test	X	**Z**					X								
HIV Test (optional) Infectious Disease Panel	X X	**A**													
Urine Drug Toxicology Screen	X	**T**	X		X	X	X	X	X	X	X	X	X	X	X
BSI, BDI, POMS		**I**	X		X		X		X		X		X		X
Bupropion or Placebo Administration		**O**									X	X	X	X	X
Neuropsychiatric Assessments		**N**				X				X					
Cue Induced Craving			X	X											
CYP2D6 genotyping (optional)	X														
Adverse Events	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Methamphetamine Challenge Session #			**1**	**2**		**3**									
0 or 15 mg methamphetamine i.v.			X	X											
30 mg methamphetamine i.v.						X									
VAS			16X	16X		16X									
Continuous BP, HR, ECG Monitoring			X	X		X									
ARCI, Adj Scale			2X	2X		2X									
BPRS			X	X		X									
Methamphetamine Blood PK	X[a]		13X	15X	2X	13X	2X	1X	1X	2X					
Methamphetamine Urine PK	X[b]					X	X	X	X	X					

*Screening may be conducted in the inpatient setting at UCLA; however, all screening will be conducted in the outpatient setting at UTHSCSA.
[a] and [b]Conducted on days –3, –2 and –1 in the inpatient setting at UCLA (details in the Note in Section 12.1).

Appendix I: Time and Events Schedule Continued

Study Phase				**Treatment Challenges**											**Dis-charge**	**Follow-up**	
Study day	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**36**	**43**
12-lead ECG															X		
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Chemistries				X											X		
Hematology				X											X		
Pregnancy Test				X											X	X	
Urine Toxicology Screen	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
BSI, BDI, POMS		X		X		X		X		X		X		X	X		
Bupropion or Placebo Administration	X	X	X	X	X	X	X	X	X	X	X	X					
Bupropion Blood Levels				2X	2X			2X									
Neuropsychiatric Assessments								X				X					
Cue Exposure				X	X												
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Methamphetamine Challenge Session #				**4**	**5**			**6**									
0 or 15 mg methamphetamine iv				X	X												
30 mg methamphetamine iv								X									
Continuous BP, HR, ECG Monitoring				X	X			X									
VAS				16X	16X			16X									
ARCI, Adj Scale				2X	2X			2X									
BPRS				X	X			X									
Methamphetamine Blood PK				13X	15X	2X		13X	2X	1X	1X	2X					
Methamphetamine Urine PK								X	X	X	X	X					

APPENDIX II: Schedule of Blood Collections

	Volume	Type[a]	a. m.																		Total volume
				-5	2m	5m	15m	30m	60m	90m	2h	3h	4h	6h	8h	12h	24h	36h	48h	60 h	72h	
Screening, and days 18, 29																						
Hematology	10mL	P	X																			30mL
Chemistry	10mL	S	X																			30mL
Methamphetamine PK[d]	5 mL	P																				30 mL
Screening																						
CYP2D6 Genotyping	30 mL	P	X																			30 mL
Days 18, 19, 22																						
Bupropion Blood level	5mL	P	2X[b]																			30mL
Days 2, 3, 5, 18, 19, 22																						
Methamphetamine PK	5mL	P		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[c]	X[c]	X[c]	X[c]	490 mL
Total Volume over Study																						**640 mL**

[a]Sample type is P = plasma; S = serum, m = minutes and h = hours.
[b]Two samples, one taken at 7:00 a.m. before bupropion administration for trough levels and one at 10:00 a.m. for peak levels.
[c]Only after the 30 mg methamphetamine infusions.
[d]Two samples per day (at 8 a.m. and 8 p.m) will be collected for quantitative blood methamphetamine test at screening on days –3, –2 and –1 from patients admitted to GCRC at the UCLA site and with urine test positive for methamphetamine.

APENDIX 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, two oxygen outlets, two compressed air outlets, humidifiers, heated nebulizers and one bedside monitor for ECG, Respiratory efforts (by Respirace) Blood Pressure (By Finger Plethysmography or FinaPress and pulse oximetry).

2) In addition, the Unit will have an intubation tray and crash cart with ECG, defibrillator and pacemaker.

3) Medications will be located in the locked medication cabinets and crash cart.

4) Procurement of equipment and medications will be handled by the nurse through Research Pharmacy Service, Bio Medical Engineering, SPD (crash cart) and Respiratory Therapy.

5) The integrity of the emergency drug system will be maintained by the Nursing Staff every 24 hours. In addition, Pharmacy Service will check expiration dates on all medications in the Unit on a monthly basis.

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/methamphetamine infusion.

   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 associated with stable B/P > 90/60 = Stable V-tach
2) Ventricular tachycardia on ECG associated with a fall in B/P < 90/60, change in mental status, chest pain, or CHF = unstable V-tach.

b) Procedure: stop study drug/ methamphetamine infusion.

For Stable Ventricular Tachycardia*:
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) Give Lidocaine 1 mg/kg I.V. bolus, followed by Lidocaine drip 2 mg/min

*if patient pulseless treat as ventricular fibrillation.

To effectively deliver a synchronized or synchronous electrical current to the myocardium to terminate lethal arrhythmias using R2 Cath-Pads.

EQUIPMENT AND SUPPLIES

1. LifePak 4
2. R2 Cath-Pads
3. R2 cable adapter

PROCEDURE:

ACTION	**RATIONALE**
A. Expose patient's upper torso	
B. Clean and dry skin sites, preferably with a coarse, dry towel. Shave as needed--remove lotions with alcohol and let dry.	
C. Apply R2 Cath-Pads Tm	
1. Remove pads from package and pull apart lead wires to desired length.	
2. Remove protective cover to expose gel and adhesive area. DO NOT use if gel area is dry.	2. Store R2 pads flat in a cool dry place.
	3. Apply large posterior pad just below scapula and the smaller anterior pad over

the cardiac apex with the flat edge of half circle toward head. To apply pad, adhere one edge of the pad, then tightly roll pad into place, pressing over adhesive area only.	depolarize a critical mass of the myocardium. The blue half circle on the apex pad is an area of radio opacity.
D. Plug pad connector into the R2 cable Adapter attached to the Life Pak 4.	D. Check 4 prong connector of patient cable before use. Do not use if damaged.
E. Turn Life Pak 4 on and set ordered parameters, i.e., synchronized or unsynchronized cardioversion and energy level.	
F. Depress charge button on Life Pak 4 after desired energy lever is selected.	F. Charge switch allows capacitor to charge.
G. To deliver countershock, depress 4 red button on R2 cable simultaneously.	G. Prior to delivery of countershock ensure that all personnel are CLEAR of the patient area.
H. Document the following on the code arrest form and progress notes: 1. Time of countershock 2. Watt/sec (joules) used in each attempt 3. Effect-include ECG rhythm strip, BP/P 4. Complications, if any	
I. Remove pads by peeling back parallel to the patient's skin.	I. Do not remove pads by pulling directly away from skin as bruising may result.

3. For countershock to be effective the current between two electrodes must

3) Ventricular Extrasystoles

a) Recognition: Ventricular extrasystoles, single or multiple, unifocal or multifocal

b) Procedure: Discontinue study drug/ methamphetamine 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 B/P below 90/60, change in mental status, chest pain, or dyspnea.

b) Procedure: stop study drug/ methamphetamine 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/ methamphetamine 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/ methamphetamine 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 by FinaPress: 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. These parameters were selected based on the clinical experience of Dr. Williams and are also those used by Dr. Tom Kosten.

b) Procedure: Stop study drug/ methamphetamine infusion. 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: Epileptiform seizure activity seen on EEG monitoring.

b) Procedure: Stop study drug/ methamphetamine infusion. 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. If seizures persist establish an airway and maintain adequate oxygenation.

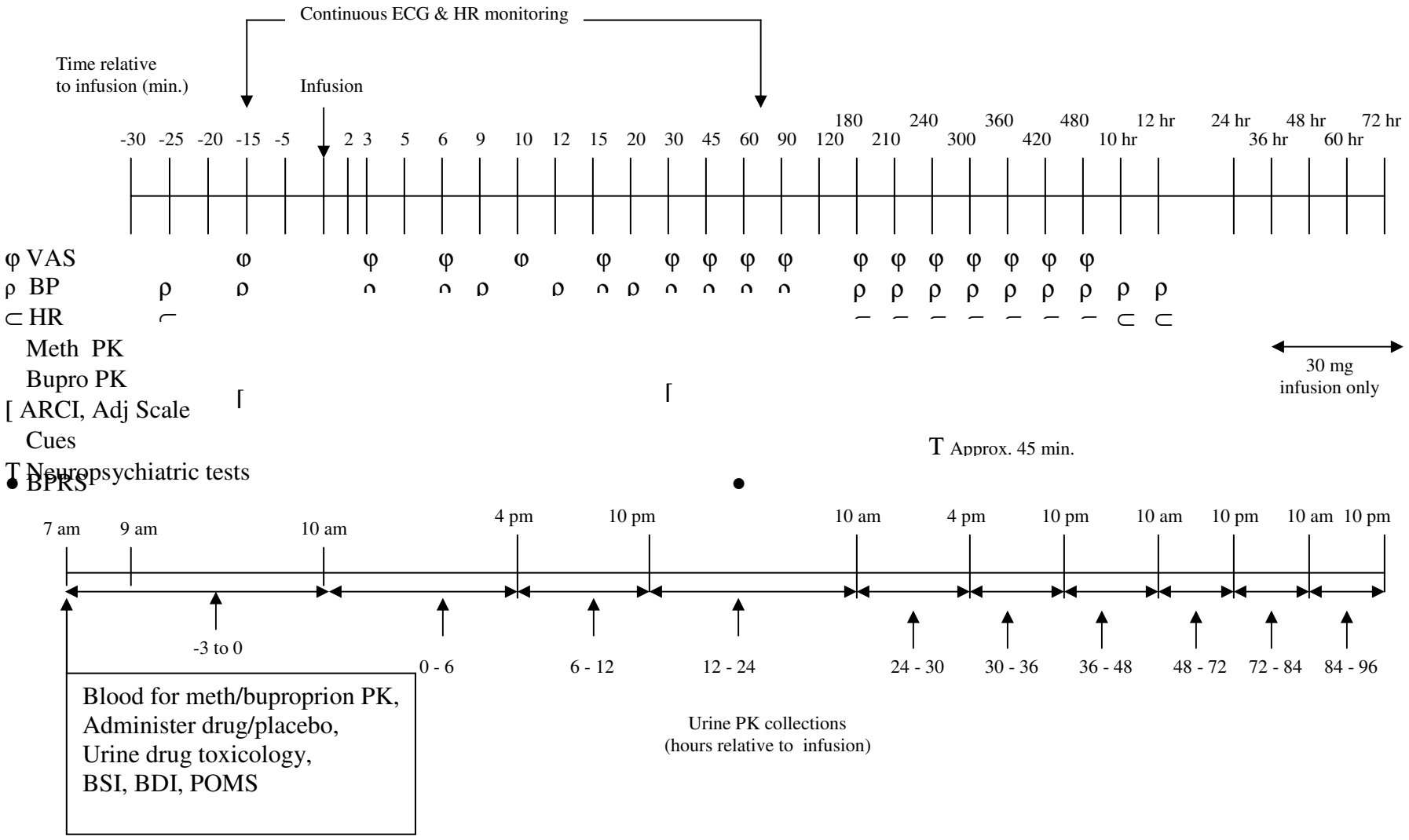
(iv) Chest Pain

a) Recognition: By complaint
b) Procedure: Discontinue study drug/ methamphetamine 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 IVPush and review 12 lead ECG for evidence of myocardial ischemia. If chest pain persist give Phentolamine 1 mg IV or Verapamil 5 mg IV over 3 minutes.

(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/ methamphetamine infusion. Maintain patient in supine position. If symptoms and signs continue, give normal saline bolus of 500 cc over 20 minutes, I.V.

Appendix IV: Challenge Session Schedule



APPENDIX V: Procedure for Collection, Storage, and Shipping of Blood Samples for Methamphetamine/ Methamphetamine Metabolite Levels and Bupropion/Bupropion Metabolite Levels

Blood collection tubes (l0 cc, green-stoppered-Vacutainers), and plasma storage and shipping materials will be provided by the testing laboratory. Any questions about blood collection should be addressed to Dr. Nora Chiang at MOD/NIDA (301-443-5280). The address of the laboratory will be specified in the study operations manual.

Blood Drawing Procedure:

1. Blood drawn from all subjects should be considered infectious and extreme caution should be used to avoid needle sticks and direct contact with blood or plasma.

2. Using the 10 cc green-stoppered Vacutainers provided:

   a. Draw two tubes of blood, filling them as completely as possible.
   b. Invert tube 8-10 times to disperse heparin.
   c. Centrifuge the blood (3000 x g for 15 min.) immediately to prevent hemolysis.
   d. Using a disposable pipet, immediately transfer the plasma from the tubes to a single plastic plasma storage vial provided by laboratory, and secure the cap tightly.
   e. Label the vial as described below.
   f. Freeze sample at -20°C immediately after transferring to shipping vial. Store in an upright position. Keep frozen until shipment.

Labeling Procedure:

1. Use the labels provided by the testing laboratory to label vials.

Center # _____ Subject # _____ Date collected _____ Time collected_____

2. With indelible black ink complete the label with the following information: center number, subject number, and date and time of collection. After affixing the label to the vial, cover it with transparent tape.

3. Complete the case report form containing the same information on the plasma samples

Shipping Procedure:

Retain all specimens (from screening and treatment) for all randomized subjects. Ship plasma samples once a month to the testing laboratory. Ship only on Monday through Wednesday, as no one will be available in the lab on weekends to receive the shipment. When ready to ship:

1. Line Igloo ice chest (provided by the laboratory) with a plastic bag (13 gallon waste container size).

2. Place approximately 10 pounds of dry ice (roughly two slabs) in ice chest. Place the ice in the bottom and compress with a hammer. Caution: Do not touch dry ice with your bare hands.

3. Cover the dry ice with a layer of newspaper.

4. Fill out as many pages of the Plasma Sample Shipping Log as are needed (be sure to number each page of the log in the Page "x" of "x" field) and make 2 copies. Put each vial of plasma into a ziplock bag containing an absorbent pack.

5. Place containers in ice chest, and then fill remaining space with crumpled newspaper. Close plastic liner bag.

6. Close ice chest and place it into the outer cardboard. Place the original of the Plasma Sample Shipping Log in envelope and include in cardboard container.

Please send one copy of the log to DCC and retain the other copy in the Specimen Shipping Log Binder (supplied by DCC).

7. Repeat steps 1-6 if additional ice chests are needed.

8. Apply "biohazard" label to container and call Federal Express for pick-up.

9. Ship to the testing laboratory using the Federal Express airbill provided by laboratory pre-printed with receiver's address.

10. After package is picked up by Federal Express, notify the laboratory to expect shipment.

Supplies:

Items provided by Laboratory include:	**Items to be obtained at site:**
10 cc green-stoppered, heparinized Vacutainers	Centrifuge
Plastic plasma shipping vials.	Disposable pipets
Labels for plasma shipping vials	13 gallon plastic bags
Ziplock bag with absorbent pad	Dry ice
Igloo ice chest cardboard shipping container	
Pre-printed Federal Express Airbills	
Biohazard labels	

Plasma Sample Shipping Log

Center No.:_____

Investigator:_____

Contact Person:_____ Phone Number:_____

Shipment Date_____/_____/_____
Month Day Year

1	2	3	4	5
Subject Initials	Subject No.	Date of Collection (mo/day/yr)	Time of Collection (24 hr clock)	Comments

Page ____ of _____

APPENDIX VI: 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 VIII: 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.