Cognitive-enhancing DA Medications for Cocaine Dependence

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STUDY #: 64
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IRB NUMBER: HSC-MS-10-0510

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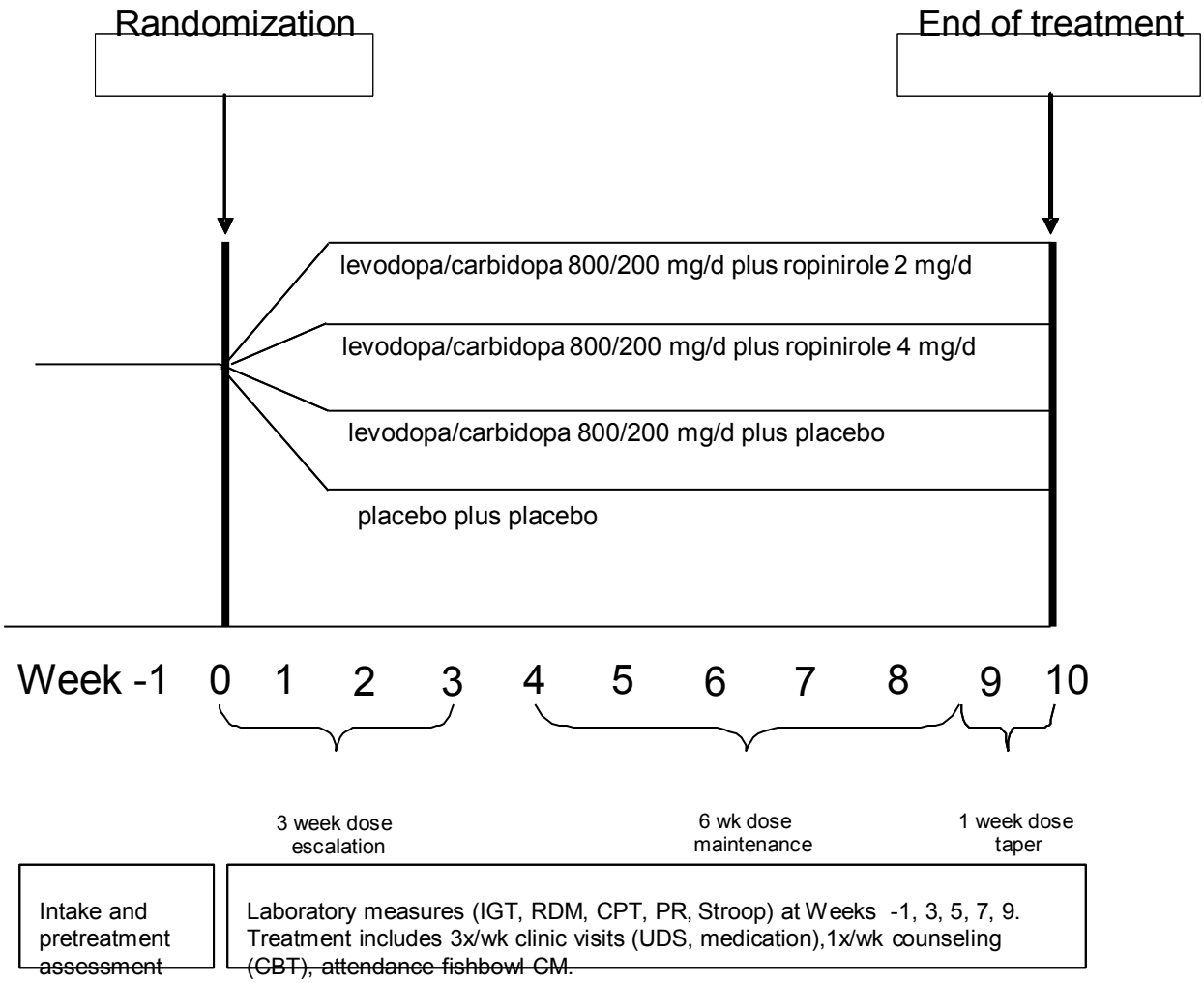
1. ABSTRACT/STUDY DIAGRAM

Most cocaine dependent patients suffer from deficits in cognitive function that, if left untreated, predict poor outcome. **Purpose**: The present study investigates a pharmacotherapeutic intervention designed to improve cocaine treatment success by combining medications that act simultaneously on dopamine, the brain system that is critically associated with chronic cocaine use and cognitive functions. **Procedures**: Treatment with levodopa/carbidopa plus ropinirole (tested at two doses) will be compared to levodopa/carbidopa alone, and placebo. Measurement of performance on behavioral/cognitive measures of decision-making, behavioral inhibition, reward motivation, and attentional bias will be conducted at treatment entry and at repeated time points during the 10-week treatment. It is hypothesized that treatment with levodopa/carbidopa + ropinirole will produce superior outcomes in terms of reduced cocaine use and increased treatment retention and that these effects will occur indirectly via improved performance on observed cognitive mechanisms. **Course of Study**: Eligible cocaine dependent patients will be randomized equally to one of four medication conditions. Outpatient treatment will last 10 weeks and consist of thrice-weekly clinic visits. The behavioral therapy platform for this trial will consist of weekly cognitive behavioral therapy (CBT). The primary outcome measure will be weekly mean proportion of cocaine non-use days. Secondary endpoints will include abstinence rates during the last 2 weeks of treatment, time in study, and medication compliance. **Enrollment**: This project requires a final intent-to-treat sample size of 200 subjects. To obtain this sample, we expect to conduct phone screens on ~ 640 individuals, of whom 320 (50%) will qualify, enroll, and start intake. Of the 320 who start intake, we expect that 200 (~60%) will complete intake and be randomized into the ITT sample. Based on these projections and recruitment rates achieved during our previous levodopa studies, 40 months will be allotted to complete study enrollment (~ 5 new subjects/month). **Recruitment**: Adult (18-55yo) men and women of all ethnic backgrounds will be recruited to participate. Participants will be non-hospitalized, self-referred persons who call in response to various advertising strategies, including newspaper/newsletter articles and announcements, public service announcements on television and radio, notices mailed to local professionals, city-wide billboards, and posters located throughout the local community. **Known Risks**: The known risks associated with the study medications (levodopa/carbidopa, ropinerole) inlude potential side effects but these are deemed minimal and will be clearly listed in the informed consent form. **Data Safety Monitoring**: This trial will adhere to general data and safety monitoring procedures. A DSM Board will be formed to provide additional, independent oversight of data related to patient safety. **IND#:** N/A. **Proposed Funding Source**: National Institute on Drug Abuse (NIDA). **Communication of Study Results**: Study results will be communicated at national scientific meetings and to all oversight entities, e.g., NIDA, IRB.



2. INFORMED CONSENT FORM

IRB NUMBER: HSC-MS-10-0510
IRB APPROVAL DATE: 9/2/2011

3. KEY STUDY PERSONNEL

Principal Investigator:	Joy Schmitz, PH.D.
Co Principal Investigator:	Scott Lane, PH.D.
Co-Investigators:	F. Gerard Moeller, MD
	Charles Green, PH.D.
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

4. DESCRIPTION OF STUDY POPULATION

4.1 INCLUSION CRITERIA

1. be between 18 and 55 years of age
2. meet DSM-IV criteria for current cocaine dependence
3. have at least 1 positive urine benzoylecgonine (BE) specimen (> 300 ng/mL) during intake
4. be in acceptable health on the basis of interview, medical history and physical exam
5. be able to understand the consent form and provide written informed consent
6. be able to provide the names of at least 2 persons who can generally locate their whereabouts.

4.2 EXCLUSION CRITERIA

1. current DSM-IV diagnosis of any psychoactive substance dependence other than cocaine or nicotine
2. have a DSM-IV axis I psychiatric disorder or neurological disease or disorder requiring ongoing treatment and/or making study participation unsafe
3. have cognitive impairment due to non-substance related factors (e.g., history of stroke, transient ischemic attacks, mental retardation, epilepsy, head injury)
4. significant current suicidal or homicidal ideation
5. medical conditions contraindicating levodopa/carbidopa or ropinirole pharmacotherapy (e.g., evidence of any movement disorder, clinically significant pulmonary disease, cardiovascular disease, liver or kidney disease, seizure disorder)
6. taking CNS active concomitant medications
7. taking medications known to have significant drug interactions with the study medication(s) (e.g., CYP P-450-2D6 inhibitors, such as tamoxifen, iron salts, pyridoxine, monoamine oxidase inhibitors, phenothiazines, selegiline, anesthetics)
8. currently or recently (last 3 months) treated for substance use or another psychiatric condition
9. having conditions of probation or parole requiring reports of drug use to officers of the court
10. impending incarceration
11. pregnant or nursing for female patients
12. inability to read, write, or speak English
13. having plans to leave the immediate geographical area within 3 months
14. unwillingness to sign a written informed consent form.

5. STRATEGIES FOR RECRUITMENT AND RETENTION

The study will be conducted at the outpatient Treatment Research Clinic (TRC), a component of the Department of Psychiatry and Behavioral Sciences Center for Neurobehavioral Research on Addictions (CNRA). Participants will be non-hospitalized, self-referred persons who call in response to various advertising strategies, including newspaper/newsletter articles and announcements, public service announcements on television and radio, notices mailed to local professionals, city-wide billboards, and posters located throughout the local community.

6. STUDY INTERVENTIONS

6.1 STUDY DRUG #1

Levodopa. The drug, levodopa (L-3,4-dihydroxyphenylalanine), is a dopamine precursor. It is combined with a decarboxylase inhibitor, which prevents the levodopa from being metabolized in the peripheral circulation before it reaches the brain. Levodopa with the decarboxylase inhibitor carbidopa (trade name Sinemet), is a highly effective symptomatic treatment for the motor disability of Parkinson's disease, a condition characterized by loss of dopaminergic function primarily in the substantia nigra. Similar to other agents used in the treatment of Parkinson's disease and also studied as potential cocaine medications (e.g., amantadine, selegiline), levodopa increases extracellular dopamine and dopamine transmission. Levodopa/carbidopa pharmacotherapy is safe and well tolerated in cocaine dependent outpatients.

Participants assigned to a levodopa/carbidopa condition will receive the sustained release formulation (Sinemet CR), titrated according to schedule below. The dosage and titration schedule have been used in our previous levodopa trials

6.2 STUDY DRUG #2

Ropinirole. The drug, ropinirole, is a DA (primarily type D_2 and D_3) receptor agonist used in the treatment of Parkinson's disease. Preliminary studies suggest that ropinirole is safe, and may reduce cocaine use. In an open-label trial (Meini et al., 2008), 39 subjects with cocaine dependence received ropinirole at 1.5 mg/day for 12 weeks. Average rates of benzoylecgonine-positive urines decreased from 90.2% at baseline to 17.8% at week 6. Twelve subjects achieved sustained cocaine abstinence for up to 10 weeks.

Participants assigned to a medication combination condition will also receive ropinirole in the extended-release formulation (REQUIP XL™), with a one-week dose titration schedule to reach fixed dose levels of 2.0 mg/d or 4.0 mg/d, depending on study condition. These doses were chosen based on a previous study of ropinirole in cocaine dependence and dosage titration recommended for Parkinson's disease to minimize risk of side effects (REQUIP XL™ prescribing information) (see titration schedule, below).

6.3 PLACEBO

Placebo. We will use a matched placebo procedure for maintaining the blind. Placebo capsules will be identical in size, color, coating and shape to the active study medication. All placebos will be packed in capsules with riboflavin added and contained in a blister pack affixed with patient instructions. Participants in all conditions will take the same number of capsules at the same scheduled times (morning/evening) per day throughout treatment. Participants will take one matching placebo twice per day, at the same time they take their active study medication.

6.4 MEDICATION DISPENSING

At each clinic visit (MWF) subjects will be administered the medication at the dispensing window and given take-home doses for intervening days. Riboflavin (50mg) will be added to the medication (and placebo) capsules and used as a marker to monitor compliance. We will use a double-dummy method involving a matched placebo for each of the two medications. Placebo capsules will be identical in size, color, coating and shape. Participants in all conditions will take the same number of capsules at the same scheduled times (morning/evening) per day throughout treatment. Participants in the single medication condition will take one matching placebo twice per day, at the same time they take their active study medication. Participants in the placebo group will take two matching placebos twice per day. This method, along with additional strategies used in our clinic to protect the integrity of blindness, will be applied.

Placebo + placebo

	Wk1	Wk2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8	Wk9	Wk10
L-dopa/carb	0	0	0	0	0	0	0	0	0	0
ropinirole	0	0	0	0	0	0	0	0	0	0
Total l-dopa/carb ropinirole	0mg 0 mg	0mg 0 mg	0mg 0 mg	0mg 0 mg	0mg 0 mg	0mg 0 mg	0mg 0 mg	0mg 0 mg	0mg 0 mg	0mg 0 mg
Morning dose	1 capsule placebo ; 1 capsule placebo	1 capsule placebo ; 1 capsule placebo	1 capsule placebo ; 1 capsule placebo	1 capsule placebo ; 1 capsule placebo	1 capsule placebo ; 1 capsule placebo	1 capsule placebo ; 1 capsule placebo	1 capsule placebo ; 1 capsule placebo	1 capsule placebo ; 1 capsule placebo	1 capsule placebo ; 1 capsule placebo	1 capsule placebo ; 1 capsule placebo
Evening dose	1 capsule placebo; 1 capsule placebo	1 capsule placebo ; 1 capsule placebo	1 capsule placebo ; 1 capsule placebo	1 capsule placebo ; 1 capsule placebo	1 capsule placebo ; 1 capsule placebo	1 capsule placebo ; 1 capsule placebo	1 capsule placebo ; 1 capsule placebo	1 capsule placebo ; 1 capsule placebo	1 capsule placebo ; 1 capsule placebo	1 capsule placebo ; 1 capsule placebo
Total pills	4	4	4	4	4	4	4	4	4	4
	Run-up			Maintenance						Run-down

Comments: High dose condition (ldopa/carbidopa + ropinirole 4 mg/d) has option to hold ropinirole dose at 2 mg/d if tolerability issues.
Blood pressure monitoring at every clinic visit.

Levodopa-carbidopa 800/200 mg/d + placebo

	Wk1	Wk2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8	Wk9	Wk10
L-dopa/carb	200/50 x 2	400/100 x 2	400/100 x 2	400/100 x 2	400/100 x 2	400/100 x 2	400/100 x 2	400/100 x 2	400/100 x 2	200/50 x 2
ropinirole	0	0	0	0	0	0	0	0	0	0
Total l-dopa/carb ropinirole	400/100 0 mg	800/200 0 mg	800/200 0 mg	800/200 0 mg	800/200 0 mg	800/200 0 mg	800/200 0 mg	800/200 0 mg	800/200 0 mg	400/100 0 mg
Morning dose	1 capsule containing 2-200/50 tablets; 1 capsule placebo	1 capsule containing 2-200/50 tablets; 1 capsule placebo	1 capsule containing 2-200/50 tablets; 1 capsule placebo	1 capsule containing 2-200/50 tablets; 1 capsule placebo	1 capsule containing 2-200/50 tablets; 1 capsule placebo	1 capsule containing 2-200/50 tablets; 1 capsule placebo	1 capsule containing 2-200/50 tablets; 1 capsule placebo	1 capsule containing 2-200/50 tablets; 1 capsule placebo	1 capsule containing 2-200/50 tablets; 1 capsule placebo	1 capsule containing 2-200/50 tablets; 1 capsule placebo
Evening dose	1 capsule placebo; 1 capsule placebo	1 capsule containing 2-200/50 tablets; 1 capsule placebo	1 capsule containing 2-200/50 tablets; 1 capsule placebo	1 capsule containing 2-200/50 tablets; 1 capsule placebo	1 capsule containing 2-200/50 tablets; 1 capsule placebo	1 capsule containing 2-200/50 tablets; 1 capsule placebo	1 capsule containing 2-200/50 tablets; 1 capsule placebo	1 capsule containing 2-200/50 tablets; 1 capsule placebo	1 capsule containing 2-200/50 tablets; 1 capsule placebo	1 capsule placebo; 1 capsule placebo
Total pills	4	4	4	4	4	4	4	4	4	4
	Run-up			Maintenance						Run-down

Levodopa-carbidopa 800/200 mg/d + ropinirole 2 mg/d

	Wk1	Wk2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8	Wk9	Wk10
L-dopa/carb	200/50 x 2	400/100 x 2	400/100 x 2	400/100 x 2	400/100 x 2	400/100 x 2	400/100 x 2	400/100 x 2	400/100 x 2	200/50 x 2
ropinirole	0 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	0 mg
Total L-dopa/carb ropinirole	400/100 0 mg	800/200 2 mg	800/200 2 mg	800/200 2 mg	800/200 2 mg	800/200 2 mg	800/200 2 mg	800/200 2 mg	800/200 2 mg	400/100 0 mg/d
Morning dose	1 capsule containing 2-200/50 tablets; 1 capsule containing placebo	1 capsule containing 2-200/50 tablets; 1 capsule containing placebo	1 capsule containing 2-200/50 tablets; 1 capsule containing placebo	1 capsule containing 2-200/50 tablets; 1 capsule containing placebo	1 capsule containing 2-200/50 tablets; 1 capsule containing placebo	1 capsule containing 2-200/50 tablets; 1 capsule containing placebo	1 capsule containing 2-200/50 tablets; 1 capsule containing placebo	1 capsule containing 2-200/50 tablets; 1 capsule containing placebo	1 capsule containing 2-200/50 tablets; 1 capsule containing placebo	1 capsule containing 2-200/50 tablets; 1 capsule containing placebo
Evening dose	1 capsule placebo; 1 capsule placebo	1 capsule containing 2-200/50 tablets; 1 capsule 2mg requip	1 capsule containing 2-200/50 tablets; 1 capsule 2mg requip	1 capsule containing 2-200/50 tablets; 1 capsule 2mg requip	1 capsule containing 2-200/50 tablets; 1 capsule 2mg requip	1 capsule containing 2-200/50 tablets; 1 capsule 2mg requip	1 capsule containing 2-200/50 tablets; 1 capsule 2mg requip	1 capsule containing 2-200/50 tablets; 1 capsule 2mg requip	1 capsule containing 2-200/50 tablets; 1 capsule 2mg requip	1 capsule placebo; 1 capsule placebo
Total pills	4	4	4	4	4	4	4	4	4	4
	Run-up			Maintenance						Run-down

Levodopa-carbidopa 800/200 mg/d + ropinirole 4 mg

	Wk1	Wk2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8	Wk9	Wk10
L-dopa/carb	200/50 x 2	400/100 x 2	400/100 x 2	400/100 x 2	400/100 x 2	400/100 x 2	400/100 x 2	400/100 x 2	400/100 x 2	200/50 x 2
ropinirole	0	2 mg	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg	2 mg
Total l-dopa/carb ropinirole	400/100 0 mg	800/200 2 mg	800/200 4 mg	800/200 4 mg	800/200 4 mg	800/200 4 mg	800/200 4 mg	800/200 4 mg	800/200 4 mg	400/100 2 mg
Morning dose	1 capsule containing 2-200/50 tablets; 1 capsule containing placebo	1 capsule containing 2-200/50 tablets; 1 capsule containing placebo	1 capsule containing 2-200/50 tablets; 1 capsule containing placebo	1 capsule containing 2-200/50 tablets; 1 capsule containing placebo	1 capsule containing 2-200/50 tablets; 1 capsule containing placebo	1 capsule containing 2-200/50 tablets; 1 capsule containing placebo	1 capsule containing 2-200/50 tablets; 1 capsule containing placebo	1 capsule containing 2-200/50 tablets; 1 capsule containing placebo	1 capsule containing 2-200/50 tablets; 1 capsule containing placebo	1 capsule containing 2-200/50 tablets; 1 capsule containing placebo
Evening dose	1 capsule placebo; 1 capsule placebo	1 capsule containing 2-200/50 tablets; 1 capsule 2mg requip	1 capsule containing 2-200/50 tablets; 1 capsule 4mg requip	1 capsule containing 2-200/50 tablets; 1 capsule 4mg requip	1 capsule containing 2-200/50 tablets; 1 capsule 4mg requip	1 capsule containing 2-200/50 tablets; 1 capsule 4mg requip	1 capsule containing 2-200/50 tablets; 1 capsule 4mg requip	1 capsule containing 2-200/50 tablets; 1 capsule 4mg requip	1 capsule containing 2-200/50 tablets; 1 capsule 4mg requip	1 capsule placebo; 1 capsule 2mg requip
Total pills	4	4	4	4	4	4	4	4	4	4
	Run-up			Maintenance						Run-down

6.5 NON MEDICATION INTERVENTIONS

Cognitive Behavioral Therapy (CBT). Participants will receive individual CBT in 50-minute weekly sessions. Including CBT will allow us to replicate the behavioral therapy condition that proved most efficacious when used previously in our levodopa and citalopram trials. Cognitive-behavioral therapy is based on the model of relapse proposed by Marlatt and Gordon. The model regards coping skills training as the key component for avoiding drug use and preventing relapse. Skills training techniques include (1) self-monitoring and functional analysis of situational factors associated with craving or drug use; (2) learning alternative non-drug responses for handling high risk situations; and (3) general lifestyle modifications (e.g., increasing pleasant drug-free events, anger management, interpersonal skills, general problem-solving). An unpublished treatment manual written by J. Schmitz (PI) and implemented in several completed studies, closely parallels the treatment content found in other published CBT manuals. All CBT sessions will be audio-taped for adherence and competence ratings using recommended procedures done in all our treatment studies. Weekly supervision will be held by a designated clinical supervisor who will provide feedback to keep CBT delivery consistent and prevent drift.

Prize-based attendance CM (Contingency Management). During Treatment, for each visit attended, subjects will earn a draw from the attendance voucher "fishbowl". The fishbowl has 500 slips in it. Many of the slips have a value of $1, some have a value of $25, one slip is worth $100, and half of the slips just say "Good Job". Subjects will earn 5 bonus draws for each week in which all 3 visits in a week (that is, Monday, Wednesday, and Friday) are attended. Vouchers for the $25 and $100 value slips will be given in the form of a gift card. For the $1 slips, $1 in cash or a voucher will be given.

The schedule of fishbowl draws for attendance and compliance is shown in Table 1 below.

Table 1. Draw Schedule

Week	1			2			3			4			5		
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Draws	1	1	1	2	2	2	3	3	3	4	4	4	5	5	5
Bonus			5			5			5			5			5
Total Draws	1	1	6	2	2	7	3	3	8	4	4	9	5	5	10

Week	6			7			8			9			10		
Visit	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Draws	6	6	6	7	7	7	8	8	8	9	9	9			
Bonus			5			5			5			5			
Total Draws	6	6	11	7	7	12	8	8	13	9	9	14			

Week	11			12			13			
Visit	31	32	33	34	35	36	37	38	39	
Draws										
Bonus										**Total: 180 Draws**
Total Draws										

7. STUDY SCHEDULE

7.1 GENERAL EVALUATION INTAKE

Treatment-seeking individuals will undergo the CNRA general evaluation protocol (HSC-MS-05-0322). Those who complete this protocol will be eligible for Study 64, based on random allocation to study method.

7.2 STUDY SPECIFIC

7.2.1 ENROLLMENT/RANDOMIZATION

An urn randomization procedure will be used to assign subjects to one of the four treatment groups. This procedure will balance groups on important pretreatment characteristics that may influence measures of cognitive performance and/or treatment outcome. The variables will include (1) severity of cocaine dependence, based on days using cocaine in past 30; (2) baseline (trait) impulsivity score, based on the Barratt Impulsiveness Scale (BIS). The BIS was chosen as a variable for the urn randomization because it has norms for high and low impulsivity in cocaine users based on previous studies and has been predictive of treatment retention.

Treatment assignment will be concealed to all clinical and research staff, including the investigators. Only the study pharmacist who dispenses the study medication will be unblinded to participants' assigned condition.

7.2.2 BEHAVIORAL LAB ASSESSMENT

The following behavioral/cognitive laboratory measures will be administered by a trained research assistant at designated time points. To ensure validity and compliance, eligibility for lab testing will require estimated premorbid IQ levels > 80 (Shipley-2) and the absence of acute cocaine intoxication on the day of testing (based on examination of DSM-IV symptoms and urine drug screen results). One hour prior to testing all cigarette-smokers will be prompted to smoke one cigarette in a designated outside area. This 60-minute window has been used in previously funded work at the CRNA to control for the potentially confounding effects of either nicotine withdrawal or acute nicotine stimulation.

The Iowa Gambling Task (IGT) is a computerized version of the original Iowa Gambling Task. Subjects are asked to choose between four decks of cards that result in theoretical monetary rewards at different rates. Each deck (labeled A, B, C, and D) contains 60 cards. Subjects must make 100 choices over the testing session. We will use versions of the IGT developed for repeated administration, provided to us through collaboration with Dr. Antoine Bechara, who developed the task. The primary dependent variable to be used in the statistical analyses will be the net score for the IGT, calculated as the total number of cards selected from the advantageous minus the disadvantageous decks [(C+D)-(A+B)] across five blocks of 20 cards each.

The Risky Decision-Making Task was developed specifically for the assessment of acute drug effects and repeated measurement over time. Like the IGT, it is a computer-based task that provides subjects with different options over 112 repeated trials, defined as non-risky (net gain

.01, no loss) and risky (gain/loss of 0.25, 0.50, 0.75, or 1.00 with gain/loss probability = 0.50). Like the IGT, the non-risky option is more adaptive over many trials. Subjects start each test session with $6.00. End-of-session earnings can range from approximately +$14.00 to -$2.00 depending of choice patterns. Unlike the IGT, earnings are real money that count toward subject payment at the end of the experimental day. The primary dependent variable will be the number of choices on the risky response option.

The Continuous Performance Test (CPT). The version of the CPT that will be used for this study is the Immediate Memory Task (IMT). The IMT is a paradigm based on the continuous performance task, originally developed as a measure of attentional capacity and the ability to withhold a prepotent response. Subjects are required to respond selectively to a series of stimuli (e.g., numbers) presented briefly for 500 ms with a 500 ms ITI. Go/No-Go paradigms have also shown sensitivity to acute stimulant effects. Increases in false alarm rates are interpreted as failures in response inhibition. Five-digit numbers are presented on a computer screen every 500 ms sec. Subjects are instructed to respond when the first number of a set is repeated. A 'hit' response is scored when a subject correctly responds. Distracter stimuli consist of five-digit numbers that are completely different from the first, and numbers in which four of the five digits match the original, with the non-matching number occurring randomly across the five digit places. A response to a distracter is scored as a 'false alarm' and operationally defined as a failure in response inhibition. The primary dependent variable will be the percent of false alarms.

The Progressive Ratio (motivation) Task. We operationally define motivation as a change in responding that is functionally related to a change in its consequences. Specifically, in the procedure described below, we interpret the allocation of behavior to a response option with increasing response requirement and corresponding increases in reward (money) value as an index of motivation. The procedure presents subjects with two mutually exclusive response options: a progressive-ratio (PR) reinforcement schedule and a fixed-time (FT) reinforcement schedule. Monetary rewards are periodically represented by a counter located near the top of the on-screen display. The PR schedule is programmed on one option (work). The initial response requirement on the work option is 10 responses, and produces a reinforcer of $0.01. After each reinforcer, the response requirement is increased by ten percent of the previous value and the reinforcer amount is increased by $0.01. Thus, each subsequent reinforcer is worth more than the previous one, but requires more work to obtain it. These parameters effectively serve to produce earnings that maintain subjects' attention, maintain PR responding throughout at least half of the session, and avoid exceptionally large ratio sizes.
Also available during the session is a second option (non-work), which is available at any time. Once the non-work option is selected, no responses are required to earn monetary rewards – money simply accumulates by being added to the counter after fixed time-intervals have elapsed. Importantly, once the non-work option has been selected, it is in effect for the remainder of the session, and this change is not reversible. The non-work option amount and time value are yoked to the performance on the work option: the reward amount is exactly 66% of that earned on the last completed PR (work), and the time interval for each reward delivery is either the time that was required to complete the last PR or 120 sec, whichever is larger.

Thus, the non-work option always delivers a smaller amount of money than the next scheduled reward on the work option. The two options are indicated by response boxes located on the right and left sides of a computer screen, and the terms work and not-work are not used. The PR and FT schedules can be thought of as work and non-work options because (a) the work option requires increasing behavioral output and the non-work option requires no behavioral output, and (b) the contingencies are arranged such that it is advantageous to remain on the work option, even when the PR requirement reaches very high values near the end of the session. The primary dependent variables of interest will be the largest PR completed on the work option.

The Cocaine Stroop. The task is administered on a desktop computer, and assesses attentional biases to cocaine-related (drug-related) and appetitive (non-drug related) stimuli vs. neutral stimuli. Drug-related, non-drug related, and neutral words are presented in separate blocks of 30 trials each. Block order is counterbalanced over participants with a short interval of a few seconds between blocks. *Stimulus Materials*: There are cocaine-related words (e.g., COCAINE, CRACK, ROCKS, HIT); neutral words consisting of outdoor features (BRIDGE, AVENUE, SIDEWALK) and indoor, household, features (e.g., ROOM, FLOOR, CABINET); and appetitive non-drug related words selected from items that our cocaine-dependent participants reported acquiring with the money they received (from CM) in previous pilot work (e.g., VACATION, FOOD, JEWELRY). Categories are matched on length and frequency of use. Participants are instructed that words written in different colors (blue, green, or red) are presented on the screen, one after the other, and that their task is to indicate as quickly and as accurately as possible which color the word is written in, by pressing one of three colored buttons on a keyboard. Participants are instructed to ignore the meaning of the word itself and just to respond to the color. On each trial, a word is presented in capital letters and remains on the screen until the participant presses a button. If the participant makes a wrong response there is a tone. If the participant makes no response within three seconds the word is removed (and there is a tone). Within each block, the order of words is randomly determined by the program for each participant under the constraint that the same color or word does not appear on two consecutive trials. The primary data analyses are focused on reaction times (RT) to make a response to each word. RTs less than 100 ms are eliminated, as are RTs on trials on which participants made an error. The cocaine Stroop effect (attentional bias) is the difference in RTs on cocaine vs. neutral words, and the difference in RTs on cocaine vs. non-drug related appetitive words. The cocaine Stroop effects are (normally distributed) difference scores reflecting the difference in reaction times across the separate stimulus types.

7.2.3 IN TREATMENT

During the 9-week treatment phase participants will be scheduled to attend three clinic visits per week (MWF). Activities conducted at these visits will include urine testing, administration of study medication, cognitive behavioral therapy, and prize-based CM for attendance. Brief (5-10 min) evaluations by the study nurse will be conducted weekly to address concerns related to side effects, concomitant medications, and general adherence to the medication regimen.

7.2.4 COMPENSATION SCHEDULE

Participants will receive $50 for completing the intake assessment phase of this study. Weekly assessments during treatment will take approximately 20 minutes to complete. Participants will earn prize bowl draws each time they attend a clinic visit (MWF) and provide a usable urine specimen. The prize-based CM is explained above (see Sect. 6.5). Behavioral tasks at Weeks -1, 3, 5, 7, and 9 will take approximately 65 minutes to complete. Participants will receive an additional $25 (gift card) for each of these assessments, plus any task-specific earnings (approx. $8). Subjects will also receive $5 for each medication pack returned and bus/parking tokens as needed.

7.2.4 Early Termination

Premature termination of a subject from the study will be considered clinically appropriate for any of the following reasons: (1) significant side effects from the study medication; (2) serious or unexpected AEs; (3) inability to comply with the study protocol; (4) protocol violation; or (5) emergence of serious medical or psychiatric illness.

7.2.5 End of Study Visit (Week 9)

At week 9, participants will be administered end of study assessments and given appropriate referrals to alternative treatment facilities in the area.

8. ASSESSMENT SCHEDULE

STUDY 64												
Forms		**Admit week**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Study 64 consent form and quiz		X										
Medication information sheet		X										
Weekly Locator		X	X	X	X	X	X	X	X	X	X	X
Con Med		X	X	X	X	X	X	X	X	X	X	X
SUR (3xwk)		X	X	X	X	X	X	X	X	X	X	X
AIMS		X	X	X	X	X	X	X	X	X	X	X
AE		X	X	X	X	X	X	X	X	X	X	X
BDI-2		X										X
BSCS		X										X
SHAPS		X										
URICA		X										
DTCQ		X										
OCDUS		X	X	X	X	X	X	X	X	X	X	X
NART-2		X										
Shipley - 2		X										
Computerized Tests												
IGT-repeat version		X			X		X		X		X	
Risky Decision Making		X			X		X		X		X	
Continuous Performance Test		X			X		X		X		X	
Progressive Ratio (PR)		X			X		X		X		X	
Cocaine Stroop		X			X		X		X		X	
Reversal Learning		X			X		X		X		X	
Activities												
Blood draw				X		X		X		X		X
Preg				X		X		X		X		X
EKG		X		X		X		X		X		X
Vitals		X	X	X	X	X	X	X	X	X	X	X
BAL (3x/wk)		X	X	X	X	X	X	X	X	X	X	X
Urine rapid Test (3x/wk)		X	X	X	X	X	X	X	X	X	X	X
Fishbowl		X	X	X	X	X	X	X	X	X	X	X

9. SAFETY ASSESSMENT

9.1 DEFINITION OF AE

An adverse event (AE) is defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure, that occurs during the course of the study.

9.2 DEFINITION OF SAE

A **serious adverse event** (SAE) is any adverse experience occurring during the course of the study or during planned follow-up. Any adverse event that meets **any of the following** criteria MUST be reported to the CPHS:

- results in death;
- is life-threatening (places the patient at immediate risk of death from the experience as it occurred);
- results in a persistent or significant disability/incapacity (substantial disruption of one's ability to carry out normal life functions);
- results in medical or surgical intervention;
- results in OR prolongs an existing inpatient hospitalization (even if the hospitalization is a precautionary measure for observation);
- is a congenital anomaly/birth defect in offspring of subjects taking the product regardless of time to diagnosis;
- is a cancer;
- is the result of an overdose, whether intentional or accidental, including a breach of protocol;
- is medically unexpected, regardless of severity

9.3. DEFINITION OF UNANTICIPATED PROBLEMS

Unanticipated problems are not synonymous with "adverse events". Unanticipated problems refer to untoward events involving any aspect of a research study, not just subjects, and can occur in clinical and non-clinical research. Some examples of unanticipated problems include:

- An investigator loses a laptop that contains confidential information about participants.
- A principal investigator is charged with a felony.
- A lab reports that blood studies performed the previous week were in error.
- A man physically abuses his wife because she agreed to take part in a research study without his permission.
- Subjects in a group counseling session become unexpectedly violent.

All unanticipated problems will be reported to CPHS via iRIS.

9.4 AE REPORTING GUIDE

Reporting of adverse events, serious and/or unexpected, will follow the CPHS guidelines found at: **http://www.uth.tmc.edu/orsc/guidelines/adv.html**