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ASSESSMENT OF POTENTIAL INTERACTIONS BETWEEN INTRAVENOUS COCAINE AND TOLCAPONE

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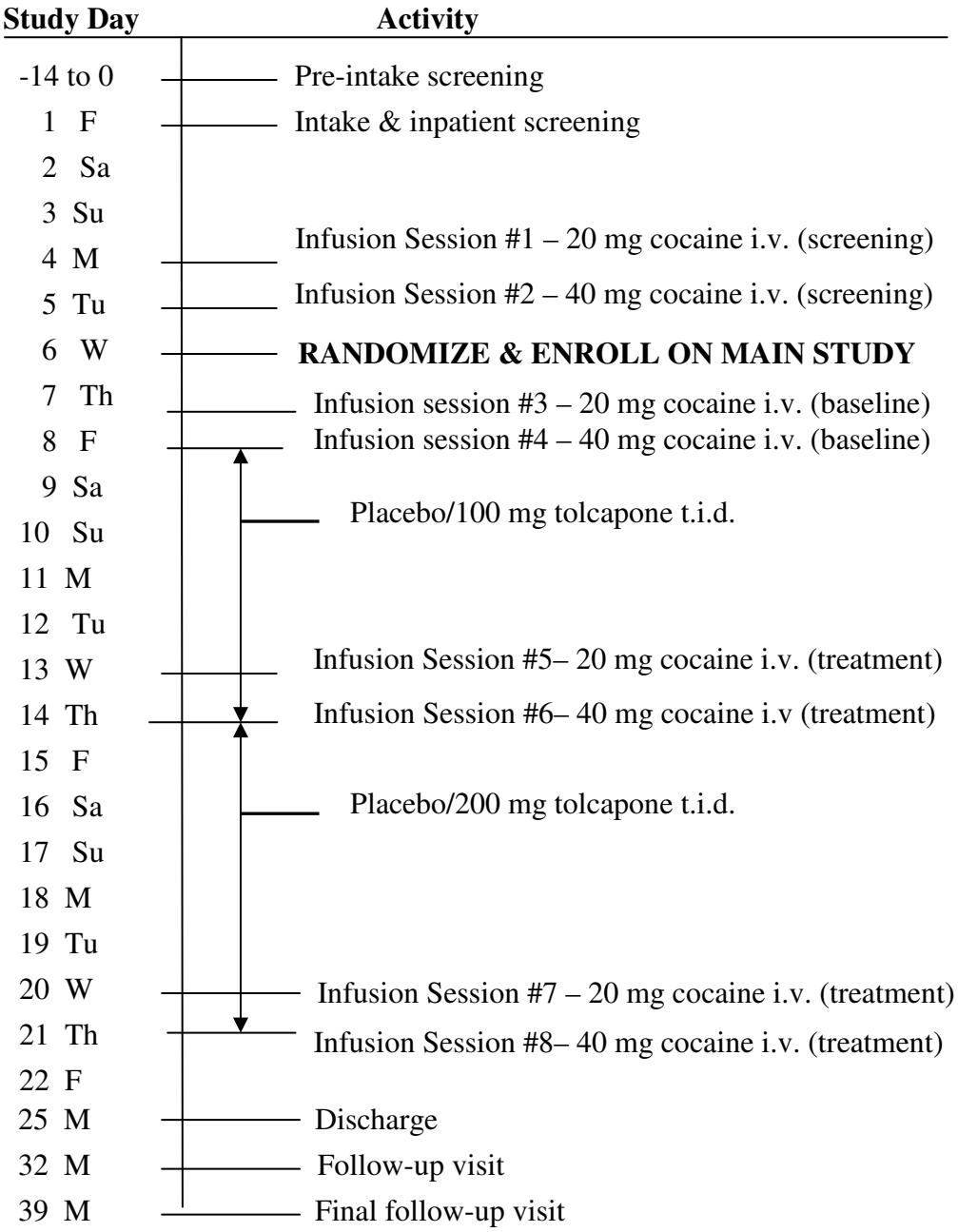
1 LIST OF ABBREVIATIONS

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 transaminase
BE	benzoylecognine
BDI	Beck's Depression Inventory
BP	Blood Pressure
BSI	Brief Symptom Inventory
BUN	blood urea nitrogen
CAP	College of American Pathologists
COMT	catechol-O-methyltransferase
CLIA	Clinical Laboratory Improvement Amendment of 1988
CRF	Case Report Form
CPK	creatinine phosphokinase
DHEA	dihydroepiandrosterone
DOPAC	dihydroxyphenylacetic acid
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
DTR&D	Division of Treatment Research and Development
ECG	electrocardiogram
GCRC	General Clinical Research Center
HIV	human immunodeficiency virus
HVA	homovanillic acid
HRBS	HIV Risk-Taking Behavior Scale
INR	international normalized ratio
i.v.	intravenous(ly)
LDH	lactate dehydrogenase
mg	milligrams
ml	milliliter
MPV	mean platelet volume
NIDA	National Institute on Drug Abuse
POMS	Profile of Mood States
SAE	serious adverse event
SCID	structured clinical interview for DSM-IV
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 cocaine infusion and treatment with tolcapone.

Primary: The primary objective of this study is to determine the safety of tolcapone treatment, compared to placebo treatment, concurrent with i.v. cocaine infusions of 20 and 40 mg, with the focus being on cardiovascular responses (HR, BP) to the i.v. cocaine infusions.

Secondary:

1. To determine peak and trough plasma levels of tolcapone during t.i.d. treatment with 100 and 200 mg of oral tolcapone.
2. To evaluate whether administration of tolcapone alters the pharmacokinetics of cocaine or its major metabolite, BE.
3. To determine the effects of tolcapone and/or cocaine on plasma levels of erythrocyte catechol-O-methyltransferase (COMT).
4. To evaluate whether tolcapone treatment alters the subjective [Addiction Research Center Inventory (ARCI), Adjective Scales, or visual analog scales (VAS)] or other cardiovascular responses (ECG parameters) to cocaine.
5. To assess the effects of tolcapone on craving for cocaine, assessed using a laboratory cue exposure paradigm.
6. To assess the effects of tolcapone on mood and personality assessments (BSI, BDI, and POMS).
7. To assess adverse events associated with investigational agents.

STUDY DESIGN: This is a double-blind inpatient study in which, after establishing eligibility by screening the responses to cocaine infusions of 20 and 40 mg i.v., subjects will be randomized into one of the two treatment groups [placebo (n = 8) or tolcapone (n = 8)]. All cocaine infusions will be preceded one hour earlier by a saline infusion. Subjects in both treatment groups will receive baseline cocaine infusions of 20 and 40 mg i.v on days 7 and 8, respectively. They will take one 100 mg capsule of tolcapone (or placebo) t.i.d. orally starting on the evening of study day 8 and through the afternoon of day 14. Subjects will receive repeated i.v. cocaine infusions (20 mg and 40 mg on days 13 and 14, respectively). They will take two 100 mg capsules of tolcapone (or placebo) orally t.i.d. starting on the evening of study day 14 and through day 21. Subjects will receive repeated i.v. cocaine infusions of 20 and 40 mg on days 20 and 21, respectively. They will also receive repeated cue exposures on days 12, 13 and 20. 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, 25 days of inpatient treatment and assessments, and two weeks of follow-up after discharge. Study completion is anticipated to be six months with 2 subjects being enrolled every 25 days.

SAMPLE SIZE: 16 subjects total; subjects dropping out before study completion will be replaced.

POPULATION: Volunteer experienced cocaine users, 18-to-45 years of age, who have used cocaine by the smoked or i.v. route on average at least twice per week for at least four of the past six weeks and a positive urine test for cocaine within two weeks of entering the study.

TREATMENTS: Subjects will be randomized on day 6 to one of the following arms:

Tolcapone: Subjects will take one 100 mg capsule of tolcapone t.i.d starting in the evening of day 8 through the afternoon of day 14, then two 100 mg capsules of tolcapone t.i.d starting in the evening of day 14 through day 21.

Placebo: Subjects will take one matched placebo capsule t.i.d. starting in the evening of day 8 through the afternoon of day 14, then two matched placebo capsules of t.i.d starting in the evening of day 14 through day 21.

ASSESSMENTS: Safety of cocaine administration in tolcapone dosed subjects will be determined by monitoring adverse events (AE), blood pressure (BP), heart rate (HR), and electrocardiogram (ECG) responses. Interactions between cocaine and tolcapone will be assessed by pharmacokinetic studies. The effect of tolcapone on cocaine craving will be assessed by a laboratory cue exposure paradigm. Other psychological assessments include Profile of Moods State (POMS), Brief Symptom Inventory (BSI), and Beck's Depression Inventory (BDI), VAS, ARCI, and Adjective Scales.

4 INTRODUCTION AND RATIONALE

4.1 Therapeutic Strategies for Treating Cocaine Abuse

A variety of neuropharmacological strategies are being pursued in the search for an effective treatment for cocaine abuse. Many focus upon dopamine. Cocaine is known to produce the major effects related to its abuse through dopaminergic mechanisms in the midbrain. Cocaine 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 cocaine 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 cocaine abuse. This second strategy is based on a combination of theory and data suggesting that chronic cocaine use depletes brain dopamine (possibly functionally, rather than physically) and that this relative depletion is experienced as increased cocaine craving; the aim here is to reduce cocaine craving and cocaine use by restoring the depleted dopamine system to normality.

4.2 Tolcapone (Tasmar®)

Tolcapone, 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. Tolcapone improves brain dopamine function and restores efficacy of l-dopa treatment of Parkinson's disease among many who become resistant to precursor therapy after chronic treatment. The concept under study is whether increasing dopamine availability by inhibiting the pathway for

extracellular degradation results in synaptic dopaminergic changes that might support use as a cocaine pharmacotherapy. Prior to a full-scale clinical trial, it is necessary to gather early Phase I data to demonstrate that tolcapone can be used safely in a population likely to use cocaine concurrently with the medication and to explore whether and how the medication might effect cocaine pharmacokinetics and pharmacodynamics.

Preclinical Evidence. Studies regarding the influence of dopamine inhibition relative to reuptake mechanisms that may provide the basis for understanding the role of dopamine in addiction are still in the early stage. Preclinical evidence suggests that the COMT inhibitor, tolcapone, itself does not alter extracellular dopamine levels (Budygen *et al.,* 1999), though it dramatically increases dopamine metabolite levels (Napolitano *et al*., 1995; Budygin *et al.,* 1997; *Budygin et al.*, 1997b; Budygin *et al.,* 1998). In studies using fast-scan cyclic voltammetry, increases in dopamine levels are observed after addition of uptake inhibitors (cocaine or nomifensine) in the caudate putamen and the nucleus accumbens (Jones *et al.,* 1995). Studies comparing these uptake inhibitors relative to the monoamine oxidase-inhibitor pargyline and to tolcapone indicate that extracellular clearance of evoked dopamine in the basolateral amygdaloid nucleus and the caudate-putamen appears almost exclusively due to cellular uptake and not extracellular degradation (Garris *et al.,* 1995). Failure to observe increases in extracellular dopamine when using agents that inhibit metabolism could be because the dopamine transport mechanism efficiently removes the dopamine before it can be measured in the synapse and current methods are not able to measure this quick effect (R.M. Wightman, personal communication). However, tolcapone causes significant increases in dihydroxyphenylacetic acid (DOPAC) and reductions in homovanillic acid (HVA), which suggests that dopamine levels are in fact altered through metabolism inhibition (Budygin *et al.,* 1999) (dopamine is converted into DOPAC by monamine oxidase, and DOPAC is metabolized into HVA by COMT). Still, the available evidence suggests that dopamine levels are regulated largely by uptake mechanisms. Further, the lack of finding significant increases in synaptic dopamine following tolcapone administration may have no bearing on the value of the medication in humans since Parkinson's patients experience dramatic relief from movement disorders when integrating a COMT inhibitor with dopaminergic medications.

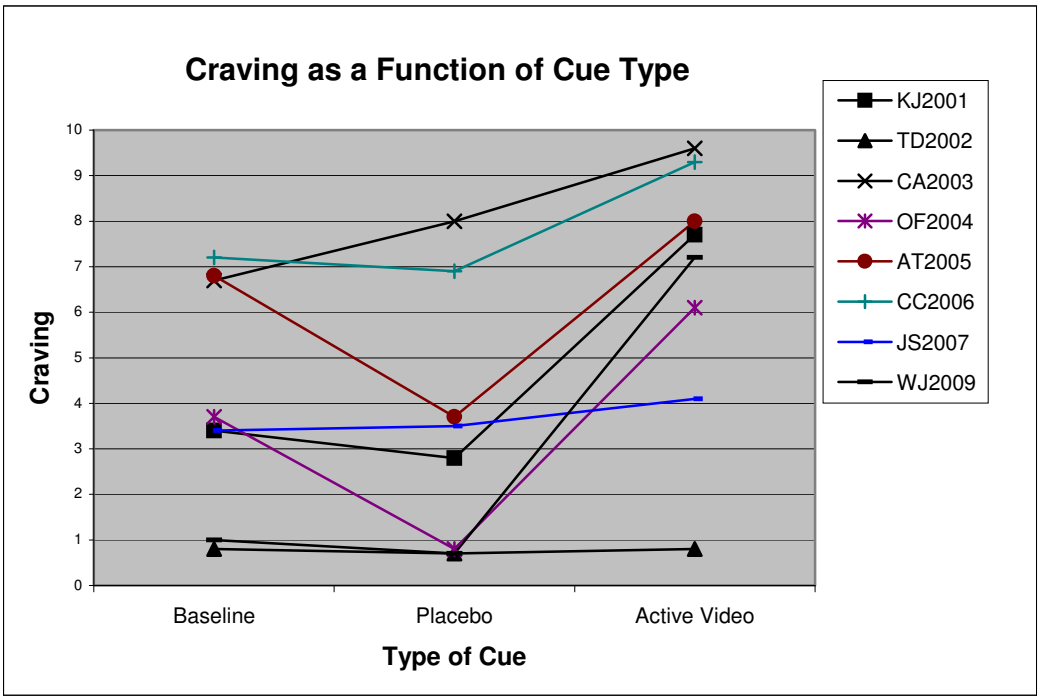
Open-Label Experience. According to one physician in our group who used tolcapone (200 mg t.i.d.) clinically with five patients (M. Sagan, M.D., personal communication), three completed 8 weeks of treatment with 78.7% of their thrice-weekly urine samples negative for cocaine metabolite. The remaining two completed 6 and 7 weeks of treatment with 10% of their urine samples negative for cocaine metabolite. All participants also received thrice weekly group psychosocial counseling. Side effects noted included: (a) reduction of cocaine craving, mood improvement, sleepiness – reported by all 5; (b) nightmares/cocaine dreams, headaches – reported by 4 of 5; (c) appetite increase, muscle aches, anxiety – reported by 3 of 5; (d) nausea, orthostatic hypotension – reported by 2 of 5; and (e) vomiting and movement disorder – reported by 1 of 5.

The theorized mechanism of action that might be responsible for these effects is likely tolcapone's reduction in central dopamine 3-O-methylation (Hauser *et al*., 1998) resulting in a theorized "smoothened delivery of levodopa to the brain" (Marsden *et al.,* 1994). COMT inhibition via tolcapone leads to reduced metabolic breakdown of dopamine in the striatum in

humans (Kaakkola *et al.,* 1994) and peripherally in rats (Gottwald *et al.,* 1997). These mechanisms may account for Parkinsons' patients realizing more available levodopa (which in turn makes available more dopamine) to their brains when treated with tolcapone and levodopa medications, the end result of which is corresponding reductions in motor fluctuation. Some similar mechanism increasing dopamine tone, may lead to corresponding changes in mood or craving that may help cocaine dependent patients in the process of recovery.

Cue-induced Craving. Based on work done by others (e.g., London, Childress, Berger and Reid) we have developed videotaped cues to induce craving for cocaine. These consist of 3-5 minute videotapes showing actors using substances that appear to be cocaine. Videotapes are available for snorting, smoking and IV use. Subjects will be asked which route is more appealing to them, and they view that video throughout the study.

These cues have been presented to 8 cocaine dependent volunteers in order to determine their efficacy at inducing craving for cocaine. Subjects rated their craving at baseline, following a neutral video (a computer instructional video) and following the "snorting" video. As shown below, most subjects responded to the active video with increased craving.



Within subjects, repeated-measures analysis of variance demonstrated that responses in the three conditions were significantly different ($F=6.7$, $df=2,6$ $p=.03$). Pairwise comparisons demonstrated that craving following the methamphetamine cue was greater than craving at baseline ($p=.01$) and greater than craving during neutral cue ($p=.006$). These data show that craving can reliably be induced in the laboratory using the videotapes we developed.

5 STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, two-arm study designed to evaluate the safety of tolcapone treatment, compared to placebo treatment, concurrent with intravenous (i.v.) cocaine infusions. After establishing eligibility including screening responses to cocaine infusions of 20 and 40 mg, subjects will be randomized into one of two treatment groups [placebo (n = 8) or tolcapone (n = 8)]. Subjects will receive repeated i.v. cocaine infusions (20 and 40 mg on two consecutive days), before and after beginning daily treatment with tolcapone 100 mg t.i.d, followed by 200 mg t.i.d., or placebo t.i.d. All cocaine infusions will be preceded one hour earlier by a saline infusion.

Cocaine and saline will be administered in a single-blind fashion. Tolcapone and placebo will be administered in a double-blind fashion. The study will assess the subjective and physiological response to cocaine, the pharmacokinetics of cocaine and its major metabolite, benzoylecognine (BE), and blood levels of tolcapone. Tolcapone is expected to reduce COMT activity and thus increase dopaminergic tone.

Subjects will be discharged from the hospital 4 days after the last dose of cocaine. Subjects will be asked to return twice for payment and follow-up at 1 and 2 weeks after completion of the protocol to assess adverse events.

6 STUDY OBJECTIVES

6.1 Primary

The primary objective of this study is to determine the safety of the tolcapone concurrent with cocaine infusions of 20 mg and 40 mg i.v., with the focus being on cardiovascular responses (HR, BP) to the i.v. cocaine infusion.

6.2 Secondary

1. To determine peak and trough plasma levels of tolcapone during t.i.d. treatment with 100 mg and 200 mg of oral tolcapone.
2. To evaluate whether administration of tolcapone alters the pharmacokinetics of cocaine or its major metabolite, BE.
3. To determine the effects of tolcapone and/or cocaine on erythrocyte catechol-O-methyl-transferase (COMT).
4. To evaluate whether tolcapone treatment alters the subjective [Addiction Research Center Inventory (ARCI), Adjective Scales, or visual analog scales (VAS)] or other cardiovascular responses (ECG parameters) to cocaine.
5. To assess the effects of tolcapone on craving for cocaine, assessed using a laboratory cue exposure paradigm.
6. To assess the effects of tolcapone on mood and personality assessments (BSI, BDI, and POMS).
7. To assess adverse events associated with investigational agents.

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 are dependent on cocaine and are non-treatment seeking at time of study.

2. Be between 18 and 45 years-of-age.

3. Meet DSM-IV criteria for cocaine abuse or dependence.

4. Use cocaine 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 benzoylecognine (BE) 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) within normal limits.

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

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

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 not:

1. Have any history or evidence suggestive of seizures or brain injury.

2. Have any previous medically adverse reaction to cocaine, 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.

9 INVESTIGATIONAL AGENTS

9.1 Tolcapone/Placebo

Tolcapone will be obtained from Roche Laboratories and formulated by the UCLA pharmacy into capsules of 100 mg of tolcapone along with matched placebo capsules according to standard pharmacy compounding procedures.

9.2 Cocaine

Human use cocaine HCl in 20 mg (10 mg/ml in 2 ml ampoule) and 40 mg (20 mg/ml in 2 ml ampoule) doses will be provided by NIDA's contractor - Research Triangle Institute, Raleigh-

Durham, NC. The compound will be stored in the pharmacy vault. Standard narcotics control procedures will govern access to the drug. Cocaine will be administered by i.v. infusion over 60 seconds by the study physician. Any unused drug will be disposed according to standard practices.

10 TREATMENT PLAN

Tolcapone Arm: Subjects will take one 100 mg capsule of tolcapone t.i.d. orally starting in the evening of study day 8 and through the afternoon of day 14 and two 100 mg capsules of tolcapone orally t.i.d. starting in the evening of study day 14 through day 21. Tolcapone capsules will be administered at 7 a.m., 3 p.m., and 11 p.m. daily.

NOTE: If the tolcapone dose increase is not tolerated, subjects will complete the study at the lower dose. If liver function tests are not within normal limits on day 14, the tolcapone dosage will not be increased to 200 mg t.i.d. and the subject will be terminated from the study with appropriate follow-up.

Placebo Arm: Subjects will take one placebo capsule t.i.d. orally starting in the evening of study day 8 and through the afternoon of day 14 and two placebo capsules t.i.d. orally starting in the evening of study day 14 through day 21. Placebo capsules will be administered at 7 a.m., 3 p.m., and 11 p.m. daily.

Cocaine/Saline (All Subjects):

The study will be single blind with respect to the cocaine dose and saline administrations.

Subjects in both treatment arms will receive saline and cocaine infusions on eight days: days 4, 5, 7, 8, 13, 14, 20, and 21. On days 4, 7, 13, and 20, subjects will receive saline i.v., followed one hour later by 20 mg cocaine i.v. On days 5, 8, 14, and 21, subjects will receive saline i.v., followed one hour later by 40 mg cocaine i.v. Cocaine will be administered by i.v. push over 60 seconds by the study physician 2 hours following administration of afternoon dose of study agents.

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 cocaine 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 25 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 will be given a

subject identification number and proceed 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 cocaine (will be repeated until a positive test is obtained within 14 days prior to intake), a 5-lead ECG, and vital signs (HR and BP). For women of reproductive potential a urine pregnancy test will be performed. Adverse events will be collected starting at clinic intake. 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 Screening

Potential candidates whose screening assessment results 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 before cocaine infusion and include a physical exam including vital signs, 12-lead ECG, medical history, laboratory analyses including hematology, blood chemistries, liver function tests, an HIV antibody test, infectious disease panel and PPD test, and urine drug toxicology tests, adverse events, 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. If none of the screening assessments completed to this point exclude the subject from study participation, the subject will complete the screening infusion sessions on days 4 and 5.

11.3 Randomization and Enrollment

If the prospective subject meets all of the study inclusion criteria, does not meet the exclusion criteria, and has tolerated the screening cocaine infusions, then the subject can be enrolled into the study. The principal investigator or a study coordinator will contact the NIDA data-coordinating center to receive randomization assignment and enroll subjects. The data-coordinating center staff will review eligibility criteria, determine the subject treatment assignment, and notify the UCLA pharmacist of the subject treatment assignment. A blocked randomization schema will be used. If subjects are terminated before completing all of the cocaine infusion sessions, replacement subjects will be included until 8 subjects have completed the study from both treatment arms.

11.4 Cocaine Infusion Sessions

11.4.1 Schedule

Intravenous (i.v.) cocaine infusions will be conducted according to the schedule shown in Table 1. Each series of repeated administrations will consist of two infusion sessions over two days in one week. During the screening and baseline infusion assessments, the subject's responses to cocaine without concomitant tolcapone or placebo administration will be assessed. During the treatment infusion sessions, the subject's responses to cocaine with concomitant tolcapone or placebo administration will be assessed. Each infusion session will be on different days. The fixed ascending sequence each week is a safety precaution.

Table 1. Cocaine Infusion Session Schedule

Study Phase	Session Number	Study Day	Infusion
Screening	Session 1	4	saline followed by 20 mg cocaine 1 hr later
Screening	Session 2	5	saline followed by 40 mg cocaine 1 hr later
Baseline	Session 3	7	saline followed by 20 mg cocaine 1 hr later
Baseline	Session 4	8	saline followed by 40 mg cocaine 1 hr later
Treatment	Session 5	13	saline followed by 20 mg cocaine 1 hr later
Treatment	Session 6	14	saline followed by 40 mg cocaine 1 hr later
Treatment	Session 7	20	saline followed by 20 mg cocaine 1 hr later
Treatment	Session 8	21	saline followed by 40 mg cocaine 1 hr later

11.4.2 Conduct of Cocaine/Saline Infusion Sessions

A study physician will administer each intravenous infusion dose over a 60-second duration. During each session, the saline injection will occur at 4 p.m. approximately one hour after study agent administration. The cocaine injection will occur at 5:00 p.m. approximately two hours after study agent administration.

For a subject to receive the first 20 mg cocaine infusion dose (session # 1), s/he must have a have drug toxicology screening that shows negative urine drug/metabolite levels for drugs of abuse (except marijuana) on day 4 before conduct of cocaine infusion session. Subjects with positive urine drug toxicologies on day 4 will be discharged.

The screening cocaine infusions on days 4 and 5 are performed to ensure that volunteers are responsive to and safely tolerate the cocaine test doses; they are also for training and adaptation purposes. Only subjects responsive to and safely tolerating both test doses of cocaine will be randomized and enrolled on the study. The cocaine infusions on days 7 and 8 serve as a baseline reference point.

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. infusion, the subjects' physiologic response will be closely monitored using repeated HR, BP, and ECG readings. BP will be taken every 5 minutes for 15 minutes

before starting the saline infusion, and every 2 minutes for 30 minutes, then at 40, 50, 55, and 59 minutes after saline and cocaine infusions. In addition to these time points, BP will also be taken at 90, 120, 150, and 180 minutes after the cocaine infusion. ECG and HR will be monitored continuously for the first 30 minutes after each infusion. In addition, subjects will be monitored for at least 1-hour after the cocaine infusion by study personnel and GCRC staff. Thereafter, nursing staff will monitor participants and take vital signs at hourly intervals for up to a total of six hours after infusions.

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 cocaine, the cocaine 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.

Liver function tests will be conducted on study days 14 and 21 (all blood chemistries, including liver function tests, are performed on days 1 and 25). If liver function tests are not within normal limits on study day 14 (the subject should have received tolcapone at a dose of 100 mg t.i.d for 6 days), the subject will be immediately withdrawn from the receiving any additional investigational agents and will be terminated from continued participation in the study.

11.4.4 Stopping Criteria for Further Cocaine Infusion

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

1. Systolic BP > 165 mm Hg;
2. Diastolic BP > 100 mm Hg;
3. HR > 130 bpm;
4. Behavioral manifestation of cocaine 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 cocaine infusion do not return to acceptable limits within appropriate time frames (e.g., 30 minutes);
2. Stopping criteria for further cocaine 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;

11.4.6 Subjective Response

During and after the saline and cocaine infusions subjects' subjective response will be closely monitored. Computerized VAS will be administered 15 minutes before, and 1, 3, 6, 10, 15, 20, 30, 45, and 55 minutes after the first i.v. infusion and 3, 6, 10, 15, 20, 30, 60, and 90 minutes

after the second i.v. infusion. ARCI and Adjective Scales will be administered 15 minutes before and at 30 and 45 minutes after the first infusion and 30, 60, and 90 minutes after the second 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. If liver function tests are not within normal limits on study day 14, subjects will be immediately withdrawn from receiving any additional investigational agents and terminated from further participation in the study.

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 ECG, labwork, and baseline assessments, $15/day for participation and a completion bonus of $50. 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.

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 cocaine 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 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 cocaine (will be repeated until a positive test is obtained within 14 days prior to intake);
7. 5-lead ECG and vital signs (HR and BP);
8. For women of reproductive potential, a urine pregnancy test will be performed.

Inpatient Screening Assessments: The following evaluations will be performed on the day of intake into the GCRC and up to day 4 before randomization and enrollment:

1. Physical exam and medical history;
2. Vital signs: BP and HR;
3. Hematology;
4. Blood chemistries, including liver function tests;
5. Liver function tests;
6. HIV antibody test;
7. Infectious disease panel and PPD test;
8. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID);
9. Qualitative urine drug toxicology;
10. 12-lead ECG;
11. Pregnancy test for women of reproductive potential;
12. BDI, BSI, and POMS;
13. Wender Utah ADHD;
14. HRBS;
15. ASI-Lite;
16. Adverse Events;
17. 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 are performed every other day;
3. Adverse events starting on day 0.

12.3 Evaluations Performed During Infusion Sessions

Table 2 shows the series of activities that occur on days when cocaine infusion sessions are scheduled. Refer to Table 1 for the timing of the infusion sessions according to the study day. Note that not all activities occur at each infusion session. Those activities that do not occur at each infusion session are noted.

Table 2. Cocaine Infusion Sessions Daily Schedule

Timepoint	Activity (occurs at all sessions unless otherwise indicated)
7 a.m.	Administer tolcapone/placebo (sessions 5 through 8)
8 a.m.	BSI, BDI, POMS Urine Toxicology
9 a.m.	Draw blood for liver function tests (sessions 6 and 8)
2:55 p.m.	Insert catheters (catheter for blood may already be in place) Draw blood for tolcapone assay and COMT assay (sessions 5, 6, 7 & 8)
3:00 p.m.	Administer tolcapone or placebo
3 to 3:45 p.m.	Cue-induced assessments (sessions 5 & 7)
3:45 p.m.	Start continuous monitoring of ECG and HR
-15 min.	VAS, ARCI, Adjective Scale, BP
-10 min	BP
-5 min	BP
Time 0 saline	**Inject saline i.v. 1 min push**
1 min	VAS
2 min	BP
3 min	VAS
4 min	BP
6 min	VAS, BP
8 min	BP
10 min	VAS, BP
12 + 14 min	BP
15 min	VAS
16 + 18 min	BP
20 min	VAS, BP
22, 24, 26, 28 min	BP
30 min	VAS, ARCI, Adjective Scale, BP
40 min	BP
45 min	VAS, ARCI, Adjective Scale Draw blood for cocaine assay (sessions 4, 6 & 8) Draw blood for COMT assay (sessions 5, 6, 7 & 8)
50 min	BP
55 min	VAS, BP
59 min	BP
60 min	**Inject cocaine i.v. 1 min push**
62 min	BP
63 min	VAS
64 min	BP
65 min	Draw blood for cocaine assay (sessions 4, 6 & 8)
66 min	VAS, BP
68 min	BP
70 min	Draw blood for cocaine assay (sessions 4, 6 & 8)

Timepoint	Activity (occurs at all sessions unless otherwise indicated)
	VAS, BP
72 + 74 min	BP
75 min	VAS
76 + 78 min	BP
80 min	Draw blood for cocaine assay (sessions 4, 6 & 8) VAS, BP
82, 84, 86, 88 min	BP
90 min	Draw blood for cocaine assay (sessions 4, 6 & 8) VAS, ARCI, Adjective Scale, BP Stop continuous ECG and HR monitoring
100, 110, 115 min	BP
120 min	Draw blood for cocaine assay (sessions 4, 6 & 8) BP, VAS, ARCI, Adjective Scale BP, HR Neuropsychiatric measures subset (sessions 4 & 8)
150 min	Draw blood for cocaine assay (sessions 4, 6 & 8) VAS, ARCI, Adjective Scale, BP
180 min	Draw blood for cocaine assay (sessions 4, 6 & 8) BP, HR
210 min	BP
240 min	BP, HR
270 min	BP, HR
300 min	BP, HR Draw blood for cocaine assay (sessions 4, 6 & 8)
360 min	BP, HR
10:55 p.m. (415 min)	Draw blood for tolcapone assay (sessions 5, 6, 7 & 8)
11 p.m.	Administer tolcapone or placebo

12.4 Evaluations at Discharge (Day 25)

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 ECG;
5. Pregnancy test for women of reproductive potential.

12.5 Clinical and Laboratory Assessment Methods

12.5.1 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.

12.5.1.1 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 time of intake.

12.5.1.2 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.

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

This instrument will be administered at time of intake 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).

12.5.1.4 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 at intake.

12.5.1.5 HIV Risk-Taking Behavior Scale (HRBS)

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

12.5.2 Medical Assessments

12.5.2.1 Physical Exam

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

12.5.2.2 Medical History

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

12.5.2.3 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 1 minute), and standing blood pressure and pulse rate (standing 3 minutes).

12.5.3 Eligibility Checklist

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

12.5.4 Daily Surveys

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

12.5.4.1 Beck Depression Inventory (BDI)

The BDI is a 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 at baseline and continue to complete this questionnaire on an every other day basis, until the end of the study.

12.5.4.2 Brief Symptom Inventory (BSI)

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

12.5.4.3 Profile of Mood States (POMS)

The POMS is a questionnaire that measures dimensions of affect or mood. It consists of 65 adjectives to which the client responds according to a 5-point scale ranging from “not at all” to “extremely”. Subjects will start the measure at baseline and continue to complete this questionnaire on an every other day basis, until the end of the study.

12.5.4.4 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/mAMP). If qualitative urine test indicates the presence of a drug of abuse, quantitative tests may be performed to monitor the level.

12.5.5 Laboratory Tests

12.5.5.1 Hematology

Blood will be collected in anticoagulant containing vacutainer tubes for hematologic assessments. Analysis of hemoglobin, hematocrit, mean corpuscular volume, white blood cell count, differential white blood cell count and platelet count will be performed. Analyses will be performed in the institutions clinical laboratory. The laboratory performing these assessments should be either directly regulated by the College of Pathologists (CAP) or the Clinical Laboratory Improvement Act of 1988 (CLIA) or indirectly according to CLIA guidelines. The laboratory will need to provide a copy of current certification. Hematologic assessments will occur at intake and discharge.

12.5.5.2 Blood Chemistries/Liver Function Tests

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),and electrolytes (Na, K, Cl, HCO_3). Liver function tests will include 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 chemistries, including liver function tests, will be performed at intake and discharge. In addition, liver function tests will also be conducted on days 14 and 21.

12.5.5.3 Pregnancy Test

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

12.5.5.4 HIV Test

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

12.5.5.5 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.

12.5.6 Neuropsychiatric Assessments

Subjects will undergo repeated neuropsychiatric assessments during the study. These tests will be conducted approximately 1 hour after cocaine administration or at the same time of day on days when cocaine is not administered. An extensive baseline evaluation will be performed on day 6, consisting of all of the measures listed below. Follow-up assessments will be performed on days 8, 19, and 21. These assessments will include the Simple Reaction Time Test, Covert Orienting Test, and n-back tests. In addition, on day 19, 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

12.5.7 Monitoring and Assessments During Cocaine Infusion Sessions

12.5.7.1 Blood Sample Collections

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

An intravenous catheter will be inserted for each infusion session, and can be maintained in place for the two consecutive days of infusion sessions, if the subject wishes. Two intravenous catheters will be placed for infusion sessions that involve repeated blood draws (days 8, 14, and 21): one will be for cocaine administration, the other for blood sample collection.

Samples will be collected for assessment of cocaine pharmacokinetics on days 8, 14, and 21 in 10 cc grey-stoppered Vacutainer™ tubes containing sodium fluoride and potassium oxalate. In order to assess tolcapone pharmacokinetics, peak and trough levels, blood will be collected in heparin-containing green-stoppered Vacutainer™ tubes on days 13, 14, 20, and 21.

The total blood loss during the study (295 mL) will be approximately 0.59 times the volume of a standard blood bank donation.

12.5.7.2 Physiology

Before and after each i.v. infusion, the subject's physiologic response will be closely monitored using repeated HR, BP, and ECG readings. BP, HR, and ECG will be measured using a "Spacelabs PC Scout" telemetry unit. BP will be taken every 5 minutes for 15 minutes before saline infusion, and every 2 minutes for 30 minutes, then at 40, 50, 55, 59 minutes after both the saline and cocaine infusions, and, in addition, 90, 120, 150, 180, 210, 240, 300, and 360 minutes after the cocaine infusion. ECG and HR will be monitored continuously for the first 30 minutes after infusion and will be stored to computer disk. Subjects will be monitored for at least 1 hour after the cocaine injection by study personnel and GCRC staff.

12.5.7.3 Subjective Response

During and after the saline and cocaine infusions subjects' subjective response will be closely monitored. Computerized VAS will be administered 15 minutes before, and 1, 3, 6, 10, 15, 20, 30, 45, and 55 minutes after the saline i.v. infusion and 3, 6, 10, 15, 20, 30, 60, and 90 minutes after the cocaine i.v. infusion. For these scales, subjects will report the degree to which they feel "any drug effect", "high", "good effects", "bad effects", "like cocaine", "desire for cocaine", "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 15 minutes before and at 30 and 45 minutes after the saline infusion and 30, 60, and 90 minutes after the cocaine 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".

12.5.8 Assessment of Cue-Induced Craving

On days 13 and 20, prior to the cocaine infusion, subjects will view a videotape that depicts actors handling and using cocaine (active cues). Subjects will be shown a neutral video that shows scenes unrelated to drug use, on day 12. Before and following exposure to the cues, subjects will rate their using the "general craving scale" and the "within session rating scale". These two instruments assess mood states and the degree to which subjects report craving.

Immediately following the craving and subjective ratings of the Cue Procedure cue, subjects will complete the Multiple Choice Questionnaire (MCQ). The MCQ is a paper and pencil questionnaire assessing the choice preference for or motivation to use a drug by asking subjects to respond to a series of choices between receiving a drug or a designated amount of money. Subjects will indicate their relative preference for a second cocaine injection versus varying amounts of money.

12.5.9 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.

12.5.10 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.

12.5.11 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, cocaine and tolcapone. There is extensive experience with these cocaine infusion procedures and they appear to be safe. The doses used are modest, the exposure periods to the agents are brief, the safety screening and monitoring are careful, and there have been no significant prior adverse events with these procedures. Tolcapone is a marketed product with which there is extensive experience and little indication of significant risk other than the 3 cases of fatal fulminant hepatic failure out of 60,000 patients providing 40,000 patient years of worldwide use. However, it is possible that the dopaminergic activities of both cocaine and tolcapone might be additive or greater when they are given together. The ascending order of cocaine doses is one protection against this risk. There is the risk of a breach of confidentiality regarding study records, but this is unlikely, since staff are well-trained and experienced in this area.

The study does not offer direct therapeutic benefit to participants. But, because it is directed toward the identification and development of effective treatment for cocaine 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 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. The International Conference on Harmonization (ICH) Guideline for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH-E2A March 1995, as implemented by the U.S. Food and Drug Administration

defines serious adverse event (SAE) or reaction as any untoward medical occurrence that at any dose:

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

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

Any SAEs due to any cause, that occur during the course of this investigation, whether or not related to the investigational agent, must be reported within 24-hours by telephone to: the Study Medical Monitor, the NIDA Project Officer, and the sponsor-investigator. The telephone report is to be followed 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 follow-up written report must be submitted in 8 days to the FDA. All AEs that are both serious and unexpected but not life-threatening or lethal must be reported to the FDA, in writing, within 15 calendar days of notification of the sponsor-investigator of the SAE. All other SAEs will be reported in an annual report or more frequently as necessary. Any additional clinical information that is obtained must be reported to the FDA, as it becomes available in the form of an information amendment. The sponsor-investigator will inform NIDA of all SAEs that occur during the study.

There can be serious consequences including ultimately, criminal and/or civil penalties for sponsors who fail to comply with FDA regulations governing the reporting of SAEs to FDA. The study investigators in this study have the responsibility of promptly reporting all SAEs to NIDA and the 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 tolcapone concurrent with cocaine infusions of 20 mg and 40 mg i.v. The primary outcome measures are cardiovascular responses (HR, BP) to the i.v. cocaine infusions.

14.3 Secondary Outcome Measures

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

1. Peak and trough plasma levels of tolcapone.
2. Pharmacokinetic parameters of cocaine and BE including Cmax, Tmax, AUC, apparent $t_{½}$, and CL, F, V, and k.
3. Erythrocyte COMT.
4. ECG effects.
5. Craving for cocaine, assessed using a laboratory cue exposure paradigm.
6. Psychological assessments including VAS, ARCI, and Adjective Scale.
7. Mood and personality assessments (BSI, BDI, and POMS).
8. Adverse events.

14.4 Analysis Plan

14.5 Primary Outcome Measures

Baseline (pre-cocaine) resting HR and BP measures will be compared to HR and BP after each cocaine injection (saline followed by 20 mg or 40 mg dose of cocaine). Changes (from baseline) in HR and BP induced by cocaine injection along with tolcapone will be compared to those without tolcapone, by cocaine dose level, using repeated measures ANOVA.

14.6 Secondary Outcome Measures

Plasma concentration-time profiles of cocaine after each cocaine injection will be analyzed to obtain pharmacokinetic parameter estimates of cocaine (Cmax, Tmax, AUC, apparent $t_{½}$, CL, F, V, and k) by individual and means computed by group with data from the two post treatment infusions being averaged by subject. Comparisons of pharmacokinetic parameter estimates of cocaine between the control and tolcapone phases will be performed for the 40 mg cocaine 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 cocaine between the two treatment arms, pharmacokinetic parameters between the two arms will also be compared during the baseline 40 mg cocaine infusion (session 4).

Changes in ECG readings will be reported as summary statistics. Psychological outcome measures (including VAS, adjective scales and ARCI) obtained during baseline will be compared, by cocaine dose level, to those collected during tolcapone treatment to determine the extent to which these measures are modified by the administration of tolcapone using repeated measures ANOVA.

Changes in erythrocyte COMT levels will be compared before and after cocaine administration by t-tests at each dose of cocaine.

Changes in BSI, BDI, and POMS scores will be compared before and after tolcapone administration using repeated measures ANOVA or generalized estimating equations.

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

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 which will be entered at the site into electronic case report forms (eCRFs). The eCRFs will be supplied by the NIDA data coordinating center. eCRFs are to be completed on an ongoing basis during the study. The medical chart and the source documents are the source of verification of data. eCRFs should be completed according to the instructions in the study operations manual. The 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 which 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 <u>all</u> 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, eCRFs, reports and other records will be identified by a coded study subject number only. Research and clinical records will be stored in a locked cabinet. Only research staff and NIDA program officials will have access to the records. Subject information will not be released without written permission, except as necessary for monitoring by the FDA, NIDA monitoring contractor or NIDA. Upon approval of the study by an IRB, an application will be filed with NIDA for a certificate of confidentiality.

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

The 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

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 tolcapone for the treatment for cocaine dependence may not be submitted for publication until the main findings of the study have been published and this study has been accepted by the FDA for filing to the IND or NDA.

17 SIGNATURES

NIDA REPRESENTATIVE

Typed Name	Signature	Date
Jurij Mojsiak, M.S. NIDA Project Officer	_____	_____
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 13.7 of this protocol.

Typed Name	Signature	Date
Thomas Newton, M.D. Principal Investigator	_____	_____

18 LITERATURE CITED

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Appendix I: Time and Events Schedule

Study Phase	**Screening/Baseline Infusions**						**Treatment Assessments/Cocaine Infusions**										
		Intake															
Study day	**-14 to 0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Informed consent	X																
Locator form/Demographics	X																
SUI	X	X[a]															
5-lead ECG	X																
12-lead ECG		X[a]															
SCID		X[a]															
Medical History/Physical Exam		X[a]															
ASI-Lite, HRBS, Wender Utah ADHD		X[a]															
Vital Signs		X[a]															
Chemistries		X[a]															
Liver Function Tests															X		
Hematology		X[a]															
Pregnancy Test	X	X[a]															
HIV Test		X[a]															
Infectious Disease Panel and PPD Test		X[a]															
Urine Toxicology Screen	X	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BSI, BDI, POMS		X[a]		X		X		X		X		X		X		X	
100 mg oral tolcapone or placebo t.i.d.									X[b]	X	X	X	X	X	X		
200 mg oral tolcapone or placebo t.i.d.															X[b]	X	X
Tolcapone Blood Levels														2X	2X		
Neuropsychiatric Assessments							X		X								
Erythrocyte COMT														2X	2X		
Cue Exposure													X	X			
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cocaine Infusion Session #					**1**	**2**		**3**	**4**					**5**	**6**		
Saline/20 mg cocaine iv					X			X						X			
Saline/40 mg cocaine iv						X			X						X		
VAS					18X	18X		18X	18X					18X	18X		
Continuous BP, HR, ECG Monitoring					X	X		X	X					X	X		
ARCI, Adj Scale					6X	6X		6X	6X					6X	6X		
Cocaine Blood PK									9X						9X		

X[a] - Intake assessments can be performed any time between days 1 and 4 before starting baseline infusions.
X[b] – Starting at the evening dose.

Appendix I: Time and Events Schedule Continued

Study Phase	**Treatment Infusions**								**Discharge**	**Follow-up**	
Study day	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**32**	**39**
12-lead ECG									X		
Vital Signs									X		
Chemistries									X		
Liver Function Tests					X						
Hematology									X		
Pregnancy Test									X	X	
Urine Toxicology Screen	X	X	X	X	X	X	X	X	X		
BSI, BDI, POMS	X		X		X		X		X		
200 mg oral tolcapone or placebo t.i.d.	X	X	X	X	X						
Tolcapone Blood Levels				2X	2X						
Neuropsychiatric assessments			X		X						
Erythrocyte COMT				2X	2X						
Cue Exposure				X							
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Cocaine Infusion Session #				**7**	**8**						
Saline/20 mg cocaine iv				X							
Saline/40 mg cocaine iv					X						
Continuous BP, HR, ECG Monitoring				X	X						
VAS				18X	18X						
ARCI, Adj Scale				6X	6X						
Cocaine Blood PK					9X						

APPENDIX II: Schedule of Blood Collections

Analyte	Volume per sample	Type[a]	a.m./ p.m.	Time (minutes) relative to saline infusion (cocaine infusion starts at 60 minutes after saline infusion)												Total Volume over study
				-30	30	45	65	70	80	90	120	150	180	300	415	
Days 1 & 25																
Hematology	10 ml	P	X													20 mL
Blood Chemistry	10 ml	S	X													20 mL
Day 1																
Infectious Diseases/HIV	2x10 ml	S														20 mL
Days 14 and 21																
Liver Function Tests	10 ml	S	X[c]													20 mL
Days 13, 14, 20 & 21																
Tolcapone Blood Level	5 ml	P	X[b]												X	40 mL
Days 8, 14 & 21																
Cocaine PK	5 ml	P				X	X	X	X	X	X	X	X	X		135 mL
Days 13, 14 & 20, 21																
COMT	5 ml	P	X[b]			X										40 mL
Total Volume of Blood Collected																**295 mL**

[a]Sample type is P = plasma; S = serum
[b]Sample collected at 2:55 p.m. before tolcapone administration.
[c]Blood for liver function tests on days 14 and 21 will be drawn at 9:00 a.m.

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 (byRespirace) 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/cocaine 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/ cocaine infusion.

For Stable Ventricular Tachycardia*:
1) Apply oxygen at 100%
2) Apply synchronized cardioversion, start with 50 joules (J). If no response go to 100 J, if still no response go to 200 J.
3) Give Lidocaine 1 mg/kg I.V. bolus, followed by Lidocaine drip 2 mg/min
*if patient pulseless treat as ventricular fibrillation.

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

EQUIPMENT AND SUPPLIES

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

PROCEDURE:

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

3. Apply large posterior pad just below scapula and the smaller anterior pad over the cardiac apex with the flat edge of half circle toward head.
To apply pad, adhere one edge of the pad, then tightly roll pad into place, pressing over adhesive area only.

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) <u>Ventricular Extrasystoles</u>

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

b) Procedure: Discontinue study drug/ cocaine 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) <u>Bradycardia-Severe</u>

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/ cocaine infusion. Give Atropine 1 mg I.V. push and obtain ECG rhythm strip.

5) Ventricular Asystole

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

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

6) Sinus Tachycardia

a) Recognition: From continuous pulse monitoring, pulse elevated over 160 BPM.
b) Procedure: immediately stop study drug/ cocaine 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/ cocaine 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/ cocaine 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/ cocaine infusion. Note heart rate and blood pressure and treat with Labetolol if significantly elevated (parameters above). Give sublingual nitroglycerine 0.4 mg and Lorazepam 2 mg IV Push and review 12 lead ECG for evidence of myocardial ischemia. If chest pain persist give Phentolamine 1 mg IV or Verapamil 5 mg IV over 3 minutes.

(v) Hypotension

a) Recognition: Drop in blood pressure to below 90/50 or subjective complaints of dizziness or fatigue associated with drop in blood pressure from baseline.
b) Procedure: Discontinue study drug/ cocaine 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 Cocaine/Cocaine Metabolite Levels and Tolcapone/Tolcapone 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 appropriate Vacutainers (see section 12.5.7.1 of the protocol):

   a. Draw blood and invert tube 8-10 times.
   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 labels to affix to vials. The following is a sample label:

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 for all randomized subjects. Ship plasma samples at arranged intervals 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 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 data coordinating center/data management center and retain the other copy in the Specimen Shipping Log Binder.

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

8. Apply "biohazard" label to container.

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 testing laboratory to expect shipment.

Plasma Sample Shipping Log

Study No.: _____

Center No.:_____

Investigator:_____

Contact Person:_____ Phone Number:_____

Shipment Date_____/_____/_____
Month Day Year

1 Subject Initials	2 Subject No.	3 Date of Collection (mo/day/yr)	4 Time of Collection (24 hr clock)	5 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 starting on day 0.

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:

- ***Unrelated:***
  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.

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

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

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

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

D. SPECIFIC INSTRUCTIONS – LABORATORY/ECG ADVERSE EVENT

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

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

E. SERIOUS ADVERSE EVENT AND UNEXPECTED ADVERSE EVENT REPORTING

24 hour Reporting Requirements

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

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

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

3-day Supporting Documentation Requirements

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

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

Follow-Up of All Adverse Events/Serious Adverse Events

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

adverse events occurring 30 days after administration of the last dose of study drug/placebo must be reported.

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

Reporting to the FDA

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

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

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

- in an annual report in all other cases.