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ASSESSMENT OF POTENTIAL INTERACTIONS BETWEEN INTRAVENOUS METHAMPHETAMINE AND ORAL SELEGILINE

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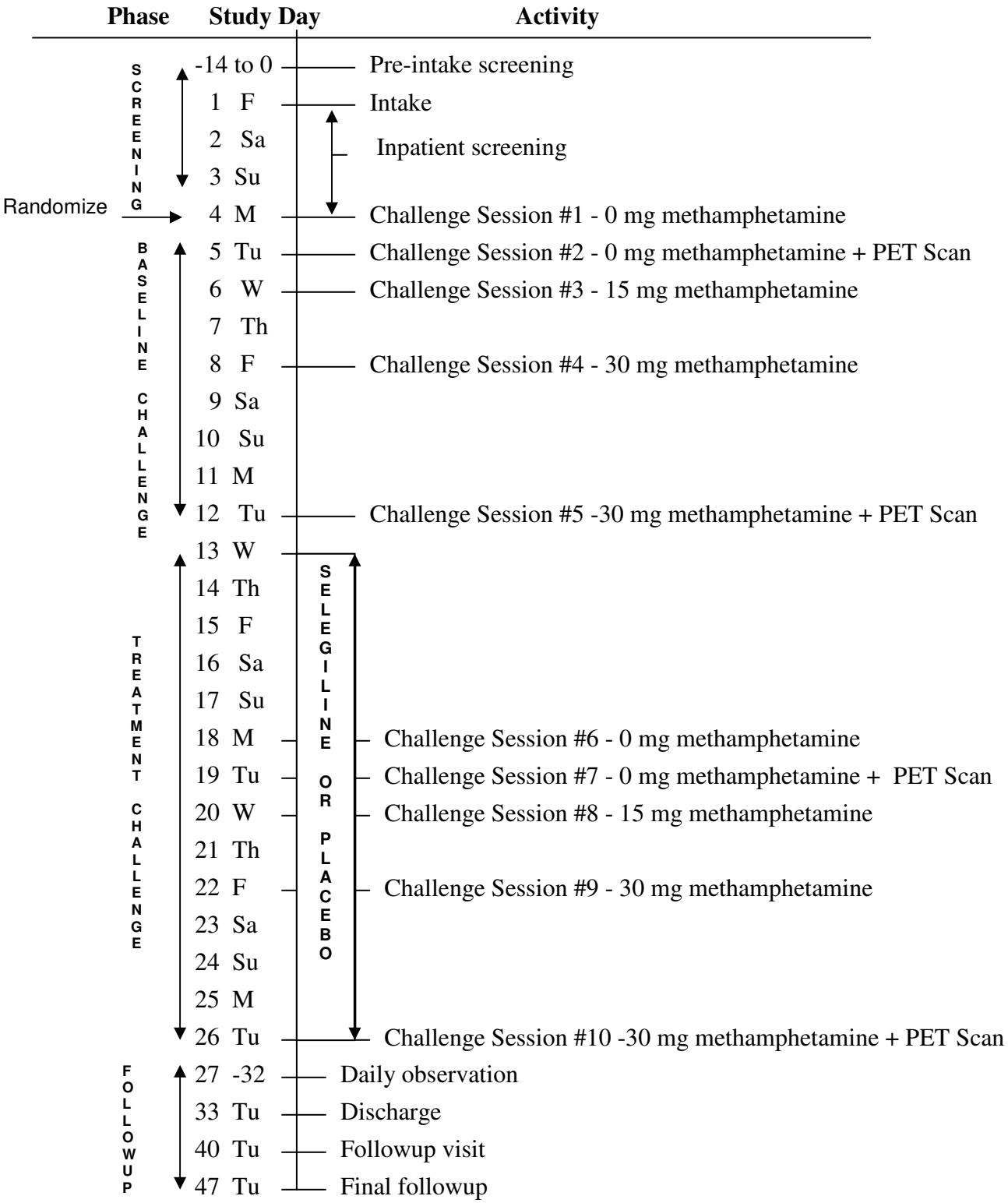
1 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvic transaminase
APTT	activated partial thromboplastin time
ARCI	Addiction Research Center Inventory
ASI-Lite	Addiction Severity Index-Lite
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminse
BDI	Beck's Depression Inventory
BP	Blood Pressure
BSI	Brief Symptom Inventory
BUN	blood urea nitrogen
CAP	College of American Pathologists
CLIA	Clinical Laboratory Improvement Amendment of 1988
CRF	Case Report Form
CPK	creatinine phosphokinase
DHEA	dihydroepiandrosterone
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
DTR&D	Division of Treatment Research and Development
EKG	electrocardiogram
[18F]-FDG	[18-fluoro]-deoxyglucose
GCRC	General Clinical Research Center
GGT	gamma glutamyltranspeptidase
HIV	human immunodeficiency virus
HRBS	HIV Risk-Taking Behavior Scale
INR	international normalized ratio
i.v.	intravenous(ly)
LDH	lactate dehydrogenase
mg	milligrams
ml	milliliter
MAO	monoamine oxidase
MPV	mean platelet volume
NIDA	National Institute on Drug Abuse
OTC	over the counter
PEA	phenylethylamine
PET	positron emission tomography
SAE	serious adverse event
SCID	structured clinical interview for DSM-IV
SSRI	selective serotonin reuptake inhibitor
SUI	substance use inventory
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 selegiline.

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

Secondary:

1. To determine plasma levels of selegiline and its metabolites, desmethylselegiline, l-amphetamine, and l-methamphetamine during chronic daily treatment with selegiline.

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

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

4. To determine the effects of selegiline and/or methamphetamine on plasma levels of phenylethylamine (PEA) and cortisol.

5. To evaluate effects of selegiline on methamphetamine induced changes in brain metabolic activity, measured using undergo [18-fluoro]-deoxyglucose (18-FDG) positron emission tomography (PET).

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

7. To assess the effects of selegiline on mood and personality assessments (BSI, BDI, and POMS) and other psychological parameters (VAS, ARCI, and Adjective Scales).

STUDY DESIGN: This is a single-blind inpatient study in which, after establishing eligibility, subjects will be randomized into one of two treatment groups [placebo (n = 8) or 5 mg twice daily oral selegiline (n = 8)]. All subjects will receive repeated intravenous (i.v.) methamphetamine challenges (0, 15, 30 mg) before placebo/selegiline administration (baseline challenge sessions) and 5 days after daily placebo/selegiline administration (treatment challenge sessions). Subjects randomized to the selegiline group will undergo 18-FDG PET and have a Magnetic Resonance Imaging (MRI) scan. 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 14 days or less of outpatient screening, 33 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 33 days.

SAMPLE SIZE: 16 subjects total; subjects dropping out before completion 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 4 to one of the following arms:

Selegiline: Subjects will take 5 mg twice daily (b.i.d) on days 13 through 26 (only once on day 26).

Placebo: Subjects will take matched placebo twice daily on days 13 through 26 (only once on day 26).

ASSESSMENTS: Safety of methamphetamine administration in selegiline dosed subjects will be determined by adverse events (AE), blood pressure (BP), heart rate (HR), and electrocardiograph (EKG) monitoring. Interactions between methamphetamine and selegiline will be assessed by pharmacokinetic studies using a between subjects design. Selegiline's effects on plasma cortisol and PEA. The effect of selegiline on methamphetamine craving will be assessed by a laboratory cue exposure paradigm and changes in VAS. Other psychological assessments include Profile of Moods State (POMS), Brief Symptom Inventory (BSI), and Beck's Depression Inventory (BDI). Changes in brain metabolic activity, measured using 18-FDG PET will also be determined before and after methamphetamine and selegiline administration. An MRI scan will be performed once during the inpatient phase in subjects randomized to receive selegiline.

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 to use (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 see if they can reduce methamphetamine abuse. 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 here is to reduce methamphetamine craving and use by restoring the depleted dopamine system to normality.

4.2 Selegiline Hydrochloride (Eldepryl®)

Selegiline, in an oral dosage form, is a marketed compound used in the treatment of Parkinson's disease, a neurological disorder resulting from dopamine depletion and dysfunction. Selegiline improves brain dopamine function and reduces the need for l-dopa treatment of Parkinson's disease.

Selegiline, also known as l-deprenyl, is a selective monoamine oxidase (MAO)-B inhibitor. MAO is an enzyme that exists in two forms, A and B, which are the primary enzymes metabolizing the major neurotransmitters dopamine, serotonin, and norepinephrine. Selegiline's selectivity for inhibiting MAO-B rather than MAO-A is a great advantage, because MAO-A inhibition carries the risk of hypertensive crisis (referred to as the "cheese reaction") following the ingestion of dietary tyramine (found in red wine, cheeses, beer, and other foods). Oral tyramine is preferentially metabolized by MAO-A during the absorption process This risk can be minimized with dietary restrictions that avoid ingestion of tyramine containing foods and beverages.

In a recent multi-center study of 134 cocaine dependent subjects, selegiline treatment was significantly associated with improvement on a composite score reflecting severity of cocaine dependence. There were very few adverse events in the study, indicating that the 10 mg oral sustained-release selegiline preparation is likely to be safe when co-administered with cocaine and taken without dietary restrictions.

Two human laboratory studies (one at Johns Hopkins and one at UCLA) have tested 10 mg daily oral selegiline in combination with i.v. cocaine challenges and have seen no suggestion of significant risk and no suggestion that selegiline enhances the euphoric response to cocaine. This dose of selegiline is known to inhibit MAO-B nearly completely and to produce about a 50% increase in tyramine sensitivity, an index of MAO-A inhibition. This degree of peripheral MAO-A inhibition appears insufficient to produce a tyramine-induced hypertensive reaction following the consumption of a normal tyramine containing meal.

The pharmacology of selegiline suggests caution, however, particularly if doses other than the recommended oral dose of 10 mg/day are used. At the oral dose of 10 mg/ day, selegiline is selective for MAO-B. But at higher doses, it loses its MAO-B selectivity and begins to inhibit MAO-A in a dose-dependent, predictable manor. It is unknown at what dose of selegiline that sufficient MAO-A inhibition occurs so as to require dietary restrictions. Data gathered at the National Institutes of Health suggest that 30 mg may produce a significant increase in tyramine sensitivity (Table 1). In a previous report (Mayer *et al.,* 1995), subjects received both 10 mg and 20 mg of oral selegiline without dietary restriction. No changes in pulse or blood pressure were seen, though clear subjective effects were noted at 20 mg, suggesting that this is a safe dose when used without dietary restrictions.

The present study will use an oral dosage form of selegiline at a dose (10 mg/day) known to be safe without dietary restrictions.

Table 1. *Adapted from Sunderland et al., (1985). Selegiline was given orally. Tyramine sensitivity is the dose (mg/hour) at which a defined change in blood pressure was seen. All treatment values are significantly different from placebo. Means only are presented. Standard deviations are available in the original manuscript.*

	Placebo	Selegiline	Selegiline	Selegiline	Tranylcypromine
		10 mg	*30 mg*	*60 mg*	*20 mg*
Tyramine sensitivity	1.65	0.59	0.22	0.10	0.08
Plasma MHPG	12.6	9.7	6.3	4.3	2.5
Platelet MAO- activity	15.2	0.4	0.2	0.6	1.1

5 STUDY DESIGN

This is a randomized, single-blind, placebo-controlled, two-arm study designed to evaluate the safety of selegiline treatment, compared to placebo treatment, concurrent with intravenous (i.v.) methamphetamine challenges.

Subjects will receive repeated i.v. methamphetamine challenges (0, 15, 30 mg) and repeated cue exposures, before and approximately 1 and 2 weeks after beginning daily treatment with selegiline 5 mg b.i.d or placebo b.i.d. Subjects will be randomized to receive either selegiline or placebo in single-blind fashion. Methamphetamine or saline will also be administered in a single-blind fashion and mock blood draws will be performed during the 0 and 15 mg methamphetamine infusions to maintain the blind. The study will assess the subjective and physiological response to methamphetamine, the pharmacokinetics of methamphetamine and its major metabolite, blood levels of selegiline and its metabolites, and neuroendocrine indices using a between subjects design. Subjects will not be told that the selegiline group is the only group that will receive 18-FDG PET. Nor will they be told the sequence of saline/methamphetamine infusions to preserve the study blind to the subjects.

Additional assessments on the 8 subjects randomized to receive selegiline will determine its effects on methamphetamine induced alterations in brain metabolic activity, assessed using 18F-FDG PET.

Subjects will be discharged from the hospital 7 days after the last doses of selegiline and methamphetamine. This is to optimize medical monitoring for adverse events, to allow for MAO regeneration, 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 completion of the protocol to ascertain that no adverse events have occurred.

6 STUDY OBJECTIVES

6.1 Primary

The primary objective of this study is to determine the safety of the selegiline 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

1. To determine plasma levels of selegiline and its metabolites, desmethylselegiline, l-amphetamine, and l-methamphetamine during chronic daily treatment with selegiline.
2. To evaluate whether administration of selegiline alters the pharmacokinetics of d-methamphetamine or its metabolites.
3. To evaluate whether selegiline treatment alters the subjective or cardiovascular response to methamphetamine.
4. To determine the effects of selegiline and/or methamphetamine on plasma levels of PEA and cortisol.
5. To evaluate effects of selegiline on methamphetamine induced changes in brain metabolic activity, measured using FDG-PET.
6. To assess the effects of selegiline on craving for methamphetamine, assessed using a laboratory cue exposure paradigm.
7. To assess the effects of selegiline on mood and personality assessments (BSI, BDI, and POMS) and other psychological parameters (VAS, ARCI, and Adjective Scales).

7 STUDY SITE

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).

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 18-45 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 within 2 weeks of entering the study.

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

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

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 EKG performed that demonstrates normal sinus rhythm, normal conduction, and no clinically significant arrhythmias.

NOTE: Recent intermittent alcohol or other illicit drug use without physical dependence is allowable.

8.2 Exclusion criteria

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

1. Have any history or evidence suggestive of seizures or brain injury (electroencephalograph need not be conducted).

2. Have any previous medically adverse reaction to methamphetamine, including loss of consciousness, chest pain, or seizure.

3. According to DSM-IV criteria as determined by structured clinical interview (SCID), have any history of major psychiatric illness other than drug dependence or disorders secondary to drug use.

4. Have any evidence of untreated clinically significant heart disease or hypertension.

5. Have any evidence of untreated or unstable medical illness (including untreated thyroid disease, autoimmune disease, unstable asthma, tuberculosis etc.).

6. If female, be pregnant or nursing. [*Females must have a negative pregnancy test (blood or urine) at or before study entry. Females must either be unable to conceive (i.e., surgically sterilized, sterile or post menopausal) or be using a reliable form of contraception (e.g. abstinence, birth control pills, intrauterine device, norplant, condoms, or spermicide). A second pregnancy test will be performed one to two weeks after study participation to determine whether pregnancy occurred during study.]*

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

8. Have any history of asthma, coughing and wheezing, or other respiratory illnesses.

9. Currently use albuterol or other beta agonist medications.

10. Have any illness, condition, and use of medications, in the opinion of the principal investigator and the admitting physician, which would preclude safe and/or successful completion of the study.

11. Have any metal devices implanted (i.e., pacemakers, infusion pumps, aneurysm clips, metal prostheses, joints, rods, plates, etc.) that are potential problems when conducting an MRI scan (dental fillings are allowed).

12. Be using a medication that could interact adversely with selegiline, with the time of administration of study agents relative to other medications based on the longest time interval of A, B, or C, below:

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

    Medications that fall into this category include:

    a. MAO inhibitors (e.g., selegiline, phenelzine, etc.) or selective serotonin reuptake inhibitor (SSRI; e.g., fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram) within 8 weeks of anticipated study entry.

    b. Psychotropic medications, centrally active anticholinergics, anticonvulsants (case by case), antiparkinsonian agents, antidepressants, antipsychotics (including lithium carbonate), anxiolytics, psychostimulants, nootropics, cerebral enhancers, vasodilators, benzodiazepine receptor agonists, reserpine, hypnotics; including: oral neuroleptics, depot neuroleptics (10 weeks), methyldopa, ergot preparations, and tricyclic antidepressants.

    c. Sympathomimetic medications: e.g., amphetamines, methylphenidate, dopamine, epinephrine, norepinephrine, levodopa, tyrosine, phenylalanine, mazindole tyrosine, over-the-counter (OTC) and prescription nasal decongestants, and appetite suppressants.

    d. L-tryptophan, metoclopramide.

    e. Meperidine (Demerol®), dextromethorphan, propoxyphene or other opiates.

    f. 5-HT receptor agonists (e.g., sumitriptan succinate [Imitrex®], zolmitriptan [Zomig®], serotonergic agonists or antagonists (e.g. cyproheptadine [Periactin®], methysergide [Sansert®]).

9 INVESTIGATIONAL AGENTS

9.1 Selegiline

Selegiline HCl 5 mg capsules for oral administration and matched placebo will be obtained from Somerset Pharmaceuticals and will be dispensed according to standard pharmacy and nursing procedures. Selegiline or placebo tablets will be administered b.i.d. at 8 a.m. and 1 p.m. except on the last day of treatment (day 26) when selegiline will just be administered at 8 a.m. On challenge session days the 1:00 p.m. dosing of selegiline or placebo can be delayed until infusion procedures are finished in case the timing of the infusion is delayed.

9.2 Methamphetamine

Human use methamphetamine HCl (10 mg/ml in 1 ml ampoules) will be obtained from NIDA. The compound will be stored in the pharmacy vault. Standard narcotics control procedures will govern access to the drug. Sterile i.v. methamphetamine preparation will be performed according to UCLA pharmacy procedures. 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

Selegiline Arm: Subjects will take 5 mg of oral selegiline HCl b.i.d. on study days 13 through 26 (only once on day 26).

Placebo Arm: Subjects will take oral placebo b.i.d. on study days 13 through 26 (only once on day 26).

Methamphetamine/Saline (All Subjects):

15 mg methamphetamine i.v.:	Study days 6 and 20
30 mg methamphetamine i.v.:	Study days 8 and 22 plus Study days 12 and 26 in only those subjects randomized to selegiline before PET analysis
Saline i.v.:	Study days 4 and 18 plus Study days 5 and 19 in only those subjects randomized to selegiline before PET analysis

11 STUDY PROCEDURES

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

11.1 Screening (Study Days –14 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 33 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 UCLA IRB. After providing informed consent, the subject is given a subject identification number and proceeds to the screening/baseline assessments phase of the study.

Screening of subjects to establish eligibility will occur initially before clinic intake and be completed after intake. Assessments performed before intake include collection of demographic information and completion of a subject locator form, a substance use inventory for the prior 6 weeks, drug use and treatment history, urine test for methamphetamine (will be repeated until a positive test is obtained within 14 days prior to intake), a 5-lead EKG, and vital signs (HR and BP). For women of reproductive potential a urine pregnancy test will be performed. An infectious disease panel will be performed including a PPD test. Adverse events will be collected starting right after the potential subject signs the informed consent form. These assessments must be completed within 14 days before clinic intake.

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 Intake (Study Day 1) and Inpatient Screening

Potential candidates, whose results of screening assessment conducted prior to intake do not exclude them from study participation, will complete intake procedures and reside full-time on the clinical research unit (GCRC) starting on a Friday and continuing until discharge or completion of the study. Screening procedures after intake will be completed on the day of intake and up to study day 4 at which time the subjects are randomized and enrolled. Intake screening assessments include a physical exam including vital signs, 12-lead EKG, medical history, laboratory analyses including hematology, blood chemistries, an HIV antibody test, and urine drug toxicology tests, a pregnancy test for women of reproductive potential, a SUI, SCID for DSM-IV Axis I Disorders, BDI, BSI, POMS, HRBS, Wender Utah Attention Deficit Hyperactivity Disorder (ADHD), and ASI-Lite assessments.

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 in the CRF package), then the subject can be enrolled into the study. The principal investigator or a study coordinator will contact the UCLA research pharmacist for treatment assignment. 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. The UCLA research pharmacist will maintain the envelopes and list of subject treatment assignments. If subjects are terminated before completing all of the methamphetamine challenge sessions, replacement subjects will be included until 8 subjects have completed the study from both treatment arms.

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 2. Each series of repeated administrations will consist of three-to-five challenge sessions in one week (only subjects randomized to receive selegiline will participate in the two challenge sessions per week that include PET). Each challenge session will be on different days and there will be one day off in between active methamphetamine challenge sessions. The fixed ascending sequence each week is a safety precaution.

During the baseline challenge sessions, the subject's responses to methamphetamine without concomitant selegiline or placebo administration will be assessed. The baseline series of challenges are for screening purposes, to ensure that volunteers are responsive to and safely tolerate the methamphetamine test doses. Only subjects responsive to and safely tolerating both test doses of methamphetamine will continue in the study. This baseline saline challenge sessions #1, 3, and 4 are also for training and adaptation purposes. In our experience, the response to initial methamphetamine challenges in the laboratory is exaggerated relative to subsequent responses, which then remain relatively stable and reliable in magnitude. Therefore, data from baseline challenge sessions #1, 3, and 4) will be excluded from data analyses.

During the treatment phase, the subject's responses to methamphetamine with concomitant selegiline or placebo administration will be assessed.

Table 2. Methamphetamine Challenge Session Schedule

Study Phase	Session Number	Study Day	Challenge
Baseline	Session 1	4	0 mg methamphetamine
Baseline (+PET)	Session 2	5	0 mg methamphetamine
Baseline	Session 3	6	15 mg methamphetamine
Baseline	Session 4	8	30 mg methamphetamine
Baseline (+PET)	Session 5	12	30 mg methamphetamine
Treatment	Session 6	18	0 mg methamphetamine
Treatment (+PET)	Session 7	19	0 mg methamphetamine
Treatment	Session 8	20	15 mg methamphetamine
Treatment	Session 9	22	30 mg methamphetamine
Treatment (+PET)	Session 10	26	30 mg methamphetamine

11.4.2 Conduct of Methamphetamine/Saline Challenge Sessions

Each intravenous challenge dose will be administered over a 2-min duration by a study physician. A rapid i.v. flow of normal saline from a bag shall also be infused into the subject for 10 minutes from the start of methamphetamine infusion, i.e. the normal saline shall be infused for an additional 8 minutes after the end of the 2-minute methamphetamine infusion. The methamphetamine or saline injection will occur at 9:00 a.m.

For a subject to receive the first 15 mg methamphetamine challenge session (session # 3), s/he must have a have drug toxicology screening that shows negative urine drug/metabolite levels for drugs of abuse (except marijuana) on day 6 before conduct of methamphetamine 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 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.

Before and after each i.v. challenge, the subjects' physiologic response will be closely monitored using repeated HR, BP, and EKG readings. BP will be taken between 7:00 and 8:00 a.m., and 3, 6, 9, 12, 15, 20, 30, 45 and 60 minutes following infusions. Thereafter, BP will be monitored every 30 minutes from 1 to 4 hours and every 60 minutes for 4 to 8 hours after infusion. EKG and HR will be monitored continuously for the first 60 minutes after infusion. Thereafter, HR will be monitored at 30 minute intervals from 1 to 4 hours and at 60 minute intervals from 4 to 8 hours after infusion.

11.4.3 Safety Precautions

A physician will perform the infusions and will be present at least 1 hour after the completion of the infusion. Thereafter, the physician will remain on the medical campus and be 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 intravenous 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 cooperate with study procedures;

11.4.5 Stopping Criteria for Further Study Participation

Further participation of the subject is stopped, 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;

If subjects meet the "Stopping Criteria for Further Study Participation" shown above during the selegiline/placebo treatment phase of the study, we will investigate the possibility of an adverse interaction between selegiline and methamphetamine. If a subject meets the stopping criteria on day 20, 22 or 26 (i.e., during treatment with drug/placebo), the blind will be broken and the investigational agents will be discontinued. If the subject was randomized to selegiline, subjects will be monitored for 2 weeks and then rechallenged with 15 mg and 30 mg of methamphetamine on different days in order to ensure that the selegiline interaction has abated. If the interaction recurs, subjects will be monitored for an additional 2 weeks and rechallenged. If the interaction recurs a second time, a telephone conference between the investigator and NIDA staff will determine appropriate management before the subject is discharged.

11.4.6 Subjective Response

During and after the methamphetamine infusions, subject's subjective responses to methamphetamine will be closely monitored. Computerized VAS will be administered between 7:00 and 8:00 a.m. (before infusion), and 3, 6, 10, 15, 30, 45, and 60 minutes after each infusion. Thereafter, VAS will be administered every 30 minutes for hours 1 to 4 and every 60 minutes for hours 4 to 8 after infusion. An ARCI and Adjective Scales will be administered between 7:00 and 8:00 a.m. and at 30 minutes after the infusion.

11.4.7 Volunteer Discontinuation

Subjects will be excluded or discharged if their behavior is disruptive, noncompliant with study procedures, or otherwise not consistent with remaining in the hospital. Subjects will be excluded

if urine toxicology indicates illicit use of illegal or legal drugs that are not allowed on this study during participation in this protocol.

11.4.8 Off-unit passes

Subjects will normally reside full-time on the GCRC throughout their study participation. In extraordinary cases subjects may be allowed a pass for the shortest period feasible at the principal 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.

11.4.9 Subject Payment

Subject payment will be determined by IRB requirements, which can change. We currently plan to reimburse subjects $20 in vouchers for initial screen, $30 to complete the medical screening, including EKG, labwork, and baseline assessments, $330 for the inpatient stay and a completion bonus of $50. Subjects that undergo 18-FDG PET will receive $50 for the first and second PET scans, and $75 and $125 for the third and forth PET scans, respectively. 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 according to the number of days they participated, but will not receive the completion bonus.

Total compensation upon completion will equal $430 or $730 for those who had PET scans. 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 and then in the inpatient setting.

Screening Assessments before Intake: The following evaluations will be performed before clinic intake and must be performed before within 14 days prior to intake.

1. Informed Consent;
2. Locator Form;
3. Demographics Information;
4. Substance use inventory for prior 6 weeks;
5. Drug Use and Treatment History;
6. Urine test for methamphetamine (will be repeated until a positive test is obtained within 14 days prior to intake);

7. 5-lead EKG and vital signs (HR and BP);
8. Adverse events;
9. For women of reproductive potential, a urine pregnancy test will be performed.

Inpatient Screening Assessments: The following evaluations will be performed on study day 1 to 4 following intake into the GCRC:

1. Physical exam and medical history;
2. Vital signs: BP and HR;
3. Hematology;
4. Blood chemistries;
5. HIV antibody test;
6. Infectious disease panel and PPD test;
7. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID;
8. Qualitative urine drug toxicology;
9. 12-lead EKG;
10. Pregnancy test for women of reproductive potential;
11. Adverse events;
12. BDI, BSI, and POMS;
13. Wender Utah ADHD;
14. HRBS;
15. ASI-Lite;
16. SUI.

12.2 Evaluations Performed Daily or Every Other Day During Inpatient Phase of Study

1. Qualitative urine drug toxicology will be monitored once daily (8 a.m.), as documented by a qualitative urine test.
2. BSI, BDI, POMS will be conducted every other day;
3. Adverse events starting on day 4.
4. Vital signs will be routinely monitored on days when the subject is not receiving infusions.

12.3 Evaluations Performed During Challenge Sessions

Table 3 shows the series of activities that occur during methamphetamine challenge sessions. Refer to Table 2 for the timing of the challenge sessions according to the study day. Note that not all activities occur at each challenge session. Those activities that do not occur at each challenge session are noted.

Table 3. Methamphetamine Challenge Sessions Daily Schedule

Timepoint	Activity (occurs at all sessions unless otherwise indicated)
7 a.m. – 8 a.m.	BSI, BDI, POMS Urine Toxicology Draw blood for trough selegiline (sessions 6, 8 & 9) VAS, ARCI, Adj Scale, BP
8 a.m.	Administer selegiline/placebo (sessions 6 through 10)
8 a.m. – 8:30 a.m.	Cue-Induced Assessments (sessions 3 & 8)

Timepoint	Activity (occurs at all sessions unless otherwise indicated)
8:30 a.m.	Insert catheters (catheters can be inserted earlier on days when 7:00 to 8:00 a.m. blood draws are performed) and start continuous monitoring of EKG and HR
8:55 a.m.	Draw blood for peak selegiline (sessions 6, 8, & 9)
8:55 a.m.	Draw baseline blood for methamphetamine assay (sessions 4 & 9 – perform mock blood draws for sessions 1, 3, 6, and 8) Draw blood for cortisol and PEA (sessions 6 & 9) Draw baseline blood for 18-FDG (sessions 2, 5, 7, & 10)
9:00 a.m. (Time 0)	Inject 18-FDG (sessions 2, 5, 7, & 10 for selegiline arm subjects only) Inject methamphetamine or saline 2 min iv infusion plus 8 additional minutes of saline following the 2 minute infusion
2 min	Draw blood for methamphetamine assay (sessions 4 & 9 – perform mock blood draws for session 1, 3, 6, and 8)
3 min	VAS, BP
5 min	Draw blood for methamphetamine assay (sessions 4 & 9 – perform mock blood draws for sessions 1, 3, 6, and 8)
6 min	VAS, BP
9 min	BP
10 min	Draw blood for methamphetamine assay (sessions 4 & 9 – perform mock blood draws for sessions 1, 3, 6, and 8) VAS
12 min	BP
15 min	VAS, BP
20 min	Draw blood for methamphetamine assay (sessions 4 & 9 – perform mock blood draws for sessions 1, 3, 6, and 8) BP
30 min	Draw blood for methamphetamine assay (sessions 4 & 9 – perform mock blood draws for sessions 1, 3, 6, and 8) Draw blood for cortisol (sessions 6 & 9) VAS, ARCI, Adj Scale, BP
45 min	Draw blood for 18-FDG before PET 18-FDG PET (sessions 2, 5, 7, & 10 for selegiline arm subjects only) BP, VAS
60 min	Draw blood for methamphetamine (sessions 4 & 9 – perform mock blood draws for sessions 1, 3, 6, and 8) Stop continuous EKG and HR monitoring BP, VAS
90 min	Draw blood for methamphetamine assay (sessions 4 & 9 – perform mock blood draws for sessions 1, 3, 6, and 8) BP, HR, VAS

Timepoint	Activity (occurs at all sessions unless otherwise indicated)
120 min	Draw blood for methamphetamine assay (sessions 4 & 9 – perform mock blood draws for sessions 1, 3, 6, and 8) BP, HR, VAS Draw blood for PEA (sessions 6 & 9) Draw blood for cortisol (sessions 6 & 9) Draw blood for selegiline (sessions 6, 8, & 9)
150 min	BP, HR, VAS
180 min	BP, HR, VAS
210 min	BP, HR, VAS
240 min	Draw blood for methamphetamine (sessions 4 & 9 – perform mock blood draws for sessions 1, 3, 6, and 8) Draw blood for cortisol (sessions 6 & 9) BP, HR, VAS
5 hours	BP, HR, VAS
6 hours	Draw blood for methamphetamine (sessions 4 & 9 – perform mock blood draws for sessions 1, 3, 6, and 8) Draw blood for cortisol (sessions 6 & 9) BP, HR, VAS
7 hours	BP, HR, VAS
8 hours	Draw blood for methamphetamine (sessions 4 & 9 – perform mock blood draws for sessions 1, 3, 6, and 8) Draw blood for cortisol (sessions 6 & 9) BP, HR, VAS
12 hours	Draw blood for methamphetamine (sessions 4 & 9 – perform mock blood draws for sessions 1, 3, 6, and 8)
24 hours	Draw blood for methamphetamine (sessions 4 & 9 – perform mock blood draws for sessions 1, 3, 6, and 8)
36 hours	Draw blood for methamphetamine (sessions 4 & 9 – perform mock blood draws for sessions 1, 3, 6, and 8)
48 hours	Draw blood for methamphetamine (sessions 4 & 9 – perform mock blood draws for sessions 1, 3, 6, and 8)
1 p.m.	Administer selegiline/placebo (sessions 6 through 9)
p.m. about 4 hours after methamphetamine infusion	Neuropsychiatric measures subset (sessions 4, 7, & 9)

12.4 Other Inpatient Evaluations

An MRI will be conducted on subjects randomized to receive selegiline according to scheduling constraints at any time during the inpatient phase of the study.

12.5 Evaluations at Discharge (Day 33)

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. BP and HR;
2. Hematology;
3. Blood chemistries;
4. 12-lead EKG;
5. Pregnancy test for women of reproductive potential.

12.6 Clinical and Laboratory Assessment Methods

12.6.1 Intake Assessments

A variety of standardized psychosocial assessments and information will be collected during screening and intake 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.

12.6.1.1 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 principal 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 at during intake screening (days 1 to 4).

12.6.1.2 Substance Use Inventory (SUI)

This instrument collects data on the type, frequency, and amounts of drugs used, as well as routes of administration. Subjects will complete this measure during screening to establish severity of drug use for the prior six weeks and at intake to assess drug use during the interval between intake and the time that the SUI was completed during screening.

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

This instrument, (Research SCID or SCID 1/P) will be administered during intake screening and serves to determine whether the subject meets the DSM-IV criteria for drug dependence and to rule out any major psychiatric disorders (e.g., affective disorders, schizophrenia).

12.6.1.4 Wender Utah ADHD

This measure determines whether criteria exist for a diagnosis of childhood attention-deficit hyperactivity disorder in adult subjects. It will be administered during intake screening.

12.6.1.5 HIV Risk-Taking Behavior Scale (HRBS)

The HRBS is a brief 11-item instrument that examines the behavior of intravenous drug users in both injecting and sexual behavior and will be collected during intake screening.

12.6.2 Medical Assessments

12.6.2.1 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 during intake screening. Height and weight should be recorded.

12.6.2.2 Medical History

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

12.6.2.3 Vital Signs

Vital signs to be assessed at intake include oral temperature, sitting blood pressure, pulse rate, respiratory rate, and standing blood pressure and pulse rate (standing 3 minutes).

12.6.3 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.

12.6.4 Daily Surveys

Qualitative analysis for urine toxicology and personality and mood states will be performed daily starting at intake for the duration of the inpatient phase of the study,

12.6.4.1 Beck Depression Inventory (BDI)

The BDI is a 22-item self-report inventory that focuses on the subject's subjective feelings of depression and is sensitive to changes in feeling status. Subjects will start the measure during intake screening and continue to complete this questionnaire on an every other day basis, until the end of the study.

12.6.4.2 Brief Symptom Inventory (BSI)

The BSI is a 53-item self-report clinical rating scale used to assess psychological distress. Subjects will start the measure during intake screening and continue to complete this questionnaire on an every other day basis, until the end of the study.

12.6.4.3 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 during intake screening and continue to complete this questionnaire on an every other day basis, until the end of the study.

12.6.4.4 Urine Toxicology

Urine toxicology for marijuana, opiates, cocaine, and methamphetamine will be monitored once daily (8 a.m.), as documented by a qualitative urine test (Syva® Rapid Test d.a.u.™ 4 THC/OPI/COC/MeAMP). If the qualitative urine test indicates the presence of COC/THC/or OPI, subjects will be disqualified. A quantitative test to monitor the level for MeAMP may be performed, if there is any indication that the subject has used MeAMP illicitly while in the study.

12.6.5 Laboratory Tests

12.6.5.1 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 intake screening and discharge.

12.6.5.2 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 intake screening and discharge.

12.6.5.3 Pregnancy Test

A blood or urine-based pregnancy test designed to measure human chorionic gonodotropin will be used during screening, during intake screening, at the time of discharge and once during followup.

12.6.5.4 HIV Test

An HIV antibody test will be performed on a serum sample collected from the subject during intake screening. An HIV test informed consent must be obtained before collecting blood for this test.

12.6.5.5 Infectious Disease Panel and PPD Test

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 rapid plasma reagin test (RPR) for syphilis will be performed.

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 only a chest x-ray will be required.

12.6.6 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 5, consisting of the measures listed below. Follow-up assessments will be performed during selegiline/placebo treatment, on days 8, 19, 22, and 32. These assessments will include the Simple Reaction Time Test, Covert Orienting Test, and n-back tests. In addition, on day 32, 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
Estimated Premorbid IQ	North American Adult Reading Test – Revised
Attention/Psychomotor Speed	Trailmaking Test-Part A, Symbol Digit Modalities Test, Simple Reaction Time Test, Covert Orienting Test
Verbal Learning and Memory	Rey Auditory Verbal Learning Test Trial 1, Trials 1-5, Delayed Recall
Executive Systems Function	Wechsler Memory Scale-III Letter-Number and Visual Spans, Verbal Fluency, Nonverbal Fluency, Trailmaking Test-Part B, Stroop Color/Word, Choice Reaction Time, n-back reaction time tests

12.6.7 Monitoring and Assessments During Methamphetamine Challenge Sessions

12.6.7.1 Blood Sample Collections

A schedule of blood collections and volumes is provided in Appendix II including collection of samples for methamphetamine pharmacokinetics, stress hormone levels, selegiline blood levels, and hematology and blood chemistry assays. Blood samples collected for methamphetamine and selegiline pharmacokinetic analysis will be prepared and shipped according to the instructions in Appendix IV.

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 (days 8 and 22): one will be for methamphetamine administration, the other for blood sample collection.

In order to limit the amount of blood drawn, samples will be collected during the 30 mg, but not the 0 and 15 mg challenge test sessions. However, to maintain the study blind, mock blood draws will be conducted during the 0 and 15 mg challenge sessions (sessions 1,3, 6, and 8). All blood samples will be collected behind a sheet during all challenge sessions. During the mock blood draws, study staff will act as if they are collecting blood behind the sheet. Samples will be collected for assessment of methamphetamine pharmacokinetics, stress hormone (cortisol), and for selegiline and its metabolites and extent of MAO inhibition (PEA). PEA is an endogenous substance normally metabolized by MAO-B; its levels will serve as an index of MAO-B inhibition In order to assess selegiline pharmacokinetics, peak and trough blood draws will be taken on days 18, 20 and 22. Total blood loss during the study will be approximately 0.77 times a standard blood bank donation (384 mL).

12.6.7.2 Physiology

Before and after each i.v. challenge, the subject's physiologic response will be closely monitored using repeated HR, BP, and EKG readings. BP, HR, and EKG will be measured using a "Spacelabs PC Scout" telemetry unit. BP will be taken between 7:00 and 8:00 a.m., and 3, 6, 9, 12, 15, 20, 30, 45 and 60 minutes following the methamphetamine/saline administration. Thereafter BP will be monitored every 30 minutes from 1 to 4 hours and every 60 minutes for 4 to 8 hours after methamphetamine infusion. EKG and HR will be monitored continuously for the first 60 minutes after methamphetamine infusion. Thereafter, HR will be monitored every 30 minutes from 1 to 4 hours and every 60 minutes for 4 to 8 hours after methamphetamine infusion.

12.6.7.3 Subjective Responses

During and after the infusions subjects' subjective responses will be closely monitored. Computerized VAS will be administered between 7:00 and 8:00 a.m., and 3, 6, 10, 15, 30, 45, and 60 minutes after each infusion. Thereafter, VAS will be administered every 30 minutes for hours 1 to 4 and every 60 minutes for hours 4 to 8 after infusion. An ARCI and Adjective Scales will be administered between 7:00 and 8:00 a.m. 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 do you think this is worth in dollars. ARCI and Adjective Scales will be administered between 7:00 and 8:00 a.m. and at 30 minutes after the infusion. 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".

12.6.8 Assessment of Cue-Induced Craving

On days 6, 11, and 20 (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 4. 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. We hypothesize that selegiline treatment will reduce cue induced craving but that placebo treatment will not.

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. Subjects will indicate their relative preference for a second methamphetamine injection versus varying amounts of money.

12.6.9 18-FDG PET Assessment

Prior work in our lab has shown that selegiline treatment is associated with reduced cocaine associated change in cerebral metabolic activity (Bartzokis, 1999). In order to determine if selegiline produces similar effects following methamphetamine administration, the subset of subjects (n = 8) assigned to the selegiline arm of this protocol will be scanned after injection of 2.5 mCi 18-FDG (injected i.v. immediately prior to saline/methamphetamine injection) using standard clinical PET methods. Subjects will be scanned 4 times, twice before selegiline treatment and twice during selegiline treatment. For each treatment, subjects will be scanned once 45 minutes after receiving a saline injection and 45 minutes after receiving methamphetamine injection. These will be done on days separated by 48 hours to avoid methamphetamine carryover effects.

Blood will be sampled to provide glucose concentration and radioactivity measures for the PET input function at 5 minutes before 18-FDG and 45 minutes after 18-FDG injection.

PET scans will be performed in the PET area, which is on the A-floor of the main hospital complex at UCLA. The methods used for administering and monitoring subjects following methamphetamine administration will be identical to those studies performed in the GCRC. Standard safety equipment is available, and the "code" team responds to this area when needed. Many standard nuclear medicine tests are performed here, including stress tests that are associated with hazards similar to those possibly imposed by methamphetamine administration.

12.6.10 Magnetic Resonance Imaging (MRI) Study

In conjunction with the 18-FDG PET scans, an MRI scan will be obtained on each subject randomized to the selegiline arm. The MRI may be done at any time during the study and exact timing will depend on scheduling constraints. These MRI images are used to delimit brain structures and regions that are not readily identified on the 18-FDG PET images. As such, the MRI data provide validation for the quantitation of the FDG activity defined in specific brain regions. Additionally, the MRI images will be used to measure volumes of the ventricles and

subregional brain regions in order to ascertain potential structural alterations consequent to chronic methamphetamine exposure.

The procedures for the MRI require the subject to enter a screened room, and lie still on a narrow bed for about 30-60 minutes while the pictures are being formed. The space is dark and enclosed and the subject will hear thumping noises. In addition, the magnetism of the machine attracts certain metals; therefore, people with these metals in them (specifically pacemakers, infusion pumps, aneurysm clips, metal prostheses, joints, rods, plates etc.) will be excluded from the study. The "metal" in dental fillings is less susceptible to this effect and is therefore allowed.

There are no known risks associated with the MRI scanning procedure since no radiation is involved, however, the magnetism of the machine does attract certain metals. Therefore, if someone with these metals in them—certain pacemakers, artificial heart valves, implanted infusion pumps, cochlear implants, spinal chord stimulators—did not disclose this fact and were to be scanned, the magnetism could affect or stop these devices from working properly. Subjects will be queried as to whether they have any of these devices implanted, and if so, will be excluded from participation. Subjects will also be informed of the consequences that could result in undergoing an MRI with such an implanted device present.

12.6.11 Adverse Events (AEs)

AEs will be assessed daily 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.

12.6.12 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 principal investigator/study physician.

12.6.13 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 FDA Form 1572

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

13.2 IRB Approval

Prior to initiating the study, the 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 investigator will ensure that a duly constituted IRB at the study site that conforms with 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 adverse events. 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.

13.3 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.

13.4 Risks and Benefit Assessment

The primary risks of this study are those of possible adverse reaction to the study drugs, methamphetamine and selegiline. 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. They have been safely used 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.

Selegiline, as an oral dosage form, 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 selegiline 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 screening challenge is one protection against this risk. Our experience safely administering cocaine to subjects receiving this dose of selegiline suggests that the combination of selegiline and methamphetamine should be well tolerated. It is possible that chronic selegiline might lose the MAO-B selectivity of acute selegiline, though this was not observed in previous studies. Repeated assessments every few days during chronic selegiline are protections against this risk. As a precaution, during the hospital stay, participants will follow a MAO-I diet. Upon discharge, subjects will be instructed to follow a MAO-I diet for three weeks (i.e., 4 weeks after the last selegiline dose). In addition, subjects will be instructed to <u>not</u> take any of the following medications one week from discharge:

1. MAO inhibitors (e.g., selegiline, phenelzine, etc.) or selective serotonin reuptake inhibitors (SSRI; e.g., fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram).

2. Psychotropic medications, centrally active anticholinergics, anticonvulsants (case by case), antiparkinsonian agents, antidepressants, antipsychotics (including lithium carbonate), anxiolytics, psychostimulants, nootropics, cerebral enhancers, vasodilators, benzodiazepine receptor agonists, reserpine, hypnotics; including: oral neuroleptics, depot neuroleptics, methyldopa, ergot preparations, and tricyclic antidepressants.

3. Sympathomimetic medications: e.g., amphetamines, methylphenidate, dopamine, epinephrine, norepinephrine, levodopa, tyrosine, phenylalanine, mazindole tyrosine, over-the-counter (OTC) and prescription nasal decongestants, and appetite suppressants.

4. L-tryptophan, metoclopramide.

5. Meperidine (Demerol®), dextromethorphan, propoxyphene or other opiates.

6. HT receptor agonists (e.g., sumitriptan succinate [Imitrex®], zolmitriptan [Zomig®], serotonergic agonists or antagonists (e.g., cyproheptadine [Periactin®], methysergide [Sansert®]).

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.

13.5 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.

13.6 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 unblinded to subjects' actual treatment assignments for the safety data. Reports from the DSMB will be sent to the principal 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.

13.7 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 principal investigator or sub-investigators according to the specific instructions detailed in this section of the protocol and in Appendix V. The occurrence of AEs will be assessed daily and an AE CRF completed weekly.

An AE is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered 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.

13.8 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 (Appendix V). 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 Study Director, and the sponsor-investigator as follows:

Medical Monitor:	**Ann Anderson, M.D.**	**Phone: 301/435-0767**
NIDA Study Director:	**Edwina Smith, RN, BC, M.S.**	**Phone: 301/443/1061**
Sponsor-Investigator:	**Thomas F. Newton, M.D.**	**Phone: 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 sponsor-investigator.

Any fatal or life-threatening SAE that is investigational agent related and unexpected must be reported by the sponsor-investigator initially to the FDA within 7 calendar days via telephone,

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

There can be serious consequences including ultimately, criminal and/or civil penalties for sponsors who fail to comply with FDA regulations governing the reporting of SAEs to FDA. The study investigators in this study have the responsibility of promptly reporting all SAEs to NIDA and the sponsor-investigator in order that the sponsor-investigator can comply with these regulations.

If a study subject withdraws from the study or if an investigator decides to discontinue the subject from the study because of a SAE, the subject must have appropriate follow-up medical monitoring. If the subject is hospitalized, medical monitoring will consist of not less than daily evaluation by physical examination, vital signs, laboratory evaluations, and if applicable, ECG monitoring for significant treatment-emergent abnormalities. Monitoring will continue until the problem prompting hospitalization has resolved or stabilized with no further change expected or is discovered to be clearly unrelated to study medication or progresses to death.

14 ANALYTICAL PLAN

14.1 Outcome Measures

14.2 Primary Outcome Measures

The primary objective of this study is to determine the safety of the selegiline 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.

14.3 Secondary Outcome Measures

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

1. Peak and trough plasma levels of selegiline and its metabolites, desmethylselegiline, l-amphetamine, and l-methamphetamine during chronic daily treatment with selegiline.
2. Pharmacokinetic parameters of d-methamphetamine and amphetamine including Cmax, Tmax, AUC, apparent $t_{½}$, and CL, F, V, and k.
3. Plasma levels of PEA and cortisol.
4. EKG effects.
5. Brain metabolic activity measured using FDG-PET.
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. Adverse events.

14.4 Analysis Plan

14.5 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 selegiline will be compared to those without selegiline, by methamphetamine dose level (saline, 15 mg and 30 mg doses), using repeated measures ANOVA.

14.6 Secondary Outcome Measures

Plasma concentration-time profiles of d-methamphetamine and amphetamine (a metabolite of 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. Comparisons of pharmacokinetic parameter estimates of d-methamphetamine and amphetamine between the placebo control and selegiline arms will be performed for the 30 mg methamphetamine dose level using t tests. Confidence intervals (90%) for each parameter will be determined. To be certain that there are no inherent differences between the pharmacokinetics of methamphetamine and amphetamine between the two treatment arms, pharmacokinetic parameters between the two arms will also be compared during the baseline 30 mg methamphetamine challenge (session 4).

Peak and trough levels of selegiline and metabolites (desmethylselegiline, l-amphetamine, and l-methamphetamine) will be compared between the saline and 15 and 30 mg dose administrations of methamphetamine using repeated measure ANOVA.

Changes in EKG 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 selegiline phase to determine the extent to which these measures are modified by the administration of selegiline using repeated measures ANOVA.

Changes in plasma PEA and cortisol and BSI, BDI, and POMS scores will be compared before and after selegiline administration using repeated measures ANOVA.

Adverse events data will be compiled and presented as summary statistics.

PET data will be quantitated using standard analytic models (Patlak), and the metabolic activity before and after methamphetamine in limbic structures will be assessed. We hypothesize that selegiline will reduce the effects of methamphetamine on cerebral metabolic activity, as we demonstrated for cocaine previously.

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

15 DATA MANAGEMENT AND CASE REPORT FORMS

15.1 Data Collection

Data will be collected at the study sites on source documents that 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 principal investigator is responsible for maintaining accurate, complete and up-to-date records for each subject. The 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 received at the NIDA data coordinating center will be reviewed. If incomplete or inaccurate data are found a data clarification request will be forwarded to the site for a response. The site will resolve data inconsistencies and errors prior to returning data to the data coordinating center. All corrections and changes to the data will be reviewed prior to being entered into the main study database. NIDA/DTR&D and the participating site will receive reports at least monthly regarding the quality and quantity of data submitted to data coordinating center.

Participating investigators agree to routine data audits by the sponsor's designated staff, audits by the staff of the NIDA data-coordinating center and by NIDA's programmatic staff. Monitors will routinely visit the site to assure that data submitted on the appropriate forms are in agreement with source documents. They will also verify that study agents have been properly stored and accounted for, subject informed consent for study participation has been obtained and documented, all essential documents required by GCP regulations are on file, and the site is 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 established procedures specified in the study Operations Manual.

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 case report forms, data correction forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence and regulatory documents (e.g., signed protocol and amendments, Ethics or Institutional Review Committee correspondence and approved consent form and signed subject consent forms, Statement of Investigator form, and clinical supplies receipt and distribution records).

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

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

15.5.2 Confidentiality of Patient Records

To maintain subject confidentiality, all laboratory specimens, CRFs, 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 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 Food and Drug Administration (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.

Authorization for protection of identity is now available to investigators engaged in research on the use and effect of psychoactive drugs under section 301 (d) of the Public Health Service Act, as amended by Public Law 93-282 (42 U.S.C. 241) (d) 0. "Such authorization affords the person to whom it is given a privilege to protect the privacy of research subjects by withholding the names or other identifying characteristics of such research subjects from all persons not connected with the conduct of the research. Persons so authorized may not be compelled in any federal, state, or local civil, criminal, administrative, legislative, or other procedures to identify such individuals," (Federal Register/Vol. 44, No. 66/Wednesday April 4, 1979/Rules and Regulations/Part VII.) The usual exemptions for audit and evaluation are allowed, but such auditors and evaluators would be bound to the same protections of subjects. The principal investigator has obtained a certificate of confidentiality. The provision of this authorization will be explained to all potential participants. Additional protection will be offered to our subjects in that identifying information will not be part of the data set and will not be available except on a need-to-know basis.

16 PUBLICATIONS OF THE STUDY RESULTS

A publication committee will be formed and comprised of representatives from NIDA and principal investigators to review and approve all documents to be submitted for publication.

NIDA and the investigative group agree that the study database will be made available to individual investigators to encourage other publications, either by a group or by an individual investigator provided that: manuscripts based on the use of selegiline 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
Edwina Smith, RN, BC, M.S. Study Director	_____	_____
Jurij Mojsiak, M.S. Project Officer	_____	_____
Nora Chiang, Ph.D. Chief, Chemistry and Pharmaceutics Branch	_____	_____
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. Project Principal Investigator	_____	_____

18 LITERATURE CITED

Bartzokis G, Beckson M, Newton T, *et al.* (1999): Selegiline effects on cocaine-induced changes in medial temporal lobe metabolism and subjective ratings of euphoria [In Process Citation]. *Neuropsychopharmacology* 20:582-90.

Carroll KM, Rounsaville BJ, Gordon LT, *et al.* (1984) Psychotherapy and pharmacotherapy for ambulatory cocaine abusers. *Arch Gen Psychiatry* 51:177-187.

Haberny KA, Walsh SL, Ginn DH, *et al*. (1995): Absence of acute cocaine interactions with the MAO-B inhibitor selegiline. *Drug Alcohol Depend* 39:55-62.

Hyman SE, Nestler EJ. (1995) Initiation and adaptation: A paradigm for understanding psychotropic drug action. *Amer J Psych* 152:51-162.

Knoll J (1989): The pharmacology of selegiline (l-deprenyl). New aspects. *Acta Neurol Scand Suppl* 126:83-91.

Ling W, Shoptaw S. (1997) Integration of research in pharmacotherapy for substance abuse: Where are we? Where are we going? *J Addictive Dis* 16; 4, 83-102.

Mayer G, Ewert Meier K, Hephata K (1995): Selegeline hydrochloride treatment in narcolepsy. A double-blind, placebo-controlled study. *Clin Neuropharmacol* 18:306-19.

McGahan PL, Griffith JA, Parante R, McLellan AT. (1982) Composite scores from the Addiction Severity Index. Washington, DC: National Institute on Drug Abuse Project DA02554 and the Veterans Administration.

Mendelson JH, Mello NK. (1996) Management of cocaine abuse and dependence. *N Eng J Med* 334:965-972.

Newton TF, Kalechstein A, Beckson M, Bartzokis G, Bridge TP, Ling W (1999): Effects of selegiline pretreatment on response to experimental cocaine administration. *Psychiatry Res* 87:101-6.

Sunderland T, Mueller EA, Cohen RM, Jimerson DC, Pickar D, Murphy DL. Tyramine pressor sensitivity changes during deprenyl treatment. (1985) *Psychopharmacology* 86:432-437.

Appendix I: Time and Events Schedule

Study Phase	**Screening**				**Baseline Challenges**									**Treatment Challenges**				
		Intake																
Study day	**-14 to 0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Informed consent	X																	
Locator form	X																	
Demographics	X																	
SUI	X	X																
Drug Use and Treatment History	X																	
5-lead EKG	X																	
12-lead EKG		X																
SCID		X																
Medical History		X																
Physical Exam		X																
ASI-Lite, HRBS, Wender Utah ADHD		X																
Vital Signs	X	X						X		X	X	X		X	X	X	X	X
Chemistries		X																
Hematology		X																
Pregnancy Test	X	X																
HIV Test		X																
Infectious Disease Panel and PPD Test		X																
Urine Toxicology Screen	X	X	X	X	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		X
10 mg oral selegiline or placebo														X	X	X	X	X
Neuropsychiatric Assessments						X			X									
Cue Exposure					X		X					X						
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Methamphetamine Challenge Session #					**1**	**2**	**3**		**4**				**5**					
0 mg methamphetamine iv					X	X												
15 mg methamphetamine iv							X											
30 mg methamphetamine iv									X				X					
VAS					18X	18X	18X		18X				18X					
Continuous BP, HR, EKG Monitoring					X	X	X		X				X					
ARCI, Adj Scale					2X	2X	2X		2X				2X					
Methamphetamine Blood PK									16X									
18-FDG PET						X							X					
MRI					Once during inpatient as convenient to scheduling													

Appendix I: Time and Events Schedule Continued

Study Phase	**Treatment Challenges**									**Follow-up**								
																Discharge		
Study day	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**40**	**47**
12-lead EKG																X		
Vital Signs				X		X	X	X		X	X	X	X	X	X	X		
Chemistries																X		
Hematology																X		
Pregnancy Test																X	X	
Urine Toxicology Screen	X	X	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		
10 mg oral selegiline or placebo	X	X	X	X	X	X	X	X	X*									
Selegiline Blood Levels	3X		3X		3X													
Plasma PEA, cortisol	2/6X				2/6X													
Neuropsychiatric assessments		X			X										X			
Cue Exposure			X															
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Methamphetamine Challenge Session #	**6**	**7**	**8**		**9**				**10**									
0 mg methamphetamine iv	X	X																
15 mg methamphetamine iv			X															
30 mg methamphetamine iv					X				X									
Continuous BP, HR, EKG Monitoring	X	X	X		X				X									
VAS	18X	18X	18X		18X				18X									
ARCI, Adj Scale	2X	2X	2X		2X				2X									
Methamphetamine Blood PK					16X													
18-FDG PET		X							X									
MRI	Once during inpatient as convenient to scheduling																	

*Selegiline is only taken once on day 26 in the morning.

APPENDIX II: Schedule of Blood Collections[a]

Analyte	Volume per sample	7-8 a.m.	Minutes relative to Methamphetamine Infusion											Hours Relative to Methamphetamine Infusion						Total Volume over study
			-5	2	5	10	20	30	45	60	90	120	240	6	8	12	24	36	48	
Days 1 & 33																				
Hematology	10 ml	X																		20 ml
Blood Chemistry	10 ml	X																		20 ml
Day 1																				
Infectious Diseases	10 ml																			10 ml
Days 18, 20, 22																				
Selegiline Blood Level	5 ml	X	X									X								45 ml
Days 18 & 22																				
Cortisol	7 ml		X					X				X	X	X	X					84 ml
PEA	5 ml		X									X								20 ml
Days 8 & 22																				
Methamphetamine PK	5 ml		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	160 ml
Days 5, 12, 19, & 26																				
18-FDG	2.5 ml		X						X											20 ml
Anytime																				
HIV Test (optional)	5 ml																			5 ml
Total Volume of Blood Collected																				**384 ml**

[a]Samples are plasma with the exception of blood chemistry which is serum and hematology which is whole blood with anticoagulant.
[b]Two samples, one between 7:00 and 8:00 a.m. before selegiline administration (trough) and one at 8:55 a.m., 55 minutes after selegiline administration (peak).

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 with 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.	3. For countershock to be effective the current between two electrodes must 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) 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 Veraperamil 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: Procedure for Collection, Storage, and Shipping of Blood Samples for Methamphetamine/ Methamphetamine Metabolite Levels and Selegiline/Selegiline Metabolite Levels

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:

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

Labeling Procedure:

1. Prepare the following label to affix to vials.

Study # _____ Center # _____ Subject # _____
Date collected _____ Time collected_____

2. With indelible black ink complete the label with the following information: study number, 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 at arranged time interval 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 (or other overnight delivery service).

10. After package is picked up by Federal Express (or other overnight delivery service), notify the laboratory to expect shipment.

Plasma Sample Shipping Log

Study No.: _____

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 V: Instructions For Evaluating and Reporting Adverse Events and Serious Adverse Events

A. GENERAL INSTRUCTIONS

1. The Adverse Event (AE) CRF must be completed daily and reviewed weekly by a study physician.

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

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

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

B. DEFINITIONS – SEVERITY OF EVENTS

Mild: Awareness of symptom, but easily tolerated.

Moderate: Discomfort enough to cause interference with usual activity.

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

C. DEFINITIONS – RELATEDNESS OF EVENTS

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

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

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

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

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

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

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

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

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

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

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

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

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

D. SPECIFIC INSTRUCTIONS – LABORATORY/ECG ADVERSE EVENT

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

All laboratory AEs should be specified as an increased or decreased test result (e.g. “increased glucose”, “decreased potassium”) or as a term that implies an abnormality (e.g., hypercalcemia, azotemia).

E. SERIOUS ADVERSE EVENT AND UNEXPECTED ADVERSE EVENT REPORTING

24 hour Reporting Requirements

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

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

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

3-day Supporting Documentation Requirements

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

- SAE Form
- Concomitant Medication CRF pages
- Adverse Events CRF pages
- Copies of source documents pertinent to the event (lab reports, ECG tracings, medical chart notes, etc.)
- Any other relevant information necessary to facilitate the investigator's judgment regarding the SAE's relatedness to the severity OR by request of the Medical Monitor/Alternate

Follow-Up of All Adverse Events/Serious Adverse Events

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

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

Reporting to the FDA

The principal investigator, who is the IND sponsor, is required to report SAEs to the FDA:

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

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

- in an annual report in all other cases.