Study: # 6850 entitled A sequenced behavioral and medication intervention for cocaine dependence

PI: Frances R. Levin

NCT# NCT01986075

Study Protocol Date: 10/31/2013

New York State Psychiatric Institute

Institutional Review Board

October 31, 2013

To: Dr. Frances Levin

From: Dr. Edward Nunes, Chairman

Subject: Approval Notice

Your protocol # **6850** entitled: **A Sequenced Behavioral and Medication Intervention for Cocaine Dependence** Protocol version date 10/16/13 and consent forms have been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **October 31, 2013 to September 22, 2014** (Reviewed by the Full Board on 9/23/13).

Consent requirements:

☐ Not applicable:

☐ 45CFR46.117 (c)(2) waiver of documentation of consent for the telephone screen.

✓ Signature by the person(s) obtaining consent is required to document the consent process.

☐ Documentation of an independent assessment of the participant's capacity to consent is also required.

Approved for recruitment of subjects who lack capacity to consent: ✓No Yes

Field Monitoring Requirements: ✓Routine Special: _____

✓ Only copies of consent documents that are currently approved by the IRB may be used to obtain consent for participation in this study.

✓ A progress report and application for continuing review is required 2 months prior to the expiration date of IRB approval.

✓ Changes to this research may not be initiated without the review and approval of the IRB except when necessary to eliminate immediate hazards to participants.

✓ All serious and/or unanticipated problems or events involving risks to subjects or others must be reported immediately to the IRB. Please refer to the PI-IRB website at http://irb.nyspi.org for Adverse Event Reporting Procedures and additional reporting requirements.

*** This study requires a Certificate of Confidentiality. Please forward when obtained.**

Cc: RFMH
CU Grants Office
CUMC-IRB

Encl: CFs

EN/Xx

Signed copy on file at IRB

Protocol Title:
A Sequenced Behavioral and Medication Intervention for Cocaine Dependence

Version Date:
10/31/2013

Protocol Number:
6850

First Approval:
N/A

Clinic:
Substance Treatment And Research Services (STARS)

Expiration Date:
Not yet accepted

Principal Investigator:
Frances Levin, MD
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Telephone: 212-543-5896

Co-Investigator(s):
Kenneth Carpenter, PHD

Research Chief:
Richard Foltin, PHD

Cover Sheet

Choose from the following that is applicable to your study
I am submitting a new protocol

Division & Personnel

Division

What Division/Department does the PI belong to?
Substance Abuse
Within the division/department, what Center or group are you affiliated with, if any?
Substance Treatment and Research Service

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.
none

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

✓ Psychiatric Assessment
✓ Collection of Biological Specimens
✓ Medication Trial
✓ Use of Placebo or Sham Treatment
✓ Psychotherapy Trial
✓ Medication-Free Period or Treatment Washout
✓ Audio or Videotaping
✓ Off-label Use of Drug or Device
✓ Internet-based Data Collection or Transmission

Population

Indicate which of the following populations will be included in this research

✓ Medically and Psychiatrically Healthy Subjects
✓ Adults
✓ Substance Users

Research Support/Funding

Will an existing internal account be used to support the project?
No
Is the project externally funded or is external funding planned?
Yes
Select the number of external sources of funding that will be applicable to this study

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes
Select one of the following
The grant/contract application is a pending review or a funding decision
Source of Funding
Federal
Institute/Agency
NIDA
Grant Name
A Sequenced Behavioral and Medication Intervention for Cocaine Dependence

Grant Number
1R01DA034087 - 01A1
Select one of the following
Single Site
Business Office
RFMH
Does the grant/contract involve a subcontract?
Yes
Subcontracted?
To
Name institution(s)

Columbia University

Study Location

Indicate if the research is/will be conducted at any of the following
✓ NYSPI
This protocol describes research conducted by the PI at other facilities/locations
No

Lay Summary of Proposed Research

Lay Summary of Proposed Research
This study will test a sequential treatment strategy in which a computer-based behavioral intervention will be combined with a medication to increase treatment response among individuals not responding to the behavioral treatment alone. We plan to enroll 155 treatment-seeking cocaine dependent participants and ask them to participate in a computer-assisted behavioral intervention based on the community reinforcement approach with contingency management (CRA + CM). Those who fail to achieve abstinence after the first 4 weeks will continue the behavioral treatment (CRA + CM) and be randomly assigned to a behavioral therapy enhancement strategy that will include either mixed amphetamine salts-extended release (MAS-ER) or placebo, over a 10-week trial. The Primary Aim is to test the hypothesis that among cocaine dependent patients who have failed to respond to an initial trial of behavioral therapy (CRA +CM), a greater proportion of individuals will benefit from the combined treatment arm (CRA+CM/MAS-ER) compared to patients in the comparison group (CRA+CM/PLACEBO).

Background, Significance and Rationale

Background, Significance and Rationale

Cocaine dependence remains a serious public health problem (SAMSHA, 2009) that has not been adequately addressed by our current clinical strategies. Psychosocial treatments can promote behavior change and constitute the backbone of our intervention efforts. However, a notable proportion of individuals fail to benefit from these strategies alone. Thus, it is important to identify those individuals less likely benefit from traditional treatment approaches, uncover the mechanisms promoting treatment response, and develop strategies to enhance the overall efficacy of our intervention efforts.

Behavioral therapies that impart skills and provide tangible incentives (contingency management, CM) for abstinence, e.g. the Community Reinforcement Approach (CRA), have shown the most robust and consistent effects in reducing cocaine use among dependent patients (Dutra et al., 2008; Higgins et al., 1994). Still, a significant proportion of individuals fail to respond to CM based interventions alone. Recent trials have suggested that combining CM interventions with medications that boost mono-amine functioning can enhance treatment response above that of either treatment alone (Kosten et al., 2003; Moeller et al., 2007; Poling et al., 2006; Schmitz et al. 2008). Our group, using an innovative imaging and treatment design, has further demonstrated that deficient dopamine transmission, measured with the PET 11C-raclopride displacement paradigm, predicts poor response to the Community Reinforcement Approach with CM (Martinez, Carpenter, et al., 2011). This finding provides a key neurobiological target, suggesting enhancing behavioral interventions with a pharmacotherapy tailored to enhance dopamine transmission may provide a useful strategy to help boost treatment response among those individuals least likely to benefit from behavioral treatments alone.

Among available medications, stimulants produce the most direct and potent augmentation of dopamine release. Several studies (Anderson, et al., 2009; Levin, 1998, Mooney et al., 2009), including a placebo-controlled trial that included mixed amphetamine salts-extended release (MAS-ER) recently completed at our center (see Significance Section), suggest an agonist replacement strategy with stimulants is effective for promoting abstinence in cocaine dependence. The beneficial effect of our medication intervention was most notable among the more severely dependent patients – a group that had a low placebo response rate and maybe less likely to respond to a behavioral therapy alone. Taken together, the above findings suggest that stimulant medication may be a particularly effective strategy for enhancing the efficacy of behavioral interventions among cocaine dependent patients who have failed to respond to behavioral therapy alone, a group we have demonstrated to evidence dopamine transmission deficits.

In light of the above findings, this proposal will be one of the first investigations to employ a sequential and integrative treatment strategy in which a medication targeting dopamine release will be used to enhance the efficacy of a behavioral intervention among individuals not responding to the behavioral treatment alone. We propose a Stage 2 treatment development trial (Behavioral and Integrative Treatment Development Program, PA-10-012) in which 155 treatment-seeking cocaine dependent participants will enter behavioral therapy based on the Community Reinforcement Approach (CRA + CM). Those who fail to achieve sustained abstinence after the first 4 weeks will continue with the behavioral treatment (CRA + CM) and be randomly assigned to receive either mixed amphetamine salts-extended release (MAS-ER) or placebo, over a 10-week double-blind trial.

Two features of this trial are designed to improve the ultimate potential for widespread adoption of this enhanced treatment strategy. First, the trial will use a web-based,

computer-delivered version of CRA+CM, the Therapeutic Education System (TES). TES has been shown in an initial trial to be equally effective as therapist delivered CRA in promoting abstinence (Bickel et al., 2008). Computer delivered interventions such as TES have the potential to circumvent significant barriers to the adoption of evidence-based practices into community-based treatments (Bickel et al., 2008; Carroll et al. 2008). Second, this trial tests a sequential treatment strategy whereby cocaine dependent patients are first treated with behavior therapy, and those who fail to respond are treated with a combined behavior therapy and medication strategy. This personally targeted approach will help guide a more judicial use of medications and the medical personnel needed to deliver them by reserving enhanced treatment strategies for the subgroup of patients that may most need it.

Specific Aims and Hypotheses

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This proposal will be one of the first investigations to employ a sequential and integrative treatment strategy in which a medication targeting dopamine release will be used to enhance the efficacy of a behavioral intervention among individuals not responding to the behavioral treatment alone. We propose a Stage 2 treatment development trial in which 155 treatment-seeking cocaine dependent participants will enter behavioral therapy based on the Community Reinforcement Approach (CRA + CM). Those who fail to achieve sustained abstinence after the first 4 weeks will continue with the behavioral treatment (CRA + CM) and be randomly assigned to receive either mixed amphetamine salts-extended release (MAS-ER) or placebo, over a 10-week double-blind trial.

The Primary Aim is to test the following hypothesis

Among cocaine dependent patients who have failed to respond to an initial trial of behavioral therapy (CRA + CM), a greater proportion in the enhanced behavioral treatment condition (CRA+CM/MAS-ER) will achieve 3-weeks or more of continued abstinence compared to patients treated with CRA+CM/PLACEBO.

We will also investigate cognitive and behavioral predictors of response to the behavioral therapy alone and the effect of medication enhancement on other indicators of treatment response: urine confirmed weekly cocaine use, craving, quality of life, and treatment retention. Potential moderators and mediators of an enhanced behavioral treatment effect, including cognitive functioning, the use of relapse prevention skills, and changes in patient commitment language will be tested.

Description of Subject Population

Sample #1

Specify subject population
Cocaine Dependent Treatment Seekers
Number of completers required to accomplish study aims
68
Projected number of subjects who will be enrolled to obtain required number of completers
155
Age range of subject population
18-60

Gender and Ethnic Breakdown

Males (total n=116): Hispanic n=35; Non-Hispanic n =81

Females (total n=39): Hispanic n=12; Non-Hispanic n= 27

American Indian: n=0

Asian: n=6 (Males=5; Females=1)

Native Hawaiian: n=0

African American: n=79 (Males=59; Females=20)

White: n=70 (Males=52; Females=18)

Description of subject population
We plan to enroll 155 adult participants who are actively using cocaine (evidenced by positive urine toxicology), are currently seeking treatment for their drug use and who meet eligibility criteria.

Recruitment Procedures

Describe settings where recruitment will occur
The Substance Treatment and Research Service (STARS) is will be the primary facility in which recruitment will occur. STARS is based at two locations in New York City. Our uptown clinic is adjacent to the Presbyterian Hospital, a large tertiary care center, which also is the main primary care provider for the local inner-city neighborhoods of upper Harlem, Washington Heights, and Inwood. We also have a large suite of treatment offices in Midtown Manhattan (1775 Broadway, 14th Floor) that has offered a more convenient location for participants traveling from NJ and the

outer boroughs of New York City (Brooklyn, Queens, and Staten Island).

How and by whom will subjects be approached and/or recruited?

Prospective participants will have contacted the clinic by phone and received a screening appointment. They will be asked to participate in a one-week uniform screening procedure that includes an evaluation by a Masters or Ph.D. level psychologist and a psychiatrist with a standard battery of measures including the Mini-International Neuropsychiatric Interview for DSM-IV disorders. These screening procedures will be covered by the Substance Treatment and Research Service umbrella screening protocol #6582R (PI: John Mariani, MD). Potential participants receive a brief telephone screening and those who are seeking outpatient treatment, meet no obvious exclusion criteria, and are willing to consider participation in research are scheduled for screening. The screening process takes place in one to two visits over a one-week period. During the screening process participants are interviewed by a clinical psychologist or certified social worker, and receive a medical and psychiatric evaluation by the psychiatrist, who makes the final determination of eligibility after reviewing all aspects of the baseline evaluation. Individuals who are not eligible or do not wish to participate in research treatment are offered referrals to other treatment programs in the community

How will the study be advertised/publicized?

We will recruit individuals with cocaine dependence through newspapers, radio and public service announcements coordinated by the NYSPI Public Relations Office. This method has proven successful in several clinical trials at STARS. All advertisements will be sent to the Institutional Review Board for approval. The first phase of recruitment is a structured telephone interview when the initial contact is made. Individuals interested in receiving treatment for cocaine dependence will be asked to come to STARS for additional screening as per protocol #6582R. Those patients who meet criteria for cocaine dependence and all other inclusion/exclusion criteria will be asked if they are interested in participating in the study.

Do you have ads/recruitment material requiring review at this time?

No

Does this study involve a clinical trial?

Yes

YOU MUST REGISTER AT ClinicalTrials.gov IMMEDIATELY UPON RECEIPT OF IRB APPROVAL AND PRIOR TO ENROLLMENT OF THE FIRST SUBJECT. YOU WILL BE PROVIDED WITH A NCT REGISTRATION NUMBER ON REGISTRATION. PLEASE REVISE THIS SECTION OF THE PROTOCOL SUMMARY FORM TO INCLUDE THE NCT NUMBER AND RE-SUBMIT AS AN AMENDMENT TO THE IRB.

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?

Yes

Describe concurrent research involvement

Protocol # 6582R: Evaluation of Potential Substance Abuse Research Participants
Principal Investigator: John Mariani, M.D.

Screening for this study will be covered by the Substance Treatment and Research Service

(STARS) umbrella screening protocol #6582R (PI: John Mariani, MD). Trained research assistants and administrative assistants under the supervision of the principal investigator conduct the initial phone screening. Under protocol #6582R, patients who contact STARS interested in research trial participation are informed that they will be asked questions of a personal nature and asked to provide verbal consent for such questions. A "phone screen" form is completed by the phone screener, which asks basic demographic information, contact information (for scheduling purposes) and description of substance use to determine whether an in-person evaluation appointment is appropriate. Individuals are also informed that if they make an initial screening appointment this “phone screen” information will be forwarded to the clinician to facilitate the first meeting.

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Cocaine Dependent Treatment Seekers
Create or insert table to describe the inclusion criteria and methods to ascertain them

Inclusion Criteria:	Ascertainment
1) Meets **DSM-V criteria for cocaine use disorder**	1). MINI
2) Used cocaine at least four days in the past month, use in the past week.	2). Self report; urine drug screen
3) Age 18-60.	3). demographic information
4) Able to give informed consent and comply with study procedures.	4). initial contact interview

Create or insert table to describe the exclusion criteria and methods to ascertain them

Exclusion Criteria	Ascertainment
1) Meets DSM-V criteria for bipolar disorder, schizophrenia or any psychotic disorder other than transient psychosis due to drug abuse.	1) MINI assessment DSM-V diagnostic algorithm.

2) Participants with MDD, with symptom severity that exceeds a HAM-D score of 20, and/or any other current Axis I psychiatric disorder as defined by DSM-V supported by the MINI that in the investigator's judgment are unstable, would be disrupted by study medication, or are likely to require specialized pharmacotherapy or psychotherapy during the study period.	2) MINI, HAM-D Psychiatric Interview
3) History of seizures, unexplained loss of consciousness, or traumatic brain injury.	3) Medical History
4) History of allergic reaction to candidate medication (amphetamine).	4) Medical History
5) Significant current suicidal risk.	5) MINI; psychiatric evaluation
6) Pregnancy, lactation, or failure in sexually active female patients to use adequate contraceptive methods.	6) Self-report, serum HCG
7) Unstable physical disorders which might make participation	7) Medical history including

hazardous such as uncontrolled hypertension, acute hepatitis, uncontrolled diabetes.	Cardiovascular risk profile, ECG
8) Elevated transaminase levels (> 3x the normal limit).	8) Medical History; Laboratory tests
9) Coronary vascular disease	9) Medical History ECG
10) History of failure to respond to a previous adequate trial of the candidate medication.	10) Self-report
11) Current physiological dependence on any other substance other than nicotine or cannabis that would require a medically supervised detoxification.	11) MINI; Medical History Psychiatric Interview
12) Currently being prescribed psychotropic medication by another physician.	12) Self-report; Psychiatric Interview
13) Are legally mandated (e.g. to avoid incarceration, monetary or other penalties, etc.) to participate in substance abuse treatment program.	13) Self-report

14) Body Mass Index (BMI) < 18kg/m2.	14) Weight and height measurement

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)
No
Waiver or alteration of consent
No
Waiver of documentation of consent
No
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
Yes
Indicate NYSPI IRB #
6582R
Describe Study Consent Procedures
Screening for this study will be covered by the Substance Treatment and Research Service (STARS) umbrella screening protocol #6582R (PI: John Mariani, MD). Trained research assistants and administrative assistants under the supervision of the principal investigator conduct the initial phone screening. Under protocol #6582R, patients who contact STARS interested in research trial participation are informed that they will be asked questions of a personal nature and asked to provide verbal consent for such questions. A "phone screen" form is completed by the phone screener, which asks basic demographic information, contact information (for scheduling purposes) and description of substance use to determine whether an in-person evaluation appointment is appropriate. Individuals are also informed that if they make an initial screening appointment this “phone screen” information will be forwarded to the clinician to facilitate the first meeting.
Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent

Bisaga, Adam, MD
Bryan, Benjamin, MD
Dakwar, Elias, MD
Evans, Elizabeth
Kelly, Meredith, MD
Levin, Frances, MD
Mariani, John, MD
Notzon, Daniel
Shakibaie Smith, Shabnam, MD
Vaughan, Barney, MD
Type in the name(s) not found in the above list
Sullivan, Maria, MD

Study Procedures

Describe the procedures required for this study
Personnel:

Frances R. Levin, M.D.: Psychiatrist with 22 years of experience in substance abuse treatment will assume scientific responsibility for all aspects of this protocol, including supervising all staff members responsible for recruitment of patients, clinical care, and collection and analysis of the data, and manuscript writing.

Kenneth Carpenter, Ph.D.: Psychologist with 12 years of experience in substance abuse research and treatment. He will provide direct clinical supervision to the interviewers, train them to conduct the structured interviews, and work closely with Dr. Levin during the clinical care, and collection and analysis of the data, and manuscript writing. He will also review all written assessments and diagnoses.

Research Psychiatrist: (Frances Levin, M.D., Maria Sullivan, M.D., Ph.D., Adam Bisaga, M.D., John Mariani, M.D., Shabnam Shakibaie, M.D., Benjamin Bryan, M.D., Elias Dakwar, M.D., Meredith Kelly, M.D., Elizabeth Evans M.D., Daniel Notzon M.D., and Barney Vaughan, M.D.). The Research Psychiatrist will meet with individuals who meet the initial criteria for cocaine dependence to determine if they may be eligible for the treatment study. S/he will evaluate the patient's eligibility for study entry. After individuals are determined to be eligible for the study based on all inclusion and exclusion criteria, the research psychiatrist will describe the study to the patient and obtain informed consent after s/he has answered all questions related to the study procedures. If the patient enters the treatment study, the research psychiatrist will meet with the patient each week to conduct the research assessments (i.e. Clinical Global Impression and the Cocaine Selective Severity Assessment), and assess and manage side effects. The research psychiatrist will be responsible for the overall clinical care, consultation and coordination of care with the clinical and research staff.

Interviewer/Therapist: (Elisa Leimsider, M.S.W., Kenneth Carpenter, Ph.D., Amy Mahony, M.A.,

Margaret Rombone, Ph.D., Jaclyn Bronstein, M.A., Paula Bertone, M.A., and Jack Grabon, M.S.W.) has a doctorate in clinical psychology, a master's degree in clinical psychology, or a master's degree in social work. S/he will be involved in conducting all interviews and assessments to ensure consistent diagnoses of substance use disorders. S/he will also be involved in patient recruitment.

Research Nurse (Marcia Loughran, R.N., M.S.N.): The research nurse will see patients enrolled in the treatment study three times a week to obtain vital signs, monitor side effects, and collect blood samples. Additional responsibilities of the research nurse will include sending all biological samples to the correct laboratories and ensuring accurate records of routine blood work and medical information.

Research Assistant (Arielle Radin, B.A.): has a Bachelor's degree in psychology and will be primarily involved in study management and coordination between the various sites. The research assistants will conduct telephone interviews and will be involved in recruiting.

a. *Screening Interviews* will be carried out by 1) therapists (Elisa Leimsider, M.S.W., Amy Mahony, M.A., Margaret Rombone, Ph.D., Jaclyn Bronstein, M.A., Paula Bertone, M.A., Jack Grabon, M.S.W. who have a doctorate in clinical psychology, a master's degree in clinical psychology, or a master's degree in social work) trained by Dr. Carpenter and 2) Psychiatrist/Physicians (Drs. Levin, Bisaga, Mariani, Shakibaie, Sullivan, Bryan, Dakwar, Kelly, and Vaughan), who have extensive experience with individuals with substance use disorders in treatment settings.

b. *Drug Administration:* Extended-release mixed amphetamine salts (MAS-ER), and matching placebo will be provided by the research nurse or psychiatrist. Doses and dose schedule are described below. Physiological effects (heart rate and blood pressure) and side effects will be monitored three times a week. The research psychiatrist (Drs. Bisaga, Mariani, Shakibaie, Sullivan, Bryan, Dakwar, Huynh, Kelly, Evans, Notzon and Vaughan) will determine medication dose adjustments with consultation from the Principal Investigator (Dr. Levin). Consultations with Dr. Levin will take place at a weekly meeting with the research psychiatrists where all patients enrolled in the study will be discussed. Dr. Levin will also be available to the research psychiatrists by telephone or pager if a more immediate consultation about a patient's medication dose is needed.

c. *Behavioral assessments* will be carried out by trained interviewers/therapists (Elisa Leimsider, M.S.W., Amy Mahony, M.A., Margaret Rombone, Ph.D., Jaclyn Bronstein, M.A., Paula Bertone, M.A., Jack Grabon, M.S.W.) under the supervision of Dr. Carpenter.

d. *Computer-assisted Behavioral Therapy*. Monitoring and discussion of the computer delivered coping skills treatment program will be carried out by trained interviewers/therapists (Elisa Leimsider, M.S.W., Amy Mahony, M.A., Margaret Rombone, Ph.D., Jaclyn Bronstein, M.A., Paula Bertone, M.A., Jack Grabon, M.S.W.) under the supervision of Dr. Carpenter.

General Design:
155 subjects whom meet criteria for cocaine dependence, and all other study inclusion and

exclusion criteria (described above) will begin a 4-week computer-assisted behavioral intervention. Those participants not responding to the behavioral intervention will begin a 10-week double-blind, placebo-controlled treatment trial. Subjects will be randomized to receive either placebo or MAS-ER. Table 1 shows the overall design

1. Design Overview

We will investigate the effect of augmenting a self-directed version of the Community Reinforcement Approach (CRA; Budney & Higgins, 1998) with Mixed Amphetamine Salts-Extended Release (MAS-ER) to improve treatment response among cocaine dependent patients who do not benefit from the behavioral intervention alone. Patients who do not respond by week four of the CRA+CM intervention will be randomized to a 10-week double blind design to test the combined effects of CRA+CM/MAS-ER against a CRA+CM/PLACEBO control condition. Participants who are randomized to the combination behavioral treatment and medication arm (CRA+CM/MAS-ER) will have their dose titrated to 60 mg MAS-ER daily (over 2 weeks) and maintained on this dose through week 13 of the trial. During week 15, participants will be tapered off the medication (see Table 1. below). Patients responding to the CRA+CM intervention in the first four weeks of treatment will continue with the behavioral intervention and be assessed in parallel to the two (CRA+CM/MAS-ER and CRA+CM/PLACEBO) enhanced treatment arms.

Randomization: Those patients randomized to the placebo group will continue to receive CRA+CM and placebo throughout the treatment. Patients randomized to the CRA+CM/MAS-ER group will begin receiving medication at the start of week 5 and will receive a stable dose of MAS-ER by study week 7.

Dosing Schedule: Subjects will take capsules (PBO or MAS-ER) as titrated in Table 2 below.

Medication Lead-out: During week 15 patients assigned to active medication have their medication tapered. The purpose of the placebo lead-out is to keep patients blind to the exact point of medication discontinuation, and afford systematic observation of effects of medication discontinuation.

27 Week Outcome: Twelve weeks after study completion (27 weeks after enrollment) an attempt will be made to evaluate all participants to explore whether there may be effects of treatment that endure or emerge after medication discontinuation. In exploratory analyses, outcome at 27 weeks will be compared among three groups: those originally assigned to continue behavioral therapy alone, patients assigned to receive either medication or placebo. Group comparisons will be conducted on the main primary and secondary outcomes.

Medication: MAS-ER, and matching placebo will be prepared by our pharmacy at the NYSPI,

packaged in matching gelatin capsules with lactose filler in each capsule. The research pharmacist, who has no contact with patients, is the only non-blind member of the research team. At each weekly visit the psychiatrist orders the dose of double-blind medication for the coming week according to the schedule (shown in Table 2). The psychiatrist will adjust the dose according to tolerability. MAS-ER or matching placebo will be given in a fixed-flexible dose schedule with the MAS-ER dose titrated to 60 mg per day.

MAS-ER or matching placebo will be taken once per day in the morning or early afternoon since it may be activating. The medication will be packaged in gelatin capsules with lactose filler plus **25 mg** of riboflavin. MAS-ER or matching placebo are given in a “fixed-flexible" dose schedule with the dose titrated to 60 mg per day or the maximum tolerated dose. The standard dose titration will be 10 mg per day for the days 8-9, 20 mg per day for days 10-12, 30 mg per day for days 13-14, 40 mg per day for days 15-18, 50 mg per day for days 19-21 and 60 mg for the remainder of the study. MAS-ER is FDA approved for the treatment of ADHD in doses up to 60 mg per day.

If a patient does experience any uncomfortable side effects, the dose will not be raised, and if necessary, the dose will be lowered. If the patient cannot tolerate at least 20 mg/day of MAS-ER the medication will be discontinued. Patients will be encouraged to set a quit date three weeks after starting study medications (the end of the titration phase of MAS-ER). During week 14 patients on active medication will be **tapered off MAS-ER.**

Planned/unplanned absences that would require the patient to be given more than one week worth of medications will be considered on a case-by-case basis. In the case of unplanned absences, up to one week of medication can be shipped via FedEx with signature upon receipt. This will allow patients who miss their scheduled appointments to remain on stable medication.

We will evaluate the adequacy of the double-blind by asking patients which treatment drug they thing they are receiving. The blinded nurse will also be asked to report which drug s/he thinks each patient is taking. The research staff (i.e., therapist, nurse, research assistant and psychiatrist) that administers medications and/or conducts interviews and assessments will be blind to medication condition, urine toxicology results, and medication blood levels during the course of the 10-week trial. The non-blinded pharmacist will be the only ones who have access to this information during the trial. However, a sealed envelope will be kept in a locked office if the Principal Investigator needs to break the blind in an emergency situation. At the completion of the 10-week trial, or at the conclusion of the patient’s involvement in the trial (if they do not complete all 10 weeks), patients will learn their treatment assignment.

Computer-assisted CRA with Contingency Management: All consented patients will begin the trial receiving CRA+CM delivered in a computer-assisted treatment format. Patients will be asked to attend the clinic 3 times per week for urine toxicology, and on 2 of those occasions, participate in a 30-40 minute session using the self-directed version of the Community Reinforcement Approach (CRA+CM). CRA+CM is a well-established skills oriented treatment for cocaine dependence that utilizes tangible incentives to promote abstinence (Budney & Higgins, 1998). This treatment has

been utilized in other studies in our clinic (Martinez, Carpenter et al., 2011; Carpenter et al., 2008). The Therapeutic Education System (TES), an empirically supported intervention itself (Bickel, Marsch, et al., 2008), is delivered via effective informational and multimedia technologies, includes 32 core interactive, multimedia modules, beginning with basic cognitive behavioral relapse prevention skills (e.g. drug refusal skills) and moving on to improving psychosocial functioning, (e.g. employment status, social relations) and HIV risk reduction. All TES sessions will occur in a private office equipped with a PC and headphones; with clinical staff in close proximity to ensure compliance and clinical support.

TES is self-directed and includes a training module to teach individuals how to use it. All text is accompanied by audio to assist individuals with reading challenges and it employs personalized content for patients (e.g. personalized functional analysis) and a variety of interactive exercises to better enhance learning (e.g., graphics). TES is designed to address substance use in general and is inherently flexible, addressing the substance use-related problems with which individuals may present. All patients will work through the modules in a standard sequential order. The "fluency-based" Computer-Assisted Instruction (CAI) will continually assess a participant's grasp of the material and adjust the pacing and level of repetition of skills to promote mastery of the information being introduced. The electronic reporting system will allow counselors to view summaries of the participant's progress. Every other week (bi-weekly) individuals will meet with their counselor (on visit three of those weeks) for approximately 30 minutes to review their progress in treatment and revise the sequence of treatment modules if warranted.

Contingency Management Procedures: The CM component will follow the efficacious prize-based incentive procedures employed in other community based drug treatment studies (Petry et al., 2004; 2005), that reduce cocaine use and offset the cost of high magnitude vouchers. Patients receive draws from a prize bowl for each urine testing negative for benzoylecgonine. Failure to submit a scheduled specimen will be treated as cocaine positive. Each draw has a probabilistic chance of yielding one of four outcomes: an encouraging statement (e.g. 'good job'), a small prize valued at $2.50, a large prize valued at $20, or a jumbo prize valued at $100. The probability for each particular outcome is fixed for every draw and is based on the relative number of slips for each prize category in the prize bowl. Using Petry et al's (2005) framework, each prize bowl will have 500 prize slips. 250 slips will be the encouraging statement (50% of the total slips), 209 slips will be for small prizes (41.8%), 40 slips will be for large prizes (8%), and 10 slips will be the jumbo prize (0.2%). Patients will earn 1 draw for every week in which all urines are benzoylecgonine negative, thus employing the escalating incentive structure employed in other CM based treatments (Higgins et al., 1993; Petry et al., 2005). The escalating schedule will increase to a maximum of 10 draws. Consistent with Petry et al.'s (2005) prize bowl procedure, a single large prize will be awarded when a participant first achieves 2 weeks of abstinence to offset the low rate of reinforcement (low number of draws) during the beginning of the program. Abstinence from cocaine is confirmed by on-site urine testing (Abuscreen On-Trak system, Roche Diagnostics).

Patients are given immediate feedback on the toxicology results and are updated on the amount of draws earned to that point in time. A participant never loses the prizes earned.

Audiotaping of Counseling Sessions: *Counseling sessions will be digitally recorded for purposes of supervision, treatment fidelity, and for the psycholinguistic coding of sessions at Baseline and Week 5. Participants will be asked to consent for the audiotaping of their counseling sessions. All digital files will be stored on a secure computer dedicated for that purpose alone. The computer will not be connected to the internet.*

Assessment of Side Effects and Medication Compliance: The research nurse and psychiatrist will query about side effects related to the study medication. Reported side effects and other treatment emergent events since the past visit will be recorded; additionally, the severity of the side effect/treatment emergent event, the action taken, and the continuation or resolution of the side effect/treatment emergent event will be documented.
a) Ongoing medical assessments. At each visit, the research nurse will monitor vital signs (heart rate and blood pressure) and inquire about medication-related side effects. Inability to tolerate medication side effects will result in the reduction or temporary discontinuation of study medications. Blood pressure and heart rate assessments that indicate SBP>140, DBP>90, sitting quietly HR>100 for two consecutive weeks will result in the discontinuation of study medications. Vital signs assessments indicating SBP>160, DBP>110, sitting quietly HR>110 on any visit will result in immediate discontinuation from the study medications. The Side Effect Questionnaire consists of 2 parts: 1) self-reported side effects obtained by the nurse using an open format and 2) a checklist of symptoms rated from absent to severe, incorporating the major organ systems (e.g., gastrointestinal, neurological, cardiovascular). Patients may be removed from the study if they repeatedly miss study visits.

The research psychiatrist will meet with the patient once a week. At each weekly visit, s/he will discuss side effects of medication, review the Side Effect Questionnaire, will evaluate all reported vital signs and review cardiac risks to determine whether the dose is being tolerated, and assess substance use trends for clinical worsening. Cardiac risks will be documented in a structured progress note. If blood pressure and heart rate are consistently above cut-off levels as described above then the medication dose will be lowered or discontinued. If clinically indicated (e.g., side effects are not tolerable, chest pains, fainting, arrhythmias), the research psychiatrist will discontinue the medication.
You can upload charts or diagrams if any
Table 1 PSF.pdf
Table 2 PSF.pdf

Criteria for Early Discontinuation

Criteria for Early Discontinuation

Removal from the Study for Worsening of Substance Abuse: Participants whose substance abuse significantly worsens during the course of treatment will be removed and treated clinically. If necessary, a referral for inpatient treatment will be made. This involves clinical judgement on the part of the treating psychiatrist(s) who are experienced with this population. This does not include transient modest worsening of drug use since substance dependence is a chronic relapsing condition. If more intensive treatment is deemed necessary, the participant will be offered continued weekly meetings with the physician and their counselor until appropriate referral can be made.

Drop-out criteria during the screening and study period include:

1) If the patient develops serious psychiatric symptomatology (weekly psychiatric evaluation, CGI > 6 (much worse than baseline) for two consecutive weeks).

2) If the patient develops signs of cardiovascular instability (weekly vital signs and clinical evaluation; pulse at rest > 100 or BP at rest > 140/90 mm Hg for more than 2 weeks or SBP > 160, DBP > 110, sitting quietly HR >110 on any visit will result in immediate discontinuation of study medication).

3) Cardiac risks defined as chest pains, fainting, or arrhythmias.

4) If the patient's continued cocaine use even if improved from baseline, places them at risk for self-destructive behavior or otherwise places them at significant risk (weekly clinical evaluation; CGI > 6 (much worse than baseline) for two consecutive weeks).

5) If the patient becomes pregnant (monthly urine pregnancy testing).

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens
Approximately 20 ml of blood (4 teaspoons) will be drawn at the time of baseline assessment and study completion for routine analyses (hematology, blood chemistry (including liver function tests), TSH, and blood pregnancy test for women). They may be repeated during the study if clinically indicated.

Quantitative urine toxicology screens conducted at each visit (3 per week) will provide benzyolecgonine levels and serve as an objective marker of current cocaine use.

HIV testing will be offered in order to determine the HIV status of all possible participants; participants may refuse if they do not want to be tested. Nursing staff will provide Pre and Post-test counselling to assist participants with any HIV+ results. Pre-HIV test counselling discusses the possibilities of a HIV+ test and the procedures after a positive HIV test is found. Post-HIV counselling assesses for suicidal and/or homicidal ideation, along with domestic violence issues. If a person tests positive for HIV, the research psychiatrist on staff with be notified and will do a secondary evaluation for necessity of immediate psychiatric care. Additionally the nursing staff will notify the department of health and provide a list of referrals for follow-up care.

A confirmatory HIV test will not routinely be done due to the accuracy of the saliva quick test, however if a participant tests positive using the saliva quick test a confirmatory blood test will immediately be done.

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment
Screening:

Psychiatric and substance use information will be obtained in the structured screening interview. The following evaluations will be used to determine whether a patient is appropriate for study participation. These data will be collected during the initial interviews and will cover inclusion/exclusion criteria. Additionally, a brief description of the study will be provided to eligible subjects to determine if the subject is interested in participating. If so, then informed consent will be obtained. Full screening will be completed within 1-2 weeks. The majority of measures in this treatment study are standard measures.

Treatment Study Screening Procedures:

An important component of this behavioral therapy development study is to identify cognitive, verbal, and behavioral mechanisms that predict treatment response. A range of assessment instruments have been included to assess the relationship between key constructs within each of these three domains and treatment outcome. This information may provide a basis for continuing the development of more effective cognitive-behavioral treatment platforms and targeted pharmacotherapy strategies.

Initial contact and interview: The initial contact will include a brief interview to cover inclusion/exclusion criteria and a brief description of the study will be given to the patient to determine if the patient is interested in participating. If the patient is interested then an informed screening consent will be signed by the patient and witnessed by a member of the research staff.

Medical aspects: Patients will receive a full physical examination and an ECG before admission. Laboratory tests will include: hematology, blood chemistry (including liver function tests), urinalysis, and blood pregnancy test for women (45 minutes). Urine will be collected and tested for substances of abuse, three times a week for the duration of the study.

Demographic information: Patients will complete a Demographic Form, Medical and Psychiatric History Form, and Family Medical and Psychiatric History Form. These self report forms provide data on age, race, socioeconomic status, marital status, educational and occupational levels, significant medical history, and current/history of major psychiatric disorder in the patient and his/her first degree relatives. Patients will also complete a Locator Form so that they can be contacted for follow-up (30 minutes).

c*. Screening and Diagnosis:* Uniform screening procedures will be used. A standardized telephone interview is followed by an appointment for those who meet general study criteria. No identifying information is recorded until the potential participant completes the study explanation and consent process; evaluation follows consent using standardized measures. Common, standardized intake and evaluation training will be conducted for all procedures and instruments.

Eligibility Determination via Physical Examination and Psychiatric Evaluation: Review of history, physical, and laboratory evaluations and the medical-psychiatric evaluation note lead to final determination of eligibility. This information will be reviewed by the study psychiatrist trained in the protocol.

Intake Evaluation, Instruments, and Outcome Measures (60 – 75 minutes): The Mini-International Neuropsychiatric Interview DSM-IV (MINI; Sheehan et al., 1998): The MINI, administered by trained clinicians (at least masters level), provides current diagnoses of substance use disorders, mood and anxiety disorders, and screens for psychotic disorders to assure study eligibility. The Conner's Adult ADHD Diagnostic Interview for DSM-IV (CAADID; Epstein et al., 2001) is also administered to assess for the presence of a DSM-IV ADHD disorder. The CAADID has been used in large-scale pharmacological trials to diagnose adults with ADHD (Michelson et al., 2003). Instruments are discussed below:

Clinical Global Impression Scale-Observer (CGI-O) (5 minutes): This modified CGI (Guy, 1976) measures global severity of cocaine related problems and improvement from baseline (7 point likert scale). The psychiatrist will make ratings using all available information to yield treatment outcome data.

Addiction Severity Index-Computerzied version (ASI; 5th Edition 1997- 40 minutes): This widely used computer administered version evaluates problem severity in seven problem areas (McLellan et al., 1992).

Timeline Follow-back (TLFB) Assessment (30 minutes): The Timeline follow-back method (Sobell and Sobell 1992) will gather self-reported cocaine use data for each day during the 28 days prior to the study enrollment and each day during the study period. As part of the TLFB interview, participants are asked to assign a dollar value to the amount of cocaine used. The TLFB will be used to corroborate urine toxicology results. Marijuana, alcohol, nicotine, and other drug use self-report data will also be gathered during the TLFB interview.

Cocaine Selective Severity Assessment (5 minutes): This clinician-rated questionnaire (Kampman et al, 2002) evaluates the occurrence and severity of cocaine dependence symptoms and is reported to predict abstinence in medication trials.

Brief Substance Craving Scale (BSCS) (5 minutes): This 16-item self-rated questionnaire (Somoza et al., 1999) assesses the frequency, intensity and amount of time spent craving cocaine and other substances.

The Risk Assessment Battery (10 minutes): This questionnaire will assess research participants for HIV related risky behaviors (Metzger et al, 1992).

Quality of Life, Enjoyment and Satisfaction Questionnaire (QLESQ): (short form- 5 minutes)). (Endicott et al.,1993). Is a self-administered 16-item questionnaire rating each item from 1 (very poor) to 5 (very good).

Systematic Assessment for Treatment Emergent Events (SAFTEE) Adverse Event Form: The research nurse or psychiatrist query the participant and log side effects and other treatment emergent events during the past week (but will also query participants at each visit), record their severity, and what action was taken, and whether they are continuing or resolved.

Implicit Relational Assessment Procedure (IRAP; Barnes-Holmes et al., 2008 – 30 minutes)). The IRAP is a computer-based task in which participants are asked to respond quickly and accurately in ways that may be similar or dissimilar to their established beliefs about cocaine use. Participants are exposed to two practice blocks and six test blocks. Each block presents the same 12 trials; 6 positive consequences of cocaine use and 6 negative consequences of cocaine use. Participants' reaction time to each item is recorded and used to calculate difference scores between the positive and negative consequence trials to yield an overall score.

Drug Stroop (15 minutes). (Carpenter et al., 2006) The drug stroop task requires participants to respond to the color (blue, red, green, yellow) of a drug related or neutral (non-drug related) word by pressing the same colored key on a response pad as quickly and accurately as possible. For each trial, a fixation-cross appears in the center of the monitor screen for 1000ms and was then replaced by a colored word. Each word remains on the screen until the participant responds or for a maximum time period of 6000ms. Two blocks of 50 trials, for a total of 100 words (20 words for each for heroin, cocaine, marijuana, mixed drug, and neutral word groups), follows 16 practice trials. A 5-minute rest period is programmed into the task following the completion of the first block of 50 words. The primary measure is interference from cocaine related words, which is calculated for each participant by subtracting their average response time on neutral words from their average response time to the cocaine words. Positive values (i.e. slower responding to the cocaine words) are interpreted as reflecting an attentional bias towards cocaine related stimuli.

DARN-C Psycholinguistic Coding System (30 minutes) Amrhein et al., 2003). Dr. Amrhein's DARN-C coding system assesses a participant's Desire, Ability, Reasons, Need, and Commitment language as it pertains to changing his/her use of cocaine. A participant's speech is coded along two dimensions, frequency and strength. This system has been used to predict treatment engagement and change over a 12-month period. Audiotaped sessions will be coded by trained raters. No identifying information or specific content from a session is transcribed. Coding procedures yield a string of numerical codes.

Wisconsin Card Sort (15 minutes), a measure of executive functioning and cognitive flexibility.

Relapse Prevention Skills: Coping Strategies Scale (CSS) – Brief Version. (4 mins) (Litt et al., 2005) The CSS is a 23-item questionnaire (originally adapted from the Processes of Change questionnaire, Prochaska et al., 1988) that assesses coping skills such as problem solving and dealing with urges to use substances of abuse.

The Behavior Rating Inventory of Executive Function (20 minutes) (Adult Version (BRIEF-A; Rabin et al., 2006) is a 75-item standardized self-report measure that assesses an individual's perception of their self-regulation in their everyday environment. It yields nine reliable subscale scores reflecting executive functioning (e.g. inhibit, self-monitor) and two broader indices: Metacognition and Behavioral Regulation. The Behavioral Regulation score is the measure of interest.

Working memory (15 minutes Letter-Number Sequencing, Wechsler, 1997), The letter number sequencing task will be utlized to assess a participant's working memory.

The discounting of delayed rewards (Delayed Discount Program, Robles et al., 2008): (15 minutes).
Please attach copies, unless standard instruments are used
TABLE 3.pdf

Off label and investigational use of drugs/devices

Choose from the following that will be applicable to your study
✓ Drug
Select the number of drugs used in this study
1

Drug #1

Name of the drug
Extended-release mixed amphetamine salt
Manufacturer and other information

Other Name: Adderall-XR

Manufacturer: Shire and Teva

Approval Status
IND is approved
IND#
79,322
Who holds the IND/IND sponsor?
IND is held by PI/CU Investigator
Levin, Frances, MD

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
Yes
Maximum duration of delay to any treatment
Once screening is completed, there is no delay for study entry for eligible patients.

The patient should receive the behavioral treatment treatment within 2 weeks after the initial screening evaluation. For those who the behavioral intervention alone will not work, will be randomized to a medication treatment arm 4 -weeks after beginning the treatment, if they have been randomized to the active medication arm. Those assigned to the placebo group will not receive active medication, but will continue to receive the behavioral treatment. CRA+CM is an evidenced based treatment program for the treatment of cocaine dependence.

Maximum duration of delay to standard care or treatment of known efficacy

Because the screening procedure sometimes requires 2-3 meetings, individuals may not begin the computer-assisted CRA+CM therapy until 2-3 weeks after their initial screening evaluation for the study.

Treatment to be provided at the end of the study

At the conclusion of the 15-week protocol, the participants will be offered supportive therapy for at least one additional month or until an appropriate referral for on-going treatment is made.

If a patient was on active medications and they were shown to be beneficial, they will be given an appropriate referral for ongoing treatment.

Clinical Treatment Alternatives

Clinical treatment alternatives

Psychotherapeutic approaches are commonly used for encouraging reduction in use or abstinence of drugs of abuse in general. There are no accepted pharmacotherapies for the treatment of cocaine dependence. These approaches include motivational enhancement and cognitive behavioral therapy, 12-step facilitation, and other methods. Alternative treatment settings for substance abuse include drug free outpatient treatment, inpatient detoxification, or residential treatment. Patients will be informed that they can request referrals for other treatment options.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period

The major risk of research participation is related to drug administration. MAS-ER has been approved for maximal use of up to 60 mg/day. Adverse events most commonly associated with amphetamine administration include: insomnia, emotional labiality, nausea/vomiting, nervousness, palpitations, elevated blood pressure, and rapid heart rate. Less common serious side effects include severe hypertension, seizures, psychosis, and myocardial infarction. The risk of abuse is of concern with the administration of amphetamine but is substantially lowered by administering extended release preparations. Although amphetamines have been prescribed for several decades and no clear teratogenic risks have been described, it cannot be assumed that it is safe to administer during pregnancy. Female participants will be required to use adequate methods of birth control (condom with spermicide, diaphragm with spermicide, birth control pills). Serum pregnancy tests will be evaluated at baseline and throughout the trial.

Recently, there has been added concern of the risk of sudden unexplained death. In extremely rare cases sudden unexplained deaths have been reported in children taking Adderall. This concern caused Health Canada to remove Adderall from the market in 2/2005; however, Health Canada returned Adderall to the Canadian market in 8/2005 because of inconclusive evidence. At the February 2006 advisory panel meeting it was learned that Adderall was involved in more fatal case reports than any other ADHD/ADD drug, with 24 deaths reported from 1999 through 2003 regarding patients who took Adderall for ADHD or ADD. The warning information for all stimulant ADHD drugs includes the following:

• Sudden death has been associated with stimulants at usual doses in children and teens with structural heart abnormalities or other serious heart problems.
• Children, teens, or adults who are being considered for treatment with stimulant medicines should have a careful checkup (including family history and a physical exam) to check for heart disease.
• Patient who develop symptoms such as chest pain during exertion, unexplained fainting, or other possible heart symptoms should promptly get a heart evaluation.
• Sudden death, stroke, and heart attack have been reported in adults taking stimulant drugs at usual doses for ADHD.
Adults with such heart abnormalities should also generally not be treated with stimulant drugs.

The reports of sudden unexplained death have been reported in FDA post-marketing surveillance of Adderall/Adderall XR (that is, reports released after a medication is put on the market). Most of these cases had complicating factors, including heart disease, family history of a certain kind of heart disease (ventricular tachycardia), heat exhaustion, dehydration, near drowning, rigorous exercise and/or unexplained accumulation of the drug resulting in toxic levels. Because of how rare this problem is, it is not known whether the rate of death in association with Adderall XR differs statistically from that of the general public (about 1/100,000). The Food and Drug Administration has been reviewing these cases, and at the present time has not concluded that Adderall or Adderall XR were responsible for these deaths. The FDA is continuing to investigate these reports, and has not recommended withdrawal from the market.

Amphetamines have a high potential for abuse. Taking amphetamines for long periods of time may lead to drug addiction. Particular attention should be paid to the possibility of people obtaining amphetamines for non-therapeutic use or distribution to others. The FDA has issued a Black Box warning regarding the use of Adderall XR and amphetamines. Misuse of amphetamine may cause sudden death and serious cardiovascular adverse events.

In this study, we will protect adults from this risk by medically evaluating and monitoring them for any of the complicating factors listed above. Adults will receive a physical examination, electrocardiogram, thyroid function tests and liver function test at baseline. Vital signs will be

checked at every visit. Additionally, some medications can affect how much of this medicine enters into the bloodstream; we will monitor all other medications, including over the counter medications that the adult may take. Prescription and non-prescription medications will be monitored by patient report once per week; any potential drug interactions will be reviewed by a physician (see also exclusion criteria).

Weight loss is also a side effect of MAS-ER. Therefore, BMI will be monitored closely during the study and dose adjustments will be made if necessary. Side effects can be reduced or eliminated by lowering or discontinuing the medication.

There is a growing literature in which cocaine dependent individuals were maintained on methylphenidate or dextroamphetamine without untoward events (Grabowski et al., 2001; 2004; Levin et al., 2005; Schubiner et al., 2001). Although the medication has been well-tolerated when administered to cocaine-dependent individuals, we cannot be absolutely certain that the side effect profile will remain the same when co-administered with cocaine. The interactions between amphetamines, cocaine, or other drugs which participants may use during the study are not known at this time. Cocaine can cause seizures and serious heart problems, and it is not known whether amphetamines would alter these risks. Therefore, patients with histories of convulsions or heart disease will be excluded. Patients will be informed about the common side effects of MAS-ER and warned about the possibility of interactions between this medication and cocaine or other drugs. Participants in this study are identified as users of other drugs. To the extent that they do not reduce or eliminate other drug use, risk may increase. Some of these risks are known; others are of an uncertain magnitude. Our experience with these issues is discussed below in the methods to attenuate risk.

Blood drawing may cause slight discomfort at the site of needle entry, resulting in a small bruise. Participants will be warned about this. Other risks include participants' discomfort with being asked uncomfortable questions or the psychological distress that may occur if a participant agrees to be tested for HIV.

As one progresses through the treatment study, depressive symptoms may emerge as a result of subjects using cocaine or being unable to stop using. Depressive symptoms will be monitored once a month using the Hamilton Depression Scale.

The structured interviews, rating scales, and questionnaires should add no physical risk. The major disadvantage is the time required to complete them and that some of the questions might be embarrassing to patients. Our past experience with these measures indicates that they are acceptable to participants. However, some people have found them uncomfortable and/or tiring because the interviews/assessments are long and of a personal nature. Patients are informed that they may refuse to answer any questions and may ask to stop at anytime. If participants become upset during the interviews/assessments, assistance will be made available to them.

Risks of Diversion The risks of stimulant diversion are small but not negligent. The SAMHSA National Survey on Drug Use and Health collects data on a broad array of substances of abuse, including non-medical use of prescription stimulants. For 2010, nonmedical stimulant use was

0.4%. While not insignificant, it is substantially lower than nonmedical use of tranquilizers or pain medication. The risk of abuse is of concern with the administration of amphetamine but is substantially lowered by administering extended release preparations. Nevertheless we will take several precautions to minimize the risks of abuse and/or diversion of Adderall. Adderall will be provided on a weekly basis. Patients who are found to abuse/divert their study medication will be taken off their study medication.

Describe procedures for minimizing risks

Exclusion Criteria

The exclusion criteria (see above) are designed to minimize the medical and psychiatric risks to participants as discussed above, including risks of adverse events and side effects such as intoxication. Pregnant or lactating women or those not practicing reliable birth control methods are excluded. Patients are instructed to inform their psychiatrist immediately if they suspect they may be pregnant, and urine HCG is monitored monthly during the trial.
Patients with histories of psychotic illness other than transient drug-related psychosis that in the investigator's judgment are unstable or would be disrupted by study medication will be excluded. During the study, Dr. Levin and the clinic staff will coordinate clinical care. Additionally, the treating psychiatrist monitors participants' mental status weekly.

The baseline medical evaluation includes physical examination, blood chemistry profile (including liver function tests, complete blood count, urinalysis, HCG) and electrocardiogram (ECG) is designed along with clinical history to detect chronic and unstable medical illnesses.

History of allergic or adverse reactions to MAS-ER is exclusionary.

Participants with significant suicide risk at the time of initial evaluation or history of serious suicide attempt will be excluded and referred for appropriate non-research treatment. Participants will be examined for suicidal ideation and risk during their weekly visits with the research psychiatrist and participants who develop a significant risk during the trial will be removed from the study and treated as clinically indicated.

Ongoing medical assessment

In order to minimize the risk associated with the study medication, vital signs (heart rate and blood pressure) and medication-related side effects will be monitored by the research nurse three times a week. At each weekly visit the psychiatrist will discuss side effects of medication, review the Side Effect Questionnaire, will evaluate all reported vital signs and review cardiac risks to determine whether the dose is being tolerated. Inability to tolerate medication side effects will result in the reduction or temporary discontinuation of study medications. Patients will be discontinued from study medication if they 1) cannot tolerate the medication, 2) have a medical or psychiatric emergency, 3) become hospitalized or 4) become pregnant. Patients may be removed from the trial if they repeatedly miss scheduled appointments or clinical worsening necessitates more intensive treatment.

Twelve weeks after study completion (27 weeks after enrollment) an attempt will be made to evaluate all participants to explore whether there may be effects of treatment that endure or emerge after medication discontinuation. In exploratory analyses, outcome at 27 weeks will be compared between groups originally assigned to medication or placebo on the main primary and secondary outcomes listed above and on Addiction Severity Index composite scores.

Data Safety/Monitoring Plan

Patients are closely monitored throughout the trial as described above. Drs. Levin and Carpenter, the Principal Investigators on this application will be responsible for data and safety monitoring throughout the trial. In addition to weekly clinic visits, study participation will be monitored independently by the Data and Safety Monitoring Board. The board will meet on an annual basis to assess the recruitment, progress, safety, adverse events, and serious adverse events associated with the study. The Data and Safety Monitoring Board will be comprised of three individuals: 1) Dr. Steve Donovan, an expert child and adolescent psychopharmacologist with additional expertise in substance abuse, 2) Dr. Deborah Haller- a psychologist who has run numerous clinical trials and expertise in the evaluating psychological treatments in medically compromised patients and 3) Dr. Soteri Polydorou – an internist and a graduate of our Addiction Fellowship Program who has had significant experience working within the framework of clinical trials evaluating behavioral and pharmacological treatments for substance use disorders. Individuals on the Safety Monitoring Board will be blind to study medication but can be informed by the un-blinded pharmacist if deemed necessary. If they believe that termination of the trial is warranted, the blind of all study patients will be broken.

Patient Education

All patients will be informed of the possible side effects and risks enumerated above through extensive discussions with the research psychiatrist during the consent process. Patients will be warned that risks, as yet unknown, may occur when combining the study medication with cocaine or with other street drugs or alcohol. Patients are instructed to call us if any untoward effects occur and are given the phone number of our 24-hour answering service. One of the STARS affiliated physicians is on call 24 hours per day to answer questions and handle clinical emergencies.

Methods to Protect Confidentiality

Describe methods to protect confidentiality

A Certificate of Confidentiality will be acquired for this study from the National Institute on Drug Abuse to offer protection for the privacy of subjects by protecting identifiable research information from forced disclosure (e.g., through a subpoena or court order). The Certificate of Confidentiality will allow investigators and others with access to research records to refuse to disclose information that could identify subjects in any civil, criminal, administrative, legislative, or other proceeding, whether at the Federal, State, or local level. The Certificate of Confidentiality is granted for studies that collect information that, if disclosed, could damage subjects' financial, employability, insurability, or reputation, or have other adverse consequences.

We use coded records (i.e. initials and numbers), store signed consent forms in a locked safe, and try, to the best of our ability to maintain confidentiality. Only coded records will be entered into the computer and the security of electronic data is ensured at the level of the server, the user, and the database. We do, however, point out to prospective patients, that we cannot assure that their drug histories and other personal records might not become known.

TES is a web-based interactive coping skills training program. While the treatment modules are stored on a central server maintained by HealthSim, LLC, we will chose to have the participant's responses stored on our computer systems. We will not be utilizing the HealthSim server to manage and record participants' responses. This option will allow the clinical data to be stored on a secure computer system that will be protected (i.e. behind) by the firewalls of Columbia University medical center and the New York State Psychiatric Institute.

Will the study be conducted under a certificate of confidentiality?

Yes, we will apply for the Certificate of Confidentiality

Direct Benefits to Subjects

Direct Benefits to Subjects

Benefits to participants include a comprehensive medical and psychiatric assessment, and possible improvement in their symptoms of cocaine dependence.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
Yes
Please describe and indicate total amount and schedule of payment(s).
Include justification for compensation amounts and indicate if there are bonus payments.
During screening and treatment potential participants receive $5 for each clinic visit. This amount covers the cost of a round trip travel on NY City's public transportation. To facilitate the tracking of medication compliance we pay participants $10 for returning their medication bottle each week of the trial. The money is paid regardless of compliance status. That is, participants earn $10 whether the bottle is empty or contains unused medication.

Contingency Management Program. The proposed intervention will employ a computer-assisted version of the Community Reinforcement Approach plus Contingency Management as the behavioral intervention. Participants will receive coping skills training and earn draws from a prize-bowl, as part of the CM procedures, contingent on the provision of cocaine-free urine. The CM schedule will follow an escalating schedule as implemented in other contingency management studies (Higgins et al. 1994). including the one recently completed by our group (Martinez, Carpenter et al., 2011).

Urine samples will be collected on each visit. Participants receive draws from a prize bowl for each urine testing negative for benzoylecgonine. Failure to submit a scheduled specimen will be treated as cocaine positive. Each draw has a probabilistic chance of yielding one of four outcomes: an encouraging statement (e.g. 'good job'), a small prize valued at $2.50, a large prize valued at $20, and a jumbo prize valued at $100. The probability for each particular outcome is fixed for every draw and is based on the relative number of slips for each prize category in the prize bowl. The expected earning per draw is equal to $2.845 {(0.50*($0) + .418*($2.50) + .08*($20) + .002*(100)}.

Using previously employed frameworks the prize bowl will have 500 prize slips. 250 slips will be the encouraging statement (50% of the total slips), 209 slips will be for small prizes (41.8%), 40 slips will be for large prizes (8%), and 10 slips will be the jumbo prize (0.2%). Participants will earn 1 draw for every week in which all urines are benzoylecgonine negative. The escalating schedule will increase to a maximum of 10 draws. A a single large prize will be awarded when a participant first achieves 2 weeks of abstinence to offset the low rate of reinforcement (low number of draws) during the beginning of the program. Participants can earn a maximum of 315 draws for submitting cocaine-free urine samples on 100% of the scheduled treatment visits (45 scheduled visits over the course of the 15 weeks).

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