

Protocol Title:
**Extended-Release Mixed Amphetamine Salts
(Adderall-XR) for Adult ADHD and Cocaine
Dependence (Formerly Protocol # 5502)**

Version Date:
03/19/2014

Protocol Number:
6569R

First Approval:
04/25/2012

Clinic:
**Substance Treatment And Research Services
(STARS)**

Expiration Date:
04/01/2014

Principal Investigator:
**Frances Levin, MD
Email: frl2@columbia.edu
Telephone: 212-543-5896**

Co-Investigator(s):
**Suzette Evans, PHD
John Mariani, MD**

Research Chief:
Herbert Kleber, MD

Cover Sheet

Choose from the following that is applicable to your study

I am submitting an annual continuation without modifications

Division & Personnel

Division

What Division/Department does the PI belong to?

Substance Use

Within the division/department, what Center or group are you affiliated with, if any?

STARS

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.

The Project is a multi-site trial (Columbia University and University of Minnesota). John G. Grabowski is the Principal Investigator at the University of Minnesota site.

Application for Continuation of Research

Status

Current Status of Study:

All research interventions were completed. Only data analysis is ongoing.

Funding

Have there been any changes in funding status since the prior approval?

No

Have the principal investigator and other investigators made all required disclosures of financial interest in the study sponsor/product?

Yes

Summary

Have there been any study findings, recent literature, or untoward events occurring here or at other sites in the past year which might affect the analysis of the safety, risks or benefits of study participation?

No

Have there been any serious adverse events (serious and/or unanticipated problems involving risks to subjects or others at this site which occurred in the past year)?

No

Have all study staff with a significant role in the design or implementation of the human subject components of this study received required training in human research subject protections?

Yes

Is the study covered by a certificate of confidentiality?

Yes

Certificate expiration date (mm/dd/yyyy)

09/30/2016

Overall Progress

Approved sample size

100

Total number of participants enrolled to date

93

Number of participants who have completed the study to date

51

Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?

No

Comments / additional information

Sample Demographics

Specify population

Adult ADHD and cocaine dependent individuals

Total number of participants enrolled from this population to date

93

Gender and Ethnic Breakdown

There were 93 individuals enrolled in the above reference treatment study. The gender was broken down into 84 male and 9 female. Of the 93 participants 56 were White, 12 Black, 22 Hispanic, 1 Asian, and 2 Other.

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year

2

Did the investigator withdraw participants from the study?

No

Did participants decide to discontinue study involvement?

Yes

Circumstances of discontinuation:

One participant discontinued treatment in the past year. This participant went missing and was unable to be contacted despite numerous attempts.

Procedures

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

✓ Psychiatric Assessment

- ✓ Neuropsychological Evaluation
- ✓ Collection of Biological Specimens
- ✓ Medication Trial
- ✓ Use of Placebo or Sham Treatment
- ✓ Psychotherapy Trial
- ✓ Medication-Free Period or Treatment Washout
- ✓ 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
- ✓ Adults over 50
- ✓ Substance Users

Research Support/Funding

Will an existing internal account be used to support the project?

Yes

Describe internal account

This protocol, **6569R**, entitled "Extended-Release Mixed Amphetamine Salts for Adult ADHD and Cocaine Dependence" is currently funded with the RFMH grants office. The source of funding is 1 RO1 DA23652.

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 is currently funded

Source of Funding

Federal

Institute/Agency

NIDA

Grant Name

Extended-Release Mixed Amphetamine Salts for Adult ADHD and Cocaine Dependence

Grant Number

1 RO1 DA23652

Select one of the following

Multicenter(NYSPI is the lead site)

Business Office

RFMH

Does the grant/contract involve a subcontract?

No

Study Location

Indicate if the research is/will be conducted at any of the following

- ✓ NYSPI
- ✓ Other Columbia University Medical Center Facilities

This protocol describes research conducted by the PI at other facilities/locations

No

Lay Summary of Proposed Research

Lay Summary of Proposed Research

The proposed protocol is a 3 group double-blind, placebo-controlled outpatient study of the safety and efficacy of Adderall-XR (ER-MAS) in the treatment of comorbid ADHD and cocaine dependence. Since this medication has independently shown promise in helping with ADHD and cocaine abuse, we are proposing that it may be successful in the treatment of comorbid ADHD and cocaine abuse. We plan to randomize 88 subjects in a 14-week trial. The primary objectives of the study are to determine the efficacy of ER-MAS in promoting cocaine abstinence and improvement in ADHD symptomology among cocaine-dependent patients with comorbid ADHD.

Background, Significance and Rationale

Background, Significance and Rationale

Treatment of comorbid ADHD and cocaine dependence has faced theoretical and practical difficulties. Effective interventions have remained elusive. Methylphenidate sustained-release preparations, generally effective for ADHD treatment, produce little or no benefit in ADHD/SUD populations (Levin et al., 2006a; 2006b) and no benefit in the adult non-ADHD/cocaine dependence population (Grabowski et al., 1997). Factors lessening efficacy in the ADHD/cocaine dependence treatment group include: 1) methylphenidate sustained-release having lesser efficacy

in SUD compared to sustained-release dextroamphetamine, 2) inadequate dose, and 3) retention compliance problems. Circumventing these problems to assure a valid test, we will examine Adderall-XR at 60 and 80 mg compared to placebo with contingency management procedures to enhance retention. Given the promising research using amphetamine analogs as single-agent pharmacotherapies for cocaine dependence and ADHD independently, we believe that studying the effects of this medication treating both conditions simultaneously is warranted. A nearly unique opportunity exists to treat two conditions with a single medication ER-MAS. We hypothesize that both conditions will significantly improve with the use of this single medication.

Specific Aims and Hypotheses

Specific Aims and Hypotheses

Specific Aim 1: To determine the efficacy of ER-MAS in promoting cocaine abstinence and ADHD improvement among comorbid ADHD and cocaine-dependent patients.

Primary Hypothesis: Benzoyllecognine positive urine screens will decrease with greatest to least reductions from 80mg>60mg>PBO.

Hypothesis 2: ADHD-Rating Scale will decrease with greatest to least reductions from 80mg>60mg>PBO.

Specific Aim 2: To determine the effect of ER-MAS on improving general functioning and impulsivity among comorbid ADHD and cocaine-dependent patients.

Hypothesis 4: There will be greater improved CGI scores in participants receiving d-AMPH compared to PBO.

Hypothesis 5: ER-MAS will decrease impulsivity as measured by several self-report (Barratts Impulsivity Scale) and behavioral measures (Card Sort, IMT, DMT, BART, Delayed Discounting Task) compared to PBO.

Description of Subject Population

Sample #1

Specify subject population

Adult ADHD and cocaine dependent individuals

Number of completers required to accomplish study aims

48

Projected number of subjects who will be enrolled to obtain required number of completers

100

Age range of subject population

18-60

Gender and Ethnic Breakdown

Both males and females will be recruited. All eligible subjects are accepted; however, past experience with recruitment for cocaine dependence suggests that the approximate gender distribution for this study will likely be 25 % female and 75 % male. Previous and ongoing studies at STARS have had samples comprised of approximately 45% Caucasians, and 55% ethnic minorities distributed as 24% African-American and 31% Hispanic-American. We anticipate a similar representation in this project. We will make every effort to recruit minority patients in order to ensure the generalizability of our findings to the overall treatment population.

Description of subject population

We plan to enroll 100 participants into the study who meet criteria for current ADHD and cocaine dependence.

Recruitment Procedures

Describe settings where recruitment will occur

The Project is a multi-site trial (Columbia University and University of Minnesota). The Columbia University location consists of two sites, the Substance Treatment and Research Services (STARS) of the Division on Substance Abuse and at a satellite location (STARS Downtown) situated on 1775 Broadway, 14th Floor, NY, NY 10019. STARS downtown is leased by NY Presbyterian Hospital Department of Psychiatry and will not require the involvement of additional IRBs.

Both sites were slated to randomize 75 participants to meet our targeted N=150 to complete the power analysis. To date, the University of Minnesota has randomized 45 participants. Despite this being a difficult to recruit population, the retention rates at both sites have exceeded grant expectations, with MN at a striking 86% and NY at 59%. The Columbia site met the original targeted 75 participants randomized, received approval to enroll and randomize additional patients, and expect to randomize 1-2 more this month. By combining our increased numbers with the Minnesota site we will complete the study in its collaborative fashion in the upcoming year with almost the full sample originally intended and will have exceeded the number of patients that we expected to complete the study (N= 88 rather than 82).

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

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.

All patients will receive an explanation of the study risks, benefits, treatments, procedures, and options for alternative treatments. Patients who wish to participate will be asked to sign the treatment consent form following resolution of any questions and clear indication that they understand the nature of the study and the consent form.

How will the study be advertised/publicized?

We will recruit individuals with ADHD and 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 ADHD and 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

Please provide the NCT Registration Number

NCT00553319

Concurrent Research Studies

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

Yes

Describe concurrent research involvement

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

Adult ADHD and cocaine dependent individuals

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

<p>1. Men and women between the ages of 18-60 who meet DSM-IV criteria for current cocaine dependence and adult ADHD (DSM-IV-TR).</p>	<p>1. Structured Clinical Interview for DSM-IV (SCID I); demographic information</p>
<p>2. Used cocaine at least four days in the past month</p>	<p>2. Subject self-report; urine drug screen</p>
<p>3. Must have a Body Mass Index (BMI) > 18 kg/m²</p>	<p>3. Weight and height measurement</p>
<p>4. Alcohol Breathalyzer (BraC) at consent of < 0.04%</p>	<p>4. Breathalyzer</p>
<p>5. Individuals must be capable of giving informed consent and capable of complying with study procedures.</p>	<p>5. Initial contact interview</p>
<p>6. Women of childbearing age will be included in the study provided that they are not pregnant, based on the results of a blood pregnancy test drawn at the time of screening. They must also agree to use a method of contraception with proven efficacy and agree not to become pregnant during the study. To confirm this, urine pregnancy tests will be repeated monthly. Women will be provided a full explanation of the potential dangers of pregnancy while on the study medication. If a woman becomes pregnant, the study</p>	<p>6. Medical History; serum HCG; urine pregnancy tests</p>

medication will be discontinued.

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

- | | |
|--|---|
| <p>1. Meets DSM-IV-TR criteria for bipolar disorder, schizophrenia or any psychotic disorder other than transient psychosis due to drug abuse.</p> | <p>1. Structured Clinical Interview for DSM-IV (SCID)</p> |
| <p>2. Individuals with any current Axis I psychiatric disorder as defined by DSM-IV-TR supported by the SCID-I/P that in the investigator's judgment are unstable or would be disrupted by study medication or are likely to require pharmacotherapy during the study period.</p> | <p>2. Structured Clinical Interview for DSM-IV (SCID)</p> |
| <p>3. Individuals with current major depressive disorder. However, individuals who are currently stable on a psychotropic medication for three months with a HAM-D <14 may be included.</p> | <p>3. Structured Clinical Interview for DSM-IV (SCID); psychiatric evaluation</p> |
| <p>4. Individuals physiologically dependent on any other drugs (excluding nicotine or cannabis) which require medical intervention.</p> | <p>4. Structured Clinical Interview for DSM-IV (SCID)</p> |
| <p>5. Individuals with current suicidal risk.</p> | <p>5. Structured Clinical Interview for DSM-IV (SCID)</p> |
| <p>6. Individuals with coronary vascular disease as indicated by history or suspected by abnormal ECG, cardiac symptoms, fainting, open-heart surgery and/or arrhythmia, and family history of ventricular tachycardia/sudden death.</p> | <p>6. Medical history including a cardiovascular risk profile and ECG</p> |
| <p>7. Unstable physical disorders which might make participation hazardous such as uncontrolled hypertension (SBP > 140, DBP > 90, or HR > 100 when sitting quietly), acute hepatitis (patients with chronic mildly elevated transaminases < 3x upper limit of normal are acceptable), or uncontrolled diabetes.</p> | <p>7. Medical history, physical examination and laboratory tests.</p> |
| <p>8. Individuals with a history of seizures</p> | <p>8. Medical history</p> |
| <p>9. History of allergic reaction to candidate medication (amphetamine and/or ER-MAS).</p> | <p>9. Medical history</p> |
| <p>10. Women who are pregnant or nursing</p> | <p>10. Self-report,</p> |

serum HCG

- | | |
|--|-----------------|
| 11. History of failure to respond to a previous adequate trial of the candidate medication for cocaine dependence | 11. Self-report |
| 12. Individuals who are legally mandated (e.g., to avoid incarceration, monetary or other penalties, etc.) to participate in substance abuse treatment program | 12. Self-report |
| 13. History of glaucoma | 13. Self-report |
| 14. Individuals who report use of monoamine oxidase inhibitors within 14 days of study start. | 14. Self-report |

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 #

5474R

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

Bryan, Benjamin, MD

Davis, Glen

Huynh, Toai, MD

Kelly, Meredith, MD

Levin, Frances, MD

Manubay, Jeanne, MD

Mariani, John, MD

Mogali, Shanthi, MD

Naqvi, Nasir, MD

Vaughan, Barney, MD

Type in the name(s) not found in the above list

Elias Dakwar, MD

Study Procedures

Describe the procedures required for this study

Personnel:

Frances R. Levin, M.D.: Psychiatrist with 17 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.

Suzette M. Evans, Ph.D.: Psychologist with 17 years experience in substance abuse research will supervise all research and administrative aspects of the study. This includes regular meetings with the interviewers regarding accuracy and consistency of data collection, monitoring patient flow, patient screening, and data management. She will also directly supervise the research assistant.

Kenneth Carpenter, Ph.D.: Psychologist with 8 years of experience in substance abuse research and treatment. He will provide direct clinical supervision to the interviewers and train them to conduct the structured interviews. He will also review all written assessments and diagnoses.

Research Psychiatrist: (Frances Levin, M.D., Wilfrid Raby M.D., Ph.D., Maria Sullivan, M.D., Ph.D., Adam Bisaga, M.D., John Mariani, M.D., Shabnam Shakibaie, M.D., Benjamin Bryan, M.D., Stanislav Vorel, M.D., Elias Dakwar, M.D., Gregory Tau, M.D., Ph.D., Shanthi Mogali, M.D., Nasir Naqvi, M.D. PhD., Toai Huynh, M.D., Glen Davis, M.D., Meredith Kelly, M.D., and Barney Vaughan, M.D.) The Research Psychiatrist will meet with individuals who meet the initial criteria for ADHD and 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: (Daniel Brooks, M.A., Elisa Leimsider, M.S.W., Kenneth Carpenter, Ph.D., Amy Mahony, M.A., Margaret Rombone, Ph.D., Nehal Vadhan, 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. The therapist will be responsible for conducting relapse prevention therapy. 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 two 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 (Jacob Minor, 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 (Daniel Brooks, M.A., Elisa Leimsider, M.S.W., Amy Mahony, M.A., Margaret Rombone, Ph.D., Nehal Vadhan, 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, Raby, Bisaga, Mariani, Shakibaie, Sullivan, Bryan, Vorel, Dakwar, Mogali, Naqvi, Huynh, Davis, Kelly and Vaughan), who have extensive experience with individuals with substance use disorders in treatment settings.

b. Drug Administration: Extended-release mixed amphetamine salts (ER-MAS) 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. Raby, Bisaga, Mariani, Shakibaie, Sullivan, Bryan, Vorel, Dakwar, Tau,

Mogali, Naqvi, Huynh, Davis, Kelly 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 (Daniel Brooks, M.A., Elisa Leimsider, M.S.W., Amy Mahony, M.A., Margaret Rombone, Ph.D., Nehal Vadhan, Ph.D., Jaclyn Bronstein, M.A., Paula Bertone, M.A., Jack Grabon, M.S.W.) under the supervision of Dr. Carpenter.

General Design:

88 subjects whom meet criteria for comorbid ADHD and cocaine dependence, and all other study inclusion and exclusion criteria (described above) will be assigned to the 14-week double-blind, placebo-controlled treatment trial. Subjects will be randomized to receive either placebo or ER-MAS 60mg or ER-MAS 80mg. Table 1 shows the overall design.

Table 1. Overall study design

1. Design Overview

This 14-week, three arm (two medication doses versus PBO), prospective, parallel groups, randomized PBO-controlled trial with PBO lead-in as well as medication run-up and run down weeks, will provide clear data on efficacy and safety for definitive Phase III trials, which if successful will lead to improved treatment for A-ADHD/S-SUD. The sequence diagrammed below includes: PBO lead-in to enhance compliance, assure precise diagnosis/current drug use and evaluate 'PBO response'; run-up to assure safety, and; run down/ lead out for both comfort and diminishing "blind breaking."

Single-Blind PBO Lead-In Phase: A PBO lead-in period provides a unique opportunity to establish treatment research directed behavior thus minimizing attrition, determine PBO response and other baseline characteristics, and to further verify the subject's ability to participate. Participants who meet inclusion criteria and who sign informed consent will be place on placebo, under single-blind conditions for a 1-week period (Days 1-7). The placebo lead-in phase will allow us to enter only those participants who have demonstrated a commitment to the study by attending the required study visits during the first week of treatment. Additionally, the placebo lead-in phase will allow us to assess if some participants are able to significantly decrease their cocaine use during the first week of the study. Subjects will provide urine samples and will be given capsules for 1 week; those unable to complete this rudimentary procedure will not be randomized.

Randomization: Following PBO lead-in randomization will be by computer-generated blocks of

four (two medication and two PBO assignments/block, randomly permuted order) stratified by frequency of use. Those patients randomized to the placebo group will continue to receive placebo throughout the treatment. Patients randomized to the ER-MAS groups will begin receiving medication at the start of week 2 and will receive a stable dose of ER-MAS 60mg by study day 5 and 80mg by day 7.

Medication Run-Up and Treatment: The 12-wk phase is the primary trial focus. As noted in the table, medication run-up will occur in the first week and the subjects will be maintained for 11 additional weeks.

Medication Run-Down: To diminish discomfort and to some extent protect the blind, a one-week dose run-down reversing the run-up sequence will be completed.

Dosing Schedule: Subjects will take capsules (PBO or ER-MAS), over a 7-day run up period with all subjects receiving terminal dose by Day 8 as titrated as in Table 5 below.

ER-MAS Effect: Amphetamine analogs have a variety of benefits and risks. Notably, there have been no medication related adverse events in studies of cocaine dependent populations administered d-amphetamine or methylphenidate (Grabowski et al., 2001; 2004b; Levin et al., 2006a; 2006b; 1998b; Shearer et al., 2003) despite continued cocaine abuse by some subjects. Amphetamine analogs can interact with a variety of agents but concomitant drug use will be carefully monitored. Benefits reported for d-amphetamine in the above cited subjects include diminished S-SUD at doses of 60 mg or greater (Grabowski et al., 2004b).

Medications: ER-MAS or matching placebo will be prepared by our pharmacy at the New York State Psychiatric Institute, packaged in matching gelatin capsules with lactose filler and an equal amount of riboflavin. At each weekly visit, the research psychiatrist orders the dose of medication for the coming week according to the schedule (described above). The research nurse obtains weekly medications for each patient from the pharmacist and delivers it to the patient.

ER-MAS 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 50 mg of riboflavin. ER-MAS or matching placebo are given in a "fixed-flexible" dose schedule with the dose titrated to 60 or 80 mg per day or the maximum tolerated dose. The standard dose titration will be 10 mg per day until maximum or tolerated dose is reached. Although, ER-MAS is FDA approved for the treatment of ADHD in doses up to 60 mg per day, medication doses in this study are higher than the standard recommended dosage, higher doses may be necessary for

adult cocaine abusers with ADHD who are quite tolerant to stimulant effects (Levin et al., a,b). However, side effects and risks are unknown, particularly in combination with cocaine. Higher doses of amphetamine were found to be more effective in reducing cocaine use among non-ADHD cocaine-dependent individuals (Grabowski et al., 2004b), where 60mg had high efficacy than lower doses. Additionally, Grabowski and SARC colleagues are currently conducting a further study examining 80 mg d-amphetamine SR (Spansules) in the cocaine-alone population. Therefore, for this study, doses of 60 mg/day and 80 mg/day will be compared. If tolerated, patients will ingest three capsules packaged in gelatin capsules each morning or early afternoon with either 60 mg/day or 80 mg/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 ER-MAS, 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 ER-MAS). During week 14 patients on active medication will be tapered off ER-MAS.

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 as exceptions to the protocol. 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 think 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 14-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 14 week trial, or at the conclusion of the patient's involvement in the trial (if they do not complete all 14 weeks), patients will learn their treatment assignment.

Medication Compliance, Preparation, Dosing: Medication compliance requires special monitoring including: a) riboflavin, b) amphetamine salt analytical chemistry, and c) pill counts. Riboflavin is a supplemental surrogate marker for ingestion (Fuller et al., 1983; 1986; Grabowski et al., 2001; 2004a; O'Malley et al., 1992) when administered in greater than dietary amounts. ER-MAS and PBO will be packaged in matching gelatin capsules with 50 mg riboflavin distributed across capsules with monitoring via ultraviolet fluorescence. The subject's responsibility is discussed with her/him emphasizing adherence and accuracy in reporting use and side effects. Monetary reinforcement for return of pill bottles will further enhance compliance. For ethical reasons, this procedure is not for medication ingestion but to account for medication intake or its absence. MEM system bottle caps are prohibitively expensive and the value of the combined techniques described has proven effective at both sites.

The riboflavin marker procedure and structured-pill count are complimentary measures of medication compliance where riboflavin detection provides evidence of study medication ingestion and the structured-pill count provides more detailed self-report data about pill taking. Compliance with study medication will be encouraged and problems with adherence to the study medication regimen will be managed clinically by the research psychiatrist. Patients will not be dropped from the study for medication noncompliance, although study medication may be discontinued for noncompliance or tolerability issues.

The available ER-MAS is available in capsules of 5 mg increments from 5-30 mg, which permits mixing and matching so that only three pills per day will be necessary (see table 5).

The medication capsules will contain riboflavin. This non-harmful substance will allow the clinic to verify that the study medication is being taken correctly and absorbed by the body. The urine samples obtained three times a week will be examined under a UV lamp in order to observe any fluorescence signifying the consumption of the capsules. The patient will consume up to approximately 50 mg of riboflavin daily. In addition, folic acid in the form of a 1 mg "pill" will be added to all placebo capsules in an attempt to improve the blind. The patient will receive up to 4 mg of folic acid daily. Patients will receive medication in pill bottles. In the event that participants miss four consecutive days of medication, they will be given half the dose until their next scheduled study visit.

Psychosocial Treatments: Patients will receive cognitive behavioral therapy and voucher incentives.

Cognitive Behavioral Therapy: Cognitive-Behavioral Therapy (CBT) is a robust psychotherapy for cocaine use disorders with proven efficacy (Carroll and Onken, 2005; Crits-Christoph et al., 1999; Rawson et al., 2002). Because CBT is a standard condition in pharmacotherapy trials and since participant drop-out is a consistent problem in cocaine use disorder pharmacotherapy trials, we believe that it is a reasonable platform for this study. Upon entry into the single-blind PBO lead-in, and throughout the remainder of this proposed trial, subjects will be asked to participate in manual-driven CBT. Therapy will be conducted by MA level therapists who will also provide feedback on compliance, urine screen results, substance use, and other study participation elements.

CBT is a short-term therapy directed towards the 1) cessation of drug use behavior, 2) reduction of concomitant mood symptoms including depression, anger, and anxiety, 3) prevention of future relapse, and 4) coping with ADHD symptoms. Skills to improve mood, increase the number of pleasant (non-drug related) activities, improve communication, and identify mood disruption as both a trigger and consequence of drug use will be taught during the manualized treatment. Sessions will be audio-taped, and random sessions are chosen for review by a team of therapists, and a supervisor.

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 and/or increases in blood pressure and heart rate considered unstable for two consecutive weeks (defined as SBP>140, DBP>90, sitting quietly HR>100) will result in the discontinuation of study medications. Unstable vital signs defined as 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). An ECG will be repeated at weeks 4, 9, and 14 of the trial. An ECG and clinical blood work will also be repeated during the study if the patient has significant cardiovascular symptoms and at the end of the study. Patients may be removed from the study if they repeatedly miss study visits.

On the visits during weeks 7, 13 and at follow-up when neuropsychological testing will be conducted an alcohol breathalyzer will be conducted and the level must be < 0.04% in order for the testing to be administered.

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. All participants will be re-consented between weeks 6-8 regarding anticipated risks and benefits to continued medication treatment. Participant response will be documented in the participant's record/chart.

b) Urine Riboflavin: A patients' compliance with respect to study medication will be monitored in two ways, by presence of riboflavin and pill count. The presence of riboflavin in a patients urine samples will be checked three times per week; the urine samples will be examined under a UV lamp in order to observe any fluorescence signifying the consumption of the study capsules. The absence of riboflavin in a patient's urine will not result in termination of a patient's involvement in the study. Secondly, medication compliance will be monitored by pill count on the medication bottles returned by the patient.

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation

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 and/or increases in blood pressure and heart rate considered unstable (defined as SBP>140, DBP>90, sitting quietly HR>100 for two weeks) 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.

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 a participant discontinues the medication treatment for either personal or medical reasons, such as intolerable side effect or uncontrollable high blood pressure, they will have the option to continue CBT treatment for the duration of the trial and will be able to continue earning study vouchers for attendance. However if necessary, a referral for inpatient treatment will be made. This involves clinical judgment 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 until an 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 > 5 [markedly 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 medications.)
- 3) Cardiac risks as 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). This approach will be similarly used if patients have other polysubstance use disorders, such as alcohol.
- 5) If the subject 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. Approximately, 40 ml of blood will be drawn overall (i.e., baseline and study completion = 2 x 20 ml =40 ml).

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.

Please see table 2 for the schedule of assessments and procedures.

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:

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, TSH, and blood pregnancy test for women (45 minutes). Individuals in which the clinical staff cannot determine whether there are structural abnormalities or cardiovascular disease (i.e. abnormal ECG with no cardiac symptoms) will be referred to a cardiologist to determine study eligibility. An ECG will be repeated at weeks 4, 9, and 14 of the trial. Patients will receive another physical examination and an ECG at end of study. 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 selfreport 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 firstdegree relatives. Patients will also complete a Locator Form so that they can be contacted for follow-up (30 minutes).

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

Cocaine Selective Severity Assessment (weekly): This clinician-rated questionnaire (Kampman, et al., 2002) has been used to measure level of cocaine abstinence signs and symptoms and has found to be a significant predictor of abstinence in medication treatment trials.

Barratt Impulsiveness Scale. (BIS-11) (Patton et al., 1995): This instrument is a 30-item questionnaire, which has been used, in several previous studies on impulsivity and aggression (Allen et al., 1998; Coccaro et al., 1996). In our work we found that cocaine dependent subjects scored significantly higher on the BIS and that subjects with the highest BIS scores had a worse outcome in a treatment study. The BIS will be used as one of the primary measures of impulsivity for all subjects. Due to the nature of this measure it will only be administered at baseline. It takes 5 minutes to complete.

Immediate Memory Task/Delayed Memory Task: IMT/DMT (Dougherty et al., 1999a; 2002), will be the primary impulsivity measures used. These measures were chosen to include paradigms based on two different models of impulsivity (rapid response and delayed reward). These are computerized response tasks and will be conducted at screening, weeks 7 and 13.

The Connors' Continuous Performance Test - 2nd Edition 224 (CPT-II) is a measure of motoric inhibitory control which, unlike conventional CPTs, requires the subject to respond to all targets except for the target letter. Thus, the motor system is primed to respond, and for a minority of the trials the subject must inhibit the prepotent response. The test provides measures of omission and commission errors, mean and SD reaction times (RT's) for hits, and a measure of between-block

RT changes. This is a computerized measure that will be administered at baseline and at the end of treatment at week 13. It takes 20 minutes to complete.

Drug Stroop. On the Drug Stroop task, 200 heroin, cocaine, marijuana, mixed drug, and neutral words are presented 1 at a time, in red, blue, green, and yellow fonts, on a computer screen. Participants "name" the color of each word by pressing the appropriately colored key (green, yellow, blue, and red) on a response box. Response times (msec) are recorded for the time interval between the presentation of the word and the participant's manual response to it. Interference is operationalized by response time to cocaine words * response time to neutral words. This measure will be administered at baseline, weeks 7 and 13. It takes 10 minutes to complete.

The GoStop Task (Dougherty, 2003) measures a participant's ability to inhibit responses. The GoStop presented randomly generated five digit numbers on a computer screen. The numbers appear black against a white backgrounds for 500ms, followed by a 1500ms blackout period. The three types of trials found in the Go Stop task are no stop, stop, and novel trials. A no stop trial is a number that matches the previous number and remains black. No stop trials were presented on 25% of session trials. A stop trial is a number that matches the previous number, but changes from black to red at intervals of 50, 150, 250, or 350 ms after the original presentation of the stimulus. Stop trials appeared 25% of the time, with equal probability assigned to each of the four delay intervals. These probabilities resulted in 18-20 stop trials per delay across the 10-minute testing session. A novel trial is a randomly generated 5-digit number that does not match the previous stimulus. Novel trials appeared on 50% of the session trials. Participants were instructed to click the mouse button whenever two matching numbers were presented consecutively unless they turned red. The dependent measure for the GoStop task is the proportion of inhibited responses to the total number of stop trials for each delay condition. This is a computerized task that will be administered at baseline, weeks 7 and 13.

The Balloon Analog Risk Test (BART) (Lejuez et al., 2002) is a computerized, laboratory-based measure that involves actual risky behavior for which, similar to real-world situations, riskiness is rewarded up until a point at which further riskiness results in poorer outcomes. The BART was designed to provide a context in which actual risky behavior could be examined. The computer screen shows a small simulated balloon accompanied by a balloon pump, a reset button labeled Collect \$\$\$, a permanent money-earned display labeled Total Earned, and a second display listing the money earned on the last balloon and labeled Last Balloon. Each click on the pump inflates the balloon. With each pump, 5 cents are accrued in a temporary reserve (the amount of money in this reserve is never indicated to the participant). When a balloon is pumped past its individual explosion point, a "pop" sound effect was generated from the computer. When a balloon explodes, all money in the temporary bank is lost, and the next un-inflated balloon appears on the screen. At any point during each balloon trial, the participant can stop pumping the balloon and click the Collect \$\$\$ button. Clicking this button would transfer all money from the temporary bank to the permanent bank, during which the new total earned would be incrementally updated cent by cent while a slot machine payoff sound effect played. This computerized task will be administered at baseline, weeks 7 and 13. It takes about 10 minutes to complete.

The Delayed Discounting Task (Kirby et al, 1999) consists of a fixed set of 27 choices between smaller immediate rewards and larger delayed rewards, with reward values ranging between \$11-\$85 and delays ranging between 7 days to 6 months (Petry et al 2002). The hyperbolic discounting function will be used $vp = V/(1 + kD)$, vp is the present (discounted) value of a delayed reward, V is the undiscounted value of a delayed reward, D is the delay from the present to the receipt of a delayed reward and k is a constant that is proportional to the degree of discounting (Mazur 1987). It will be conducted at baseline, weeks 7 and 13.

Please attach copies, unless standard instruments are used

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

Adderall-XR

Manufacturer and other information

The generic or chemical name for Adderall-XR® is Extended-release mixed amphetamine salt. It is manufactured by Shire for Adderall-XR® 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 treatment medication within 2-3 weeks after the initial screening evaluation if they have been randomized to the active medication arm. Those assigned to the

placebo group will not receive active medication, but will receive CBT therapy within 2 weeks after the initial screening evaluation.

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

Individuals may not begin CBT therapy until 2-3 weeks after their initial screening evaluation for the study. Screening may take up to 2 weeks, requiring 2-3 visits, and CBT is delayed until entry in to the trial.

Cognitive Behavior Therapy is administered to all patients at the beginning of the study.

Treatment to be provided at the end of the study

At the conclusion of the 14-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, based on a CGI improvement score < 2, they will be given the option of receiving medications for up to 4 weeks until an appropriate referral for ongoing treatment is made.

Clinical Treatment Alternatives

Clinical treatment alternatives

Individuals do not have to participate in this study to receive treatment for their ADHD and cocaine dependence. Stimulant medication therapies, such as methylphenidate (Ritalin) as well as certain psychotherapy methods, may be helpful in treating the symptoms of ADHD. There are also a number of different treatment approaches for cocaine dependence, such as drug-free outpatient treatment, residential treatment, or outpatient treatment, that are available without the risk of being treated with a placebo; a potential participant will be informed and may consider these treatments as alternatives to participating in this program. In addition, participants may withdraw from this study at any time and 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. The dose of Adderall-XR given in this study is higher than the FDA approved dose and therefore there are unknown risks. Although the maximal dose for ER-MAS has been approved for maximal use of up to 60 mg/day, higher are likely necessary for adult ADHD in active cocaine abusers (Levin et al., 2006a; b) who are quite tolerant to stimulant effects. Further, higher doses were found to be more effective in reducing cocaine use among non-ADHD cocaine-dependent and amphetamine abusing subjects (world literature summary, Grabowski et al., 2004b). Additionally, Grabowski and colleagues are currently conducting a further study examining 80 mg d-amphetamine SR

(Spansules) in the cocaine-alone population. Therefore, for study, doses of 60 mg/day and 80 mg/day will be compared. Adverse events most commonly associated with amphetamine administration include: insomnia, emotional lability, nausea/vomiting, nervousness, palpitations, elevated blood pressure and, rapid heart rate. One side effect common to the medication is weight loss. 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. 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 monthly throughout the trial.

Blood drawing may cause slight discomfort at site of needle entry, resulting in a small bruise. Patients will be warned about this.

An additional risk exists in any medications study. Subjects may be at greater risk if they self-administer other drugs that may interact with the treatment medication. Subjects in these studies are identified 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 uncertain magnitude. Our experience with these issues is discussed below in methods to attenuate risk.

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 and cardiac function will be tested again at the end of the medication phase of the study. 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).

Risks of Diversion The risks of stimulant diversion are small but not negligible. 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 2004, only 1.1 % of the population surveyed had used Dexedrine (amphetamine) for non-medical usage, in comparison to 1.7 % for methylphenidate. In our clinical experience prescribing methylphenidate to adults with substance use disorders, methylphenidate was rarely abused. 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 and will contain riboflavin. Patients who are found to abuse/divert their study medication will be taken off their study medication.

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.

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 serum 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, TSH) and electrocardiogram (ECG) is designed along with clinical history to detect chronic and unstable medical illnesses.

History of allergic or adverse reactions to ER-MAS 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 and/or increases in blood pressure and heart rate considered unstable (defined as SBP>140, DBP>90, sitting quietly HR>100 for two weeks) 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.

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 a participant discontinues the medication treatment for either personal or medical reasons, such as intolerable side effect or uncontrollable high blood pressure, they will have the option to continue CBT treatment for the duration of the trial and will be able to continue earning study vouchers for attendance. However if necessary, a referral for inpatient treatment will be made. This involves clinical judgment 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 until an 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 > 5 [markedly 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 medications.)

3) Cardiac risks as 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). This approach will be similarly used if patients have other polysubstance use disorders, such as alcohol.

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

Data and Safety Monitoring Plan-

Patients are closely monitored throughout the trial as described above. In addition to weekly psychiatric visits, cardiovascular side effects and suicidal events will be monitored independently (i.e., no formal involvement with the study patients) by a Safety Monitoring Board consisting of Drs. Oscar Bukstein, Soteri Polydorou, and Deborah Ascheim. They will meet on an annual basis and review data provided by the Principal Investigator, including recruitment, progress, safety,

adverse events, and serious adverse events associated with the study. Given the unknown cardiovascular risks associated with the study medication dose in cocaine abusing individuals, the board will also monitor any abnormal cardiovascular symptoms and ECGs. Individuals on the Safety Monitoring Board will be blind to the study medication but can be informed by the un-blinded pharmacist, if a study patient is on Medication "A" or Medication "B" or Medication "C" with two groups receiving active medication and the other group receiving placebo. In this way, they can observe any problematic trends associated with one of the "medications." If they deem necessary, they can also request to know whether or not the participant received active medication or placebo. If they believe that termination of the trial is warranted, the blind of all study patients will be broken.

Methods to Protect Confidentiality

Describe methods to protect confidentiality

A Certificate of Confidentiality has been 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.

Will the study be conducted under a certificate of confidentiality?

Yes, we have already received a 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 ADHD and 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.

At each of the screening visits, patients will be reimbursed \$4 for transportation. The screening process generally requires 2-3 visits. At the completion of the screening interviews, participants who finish the entire interview session will receive \$25 in cash. Participants may potentially earn approximately \$37 for completing the screening process. Patients will also be reimbursed \$4 for transportation at each study visit. As described above, patients can earn vouchers once randomized into the study for clinic attendance and participation in study procedures (i.e., completing weekly assessments, providing urine samples, attending therapy and returning the medication bottles). If an individual attends all visits (which is highly unlikely), s/he could potentially earn vouchers worth a total of \$591.50 over the 14-week study period. Patients will also be paid an additional \$5-\$25 in cash (based on their performance) at weeks 7 and 13 for completing the neuropsychological tasks.

Voucher Incentives: The use of voucher reinforcement for substance use disorder outcomes in clinical trials is now a commonly used method. A potential use of voucher reinforcement is to improve adherence to clinical trial study procedures. Participant drop-out in cocaine use disorder pharmacotherapy trials is very high, which leads to a loss of statistical power to detect differences between treatment conditions. Our research group's experience has been that voucher reinforcement can be used to encourage study visit attendance. An important distinction between voucher reinforcement for attendance versus reinforcement of abstinence is that reinforcement of attendance promotes study visit attendance by all participants, not just participants who have achieved a reduction in their cocaine use.

Once entered into the study, patients can earn vouchers with a specific monetary value if they come to their study appointments, complete the required assessments, provide a urine sample at each visit. The value of vouchers for each subsequent visit will be increased by \$0.50. Failure to attend study appointments, complete study assessments, and provide a urine sample will reset the value of vouchers back to their initial \$0.50 from which the voucher value can escalate again according to the same schedule. Attending three consecutive clinic visits following non-attendance will return the value of the voucher to the level achieved prior to the missed visit.

To further reinforce continued attendance, patients will earn a \$10 voucher each week for returning their medication bottles and any remaining medication for that week. The voucher for pill bottle return is only contingent on returning the pill bottles and any remaining pills, not for taking the medication. If an individual attends all visits, s/he could potentially earn vouchers worth a total of \$591.50 over a 14-week period. Patients will never receive the money directly and vouchers

cannot be lost once earned. Instead, voucher earnings will be redeemable for retail goods or services designated by the participant in cooperation with the therapist to increase drug-free pro-social activities (e.g., movie passes, sporting equipment, educational or vocational classes, or phone cards). This approach will be implemented to improve clinical attendance and to better monitor participant adherence to the medication regimen. If a participant discontinues the medication treatment for either personal or medical reasons, such as intolerable side effects or uncontrollable high blood pressure, they will have the option to continue CBT treatment for the duration of the trial and will be able to continue earning study vouchers for attendance.

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